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# Does keto make the difference? A comprehensive review of its impact on physical activity, cognitive function and hormonal balance

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**ABSTRACT**

**Introduction:** A well-balanced diet is essential for optimizing physical performance. The ketogenic diet, characterized by high fat and low carbohydrate intake, has become increasingly popular among athletes and fitness enthusiasts due to its potential for supporting weight loss and enhancing metabolic health. This study aims to analyze the impact of the keto diet on physical and cognitive performance, as well as to understand the mechanisms and challenges associated with its use.

**Materials and methods:** A systematic review of available studies was conducted through extensive searches in databases such as PubMed, NCBI, and Google Scholar. Data were collected from clinical and experimental studies, evaluated for methodological robustness, participant characteristics, and therapeutic effects.

**State of knowledge:** The ketogenic diet can be beneficial in endurance sports by improving fat utilization as an energy source and increasing energy stability, but its impact on aerobic capacity and time to exhaustion varies. In strength sports that require intense effort, carbohydrate restriction can negatively affect strength and muscle mass development, as glycogen is a key energy source in such activities. The ketogenic diet does not provide full benefits in high-intensity sports, such as sprints or team sports, due to limited glycogen availability. The ketogenic diet can improve body composition and metabolic efficiency in athletes, but its impact on performance depends on individual responses, and the adaptation process may involve challenges such as "keto flu." Ketogenic diet may positively impact mental health by reducing symptoms of anxiety and depression. Additionally, it may enhance sleep quality, particularly by supporting deep sleep, and potentially increase testosterone production.
**Conclusions:** The ketogenic diet can benefit endurance sports by improving fat oxidation and sustaining energy levels, though its effectiveness in high-intensity, glycogen-dependent activities is less certain. Strategies like TKD or CKD, along with performance monitoring, can help athletes optimize results.

**Keywords:** “physical activity’’, ‘‘ketogenic diet’’, ‘‘ketosis”

## INTRODUCTION

Diet plays an integral part in physical performance. Providing the right amount of micro and macronutrients can boost our capabilities, thus resulting in superior results. Recently the ketogenic diet has become more and more popular. Known for its high fat content, moderate protein, and low carbohydrate intake, it has also gained popularity among athletes and fitness enthusiasts. Originally developed to manage epilepsy, “Keto“ is widely promoted as a method for weight loss, improving metabolic health and even enhancing physical performance. This review analyzes the influence of the keto diet on performance, its physiological mechanisms behind the potential benefits and the challenges faced by athletes following this eating regimen. In this article, the examination of athletic performance on ketosis also includes cognitive aspects, as they are crucial for proper task execution.

## MATERIALS AND METHODS

This review employs a comprehensive approach by performing a broad literature regarding the influence of the ketogenic diet on athletic performance. Aspects like physiology, exercise specificity or practicality of the keto diet were taken under consideration. Extensive searches were conducted across various databases including PubMed, NCBI and Google Scholar using applicable keywords: “ ketogenic diet ”, “ ketosis”, “ keto ”, “ physical activity ”, “ physical performance ”,“ athletic performance ” and “ cognitive function ”. The analyzed data was drawn with critical evaluation of study design, participant groups, and outcomes.

## STATE OF KNOWLEDGE

### 1. The ketogenic diet

Ketogenic diet (KD) consists of high fat, low carbohydrate and sufficient protein intake. Daily caloric need in KD is derived by 70% of fat, 20% of proteins and 10% of carbohydrates [1]. There are numerous types and variations of this diet. Inter alia:

1. CKD (classic ketogenic diet). Ratio between fat and non-fats (proteins and carbohydrates combined) is 3:1 or 4:1 [2].
2. MAD (The modified Atkins Diet). Ratio between fat and non-fats is 1:1 therefore is less restrictive. The percentage of nutrients in this method presents as: 65% fat, 25% protein, 10% carbohydrates [3].
3. MCT supplementation. 60% of daily calorie intake is derived from MCT which stands for medium chain triglycerides [2].
4. VLCKD (Very Low Calorie Ketogenic Diet). Daily intake of protein ≥75 g/day, 30-50g of carbohydrates and 20g of fat. Total calorie count is exceptionally restrictive, around 600-800 kcal / day. [2].

Carbohydrates are the main energy source for the human body. After a few days of low carbohydrates intake in KD, glycogen reserves are depleted. At that point the energy source shifts towards fat. Stored fat is metabolized into free fatty acids which are used by the liver to produce ketones, another source of energy for the body. This is called physiological ketosis. A like mechanism occurs when fasting or after intensive physical workout. [4]

An example of ketogenic diet and its positive impact was shown in a study conducted by Laura RSaslow et al. [5]. It compared the effects of moderate carbohydrate diet and ketogenic diet on obese patients with prediabetes or type 2 diabetes. Individuals were divided into two groups :

1. Moderate carbohydrate intake (18 patients). In this group 50% of calorie intake was from carbohydrates, protein consumption stayed the same as before the study, and daily calorie level was kept 500 kcal lower than calculated maintenance need.

2. Low carbohydrate, high fat diet (Ketogenic diet) (16 patients). The goal was to keep blood beta-hydroxybutyrate (ketone) concentration between 0.5 and 3 mM measured twice a week, carbohydrates intake was kept below 50g per day. Protein intake stayed the same and remaining calories were derived from fat. No calorie restriction was introduced in this group. After 3 months of the intervention, the results showed that the HbA1C level reduction was significantly higher among low carbohydrate group than in the moderate carbohydrate intake group. The weight loss was higher in low carbohydrate group but according to calculations it wasn't statistically significant. Author suggests that the ketogenic diet can be a useful tool in glycemic control in type 2 diabetes.

Erin McGaugh et al. [4] state that the ketogenic diet can have a positive impact on weight loss, reduction of cardiovascular disease risk and be used to treat type 2 diabetes. Many researchers claim that KD can have a favorable impact on neurological diseases such as epilepsy , multiple sclerosis, migraine, Alzheimer's disease and Parkinson's disease. [6] Although it comes with a risk. The analysis of Chanthawat Patikorn at. Al showed excess muscle-mass loss, and elevation of LDL and total cholesterol levels [7]. The significance and usefulness of KD in everyday medical practice is yet to be examined.

## 2. Physiological mechanisms and energy dynamics of ketosis

When referring to ketone bodies, we are discussing three specific compounds: acetone, acetoacetate, and beta-hydroxybutyrate [8] In a physiological state, ketone levels typically range from 0.05 to 0.1 mmol/L in the bloodstream[9].

In physiological ketosis, as discussed in this review, blood ketone levels typically reach a maximum of 7–8 mmol/L without alterations in blood pH. In contrast, during ketoacidosis, ketone levels can exceed 20 mmol/L more than two to three times higher resulting in a significant reduction in blood pH.[10]

Ketogenesis occurs primarily in the mitochondria of hepatocytes. Fatty acids are transported into the mitochondria via carnitine palmitoyltransferase, where they undergo beta-oxidation to form acetyl-CoA. Two molecules of acetyl-CoA are then converted into acetoacetyl-CoA by the enzyme thiolase. This intermediate is subsequently transformed into HMG-CoA by HMG-CoA synthase. HMG-CoA lyase catalyzes the conversion of HMG-CoA into acetoacetate. Acetoacetate can be decarboxylated non-enzymatically to form acetone or reduced by beta-hydroxybutyrate dehydrogenase to produce beta-hydroxybutyrate. Once beta-hydroxybutyrate reaches extrahepatic tissues, it is converted back to acetoacetate through the action of beta-hydroxybutyrate dehydrogenase. Acetoacetate is then reconverted into acetyl-CoA via beta-ketoacyl-CoA transferase. Acetyl-CoA enters the citric acid cycle, and through oxidative phosphorylation, generates approximately 22 ATP molecules per acetyl-CoA. In contrast to beta-hydroxybutyrate, acetone is not reconverted into acetyl-CoA. [11]

The process of ketosis is highly dependent on the availability of free fatty acids, which are subject to β-oxidation in liver mitochondria. Key regulatory mechanisms include lipolysis in adipocytes, which is hormonally controlled, and the activity of enzymes such as CPT1 and HMG-CoA synthase. Phosphorylation of HMG-CoA synthase enhances its activity in response to increased demand for ketone bodies. Insulin, the primary regulatory hormone, inhibits ketogenesis by suppressing lipolysis, stimulating lipogenesis, and blocking β-oxidation. During fasting, reduced insulin levels and increased glucagon levels relieve the inhibition of CPT1, thereby promoting ketogenesis. This process is further supported by stress hormones, such as cortisol and catecholamines. Ketogenesis is also regulated at the transcriptional level, with a pivotal role played by PPARα, a lipid-activated receptor. PPARα controls the expression of genes involved in fatty acid breakdown and ketone body production. One of the hormones induced by PPARα is FGF21, which facilitates lipolysis and ketogenesis. Deficiency of FGF21 leads to impaired lipid metabolism. FGF21 also represents a promising therapeutic target for the treatment of obesity and diabetes. At the epigenetic level, β-hydroxybutyrate functions as a signaling molecule, inhibiting histone deacetylases and activating genes involved in oxidative stress protection. β-hydroxybutyrate can also enhance the expression of brain-derived neurotrophic factor in the brain, improving cognitive function and supporting metabolic adaptation during fasting. Through multi-level regulation including hormonal, transcriptional, and epigenetic mechanisms ketosis plays a significant role in metabolism, with potential applications in the treatment of metabolic and neurodegenerative diseases. [12]

## 3. Impact on performance in various types of sports

In endurance sports, such as long-distance running or cycling, KD is used by some athletes because it increases fat burning, allowing for the use of more sustainable energy reserves in the body [13,14]. In a study conducted by JS Volek et al., the impact of a low-carbohydrate diet was analyzed on twenty elite ultramarathon runners and Ironman triathletes. They were divided into two groups: one group consumed a traditional high-carbohydrate diet, while the other followed a low-carbohydrate diet for an average period of 20 months.

The athletes performed a maximal graded exercise test on a treadmill and a 180-minute submaximal run at 64% VO2max on the treadmill to determine metabolic responses. It was shown that endurance athletes on the keto diet not only rely less on glycogen but also exhibit a higher rate of fat oxidation, which helps them maintain performance for a longer time [14].

Research indicates that KD may promote energy stability in endurance athletes, although its impact on maximal oxygen uptake (VO2max) and time to exhaustion is varied. A meta-analysis by J. Cao et al. suggests that KD does not unequivocally improve aerobic capacity but may support fat oxidation efficiency during endurance exercise, especially under low carbohydrate availability [13].

In the case of strength sports, such as weightlifting, KD may not support maximal increases in strength or muscle mass. Studies show that while KD may contribute to fat tissue reduction, it may simultaneously fail to provide adequate support for muscle mass growth and strength performance due to carbohydrate restriction, which is a primary energy source in intense resistance training [15,16,17]. Findings reviewed by Gómez-Urquiza et al. also support that while KD can maintain or even increase some strength measures, they do not consistently enhance anaerobic performance due to reduced glycogen storage, which is more critical in anaerobic, high-intensity activities than in endurance sports [17].

Sports that require intense effort, such as sprints or team sports, may also not achieve the full benefits of the KD. This is due to the fact that carbohydrate restriction can affect the ability to rapidly generate energy during high-intensity efforts, where muscle glycogen utilization is typically preferred [18,19].

## 4. Challenges for the athlete on a ketogenic diet - adaptation phases and the ‘keto flu’. Impact on the immune system

The ketogenic diet (KD) has gained popularity among athletes seeking to enhance performance and body composition. However, the transition to a KD involves several challenges, particularly during the adaptation phase when the body shifts from utilizing glucose to ketones as its primary energy source. This adaptation phase is crucial yet often difficult for athletes.

Harvey and Schofield [20] conducted a qualitative study highlighting the lived experiences of healthy adults on a ketogenic diet, revealing that many individuals encounter various physical and psychological symptoms during the adaptation phase. These symptoms can include fatigue, headaches, and irritability, collectively termed "keto flu." Such experiences are critical for athletes to understand as they may impact training performance and overall well-being. Another study analyzed 448 posts from 300 unique users discussing the keto flu, with 101 users reporting symptoms, leading to 256 symptom descriptions. The most common symptoms included flu-like symptoms (44.6%), headache (24.8%), and fatigue (17.8%), with severity categorized as mild, moderate, or severe among participants. Symptoms typically peaked within the first week and resolved by a median of 4.5 days. Users suggested remedies such as increasing sodium intake and supplementing with electrolytes to alleviate symptoms [21].

Moreover, the timing of adaptation to different qualities of ketogenic diets has been examined by Towsley [22]. Time of the adaptation to a ketogenic diet may take approximately two to three weeks, with no significant differences between high-quality ketogenic diets (HQKD) and low-quality ketogenic diets (LQKD). Out of 11 participants, 5 completed the study, resulting in a 55% dropout rate. Those who adhered to the dietary intervention maintained an average compliance of 94.1% over 26 out of 28 days. Ketone levels fluctuated, reaching up to 80 mg/dL for LQKD and 40 mg/dL for HQKD, while control group levels remained stable at 0–5 mg/dL. Participants reported various ketogenic induction symptoms, including lightheadedness and muscle weakness (100% in HQKD) and headaches (100% in LQKD). Fasting blood glucose levels decreased significantly, with HQKD dropping from 77.5±19.1 mg/dL to 69.5±3.5 mg/dL and LQKD from 92.0±1.4 to 83.5±2.1 mg/dL. The findings suggest that while adaptation can occur within a few weeks, individual responses may vary, highlighting the need for further research on dietary quality's impact on health outcomes during ketogenic diet adherence.

Nutritional supplements can significantly alleviate symptoms associated with the "keto flu" during the transition to a ketogenic diet. The review by Harvey et al. [23] highlights several key supplements that can expedite ketosis and reduce discomfort. Key supplements include electrolytes such as sodium, potassium, and magnesium, which are essential for fluid balance and can reduce symptoms like cramps and fatigue by up to 40% when supplemented. MCT oil (Medium-Chain Triglycerides) provides a rapid source of ketones, enhancing ketone production by 25-50% and helping to alleviate energy dips. Omega-3 fatty acids may reduce inflammation and improve mood, stabilizing mood in up to 60% of individuals experiencing keto flu symptoms. B vitamins, particularly B6 and B12, are vital for energy metabolism, with supplementation potentially improving energy levels by approximately 30%. Additionally, fiber supplements can prevent digestive issues like constipation, reducing gastrointestinal discomfort by 50%. The review emphasizes that tailored supplementation can lead to a 40% reduction in keto flu symptoms, and MCT oil users may experience a 25% faster onset of ketosis compared to those relying solely on dietary changes. Integrating these supplements can ease the transition into ketosis effectively.

In terms of performance, Burke [24] discusses the implications of a ketogenic low-carbohydrate, high-fat diet for elite endurance sports. The findings suggest that while some athletes may thrive on a KD, others might experience diminished performance due to inadequate glycogen stores. The study suggests that approximately 30% of endurance athletes may not respond favorably to a KD, highlighting the importance of understanding individual responses to dietary changes.

Resistance training is another area where the ketogenic diet's effects have been studied. Valenzuela et al. [18] found that KD participants experienced significant improvements in body composition, including weight and fat mass reduction, along with potential strength gains, though these varied by individual adherence. Concerns about fat-free mass (FFM) loss exist, which could affect muscle growth. Conversely, Vargas-Molina et al. [25] noted difficulties in managing training loads on a KD, emphasizing the need for careful monitoring of training intensity and volume. Despite some FFM reduction, physical performance may remain stable if training is adjusted accordingly.

A systematic review reported an average weight loss of 3.67 kg (95% CI: -4.44 to -2.90; $p < 0.001$) and a fat mass reduction of 2.21 kg (95% CI: -3.09 to -1.34; $p < 0.001$) among KD participants, with a noted FFM loss of 1.26 kg (95% CI: -1.82 to -0.70; $p < 0.001$), possibly due to water loss. While KD can improve body composition in resistance training, it requires careful management to address potential negative effects on muscle mass and performance.

The study by Shaw [26] highlights the impact of ketogenic diets (KDs) on immune function, particularly in endurance athletes. Key findings include that prolonged strenuous exercise can lead to immunosuppression and increased illness risk, especially when starting with low carbohydrate availability. Adapting to a KD increases blood ketone body concentrations, reaching up to 2.8 mmol/L post-exercise, which may enhance pro-inflammatory type-1 T-cell responses during and after exercise. Following KD adaptation, interferon-gamma (IFN-g) gene expression increased immediately after exhaustion, while interleukin-4 (IL-4) and IL-10 expressions remained unchanged, indicating a specific enhancement in pro-inflammatory responses without affecting mucosal immunity. Despite impairing exercise efficiency, mean time-to-exhaustion was preserved post-KD. The findings suggest that while KDs can transiently amplify pro-inflammatory T-cell responses after exercise, the long-term clinical implications for overall immune function remain uncertain.

Whereas the ketogenic diet presents several advantages for athletes, including potential improvements in body composition and metabolic efficiency, it also poses significant challenges during the adaptation phase. Understanding these challenges, particularly the keto flu, is crucial for athletes aiming to optimize their performance through dietary changes. Future research should continue to explore individualized approaches to dietary adaptation in sports nutrition to better support athletes' health and performance outcomes.

## 5. Dietary strategies to improve sports performance on a ketogenic diet

To optimize exercise outcomes, athletes may employ various strategies within a ketogenic diet, including Targeted ketogenic diet (TKD), Cyclical ketogenic diet (CKD) or supplementing exogenous ketones.

The targeted ketogenic diet (TKD) is a variant of the ketogenic diet designed to support athletes or individuals engaging in high-intensity physical activity. Unlike the standard ketogenic diet (SKD), which maintains a consistently low carbohydrate intake, TKD allows for additional carbohydrates around workout periods. This strategy aims to provide quick energy for physical exertion without significantly disrupting ketosis. The TKD is a relatively recent adaptation and is primarily used by athletes needing performance support [27].

A cyclical ketogenic diet (CKD) is a dietary approach that alternates between phases of very low carbohydrate intake (to maintain ketosis) and short periods of high-carbohydrate intake (carb-loading) to restore muscle glycogen. This method is especially used by athletes to preserve performance in high-intensity exercise, which relies on glycogen [28]. CKD has been proven to be not much more effective in reducing body mass or enhancing strength performance, compared to the Nutritionally Balanced Reduction Diet (RD).

Pavel Kysel et al. [29] compares effects of CKD and RD on body composition, muscle strength and endurance in young, healthy males engaged in aerobic and resistance training in a randomized controlled trial.

Both diets achieved similar reductions in body weight, body fat, and BMI; however, the CKD led to a slight but significant decrease in lean body mass and body water, unlike the RD, which preserved these metrics and thus achieved a fat-focused weight reduction. In strength assessments, the CKD maintained stable performance without significant gains, while the RD group exhibited improved strength in exercises like leg press, possibly due to the RD's continuous carbohydrate supply supporting glycogen levels and enhancing muscle adaptation. Furthermore, while CKD reduced the respiratory exchange ratio (RER), indicating a metabolic shift toward fat oxidation, it did not enhance key endurance metrics such as $VO_2max$ or peak workload. Conversely, the RD improved both $VO_2max$ and peak workload, likely as a result of sustained glycogen availability essential for aerobic performance.

In another study Pavel Kysel et al. [30] concludes that RD may more effectively enhance muscle strength and endurance in combination with exercise, potentially through its impact on musclin and osteonectin levels. Further research is suggested to explore these effects over longer durations and with a broader participant pool to validate the findings.

Exogenous ketones are ingestible ketone body supplements, typically in the forms of ketone salts and ketone esters, that increase blood ketone levels without carbohydrate restriction. They elevate the concentrations of the ketone bodies acetoacetate (AcAc) and β-hydroxybutyrate (βHB) in the bloodstream, promoting a metabolic state called "acute nutritional ketosis" . These supplements provide an alternative energy substrate that reduces glucose utilization and affects various metabolic pathways, including those involved in muscle and fat metabolism [31]. David M. Shaw et al. [32] indicates that neither ketone supplementation nor keto-adaptation consistently improves endurance performance relative to high-carbohydrate fueling strategies. For high-intensity activities, the reduction in carbohydrate utilization and potential gastrointestinal discomfort associated with exogenous ketone use can impair performance. Conversely, keto-adaptation may improve fuel utilization efficiency for prolonged low-intensity exercise but often diminishes performance in high-intensity contexts due to limited glycogen stores and reduced carbohydrate oxidation rates.

A study conducted on 10 male, recreational runners (age: 20.8 ± 1.03 years; body height: 175.6 ± 4.9 cm; body mass: 68.9 ± 5.6 kg; body fat: 13.4 ± 3.6%; lean body mass: 59.6 ± 3.1 kg; body mass index: 22.4 ± 1.9 kg/m2; running distance per week: 34.6 ± 5.5 km) showed no statistically significant difference in 5 km performance time between the ketone supplement (1430.0 ± 187.7 seconds) and placebo conditions (1488.3 ± 243.8 seconds), with a p-value of 0.100. However, the supplement group completed the run an average of 58.3 seconds faster than the placebo group, equating to a 4.06% improvement, though this difference was not statistically significant. Blood levels of R-βHB increased significantly with the ketone supplement compared to placebo, indicating effective absorption, but other physiological and perceptual metrics, such as heart rate, respiratory exchange ratio (RER), $VO_2$, and rating of perceived exertion (RPE), showed no significant differences between conditions [33].

## 6. The ketogenic diet and mental health

The ketogenic diet is gaining recognition in the context of mental health, providing a range of mechanisms that benefit the central nervous system (CNS). Its effects include reducing oxidative stress, improving mitochondrial function through decreased levels of reactive oxygen species, and mitigating inflammatory responses by inhibiting the synthesis of pro-inflammatory factors. Additionally, the ketogenic diet has a protective effect on neurons. It stimulates the production of NT-3 (neurotrophin-3), GDNF (glial cell line-derived neurothropic factor) and BDNF (brain- derived neurothropic factor)- proteins essential for neuronal development and survival. This diet also influences neurotransmitter balance by increasing GABA and glutamate levels, helping to stabilize the disrupted equilibrium of these neurotransmitters, commonly observed in various mental health disorders [34,6].

A cohort study by Garner S et al. examined the relationship between KD and mental health in two groups. In the first group, where participants adhered to the diet for an average of 23.56 ± 25.7 months, stress levels were assessed using the Perceived Stress Scale (PSS-10), and mood was measured with the Bond-Lader Visual Analog Scales (BL-VAS). Results showed that individuals on the ketogenic diet experienced lower anxiety levels, greater alertness and satisfaction, and increased calmness. In the second group, where participants followed the ketogenic diet for an average of 44.02 ± 64.97 months, depression, anxiety, and loneliness levels were assessed using the DASS-21 (Depression Anxiety Stress Scale) and a Three-item loneliness scale. Participants reported reductions in anxiety and emotional stress, as well as decreases in symptoms of depression and feelings of loneliness. The control group did not follow a specific diet, consuming a variety of foods [35]. A study by Weber SR et al. revealed that 22.3% of young athletes were at risk of developing depression, while 12.5% were at risk of experiencing anxiety[36].

In depression, levels of gamma-aminobutyric acid (GABA) are often reduced, while inflammatory cytokines- such as interleukin-6 (IL-6), interleukin-8 (IL-8), interleukin-12 (IL-12), and tumor necrosis factor-alpha (TNF-α)- are typically elevated in the central nervous system.The ketogenic diet has shown promise in normalizing these abnormalities by raising GABA levels and reducing inflammation triggered by these factors [37].

Other studies and case reports also indicate positive effects of the ketogenic diet on depressive symptoms [38,39,40].

In a study by Tidman MM et al., 16 Parkinson's patients followed a ketogenic diet for 24 weeks to examine its effects on anxiety and depression. Anxiety and depression levels were measured using the Parkinson's Anxiety Scale (PAS) and the Center for Epidemiologic Studies Depression Scale Revised (CESD-R-20). The results showed improvement in PAS scores, indicating reduced anxiety, while CESD-R-20 scores for depression showed no significant change [41].

While the ketogenic diet demonstrates promising benefits for mental health, further research is necessary to fully understand its mechanisms and determine the optimal duration for interventions. It is also noteworthy that mental health is of critical importance for professional athletes. A survey conducted among 200 adolescent athletes (aged 16-17) revealed that 91% of them experienced stress related to their sport, though only one-third viewed this stress as a motivator [42].

## 7. The ketogenic diet, sleep, and neuroplasticity mechanisms

The ketogenic diet significantly affects the functioning of the body, including sleep quality and brain neuroplasticity. Metabolic processes associated with ketosis influence neurological and hormonal pathways, which can positively modulate certain aspects of brain health and contribute to the improvement of sleep quality [4,43].

Improved sleep efficiency is one of the potential benefits of the ketogenic diet, particularly for individuals with sleep disorders, including insomnia. Research indicates that ketosis enhances the production of adenosine in the brain, a neurotransmitter that plays a critical role in the regulation of sleep [44]. Adenosine acts as a neuromodulator and cotransmitter, inhibiting the activity of excitatory neurotransmitters such as glutamate. The physiological effect of adenosine is regulated by four types of receptors, with the A1 receptor being the most prevalent in the human brain. Its interaction with the central nervous system leads to an increase in drowsiness and supports the process of falling asleep. This is particularly relevant for individuals who struggle with maintaining regular and restful sleep [45].

Research also indicates that ketones, particularly beta-hydroxybutyrate (BHB), play a crucial role in stabilizing energy levels in the brain, which may promote better sleep quality and reduce nocturnal awakenings. Produced during ketosis, BHB crosses the blood-brain barrier, supplying a consistent energy source during sleep while reducing glucose dependency, thereby supporting uninterrupted sleep. [46] [47] [48].

Adopting such a diet may also influence sleep patterns, particularly by reducing the duration of the REM phase and increasing the proportion of deep (non-REM) sleep, which promotes physical and mental recovery. The stabilization of cerebral energy levels through ketones may minimize sleep disruptions; however, prolonged suppression of the REM phase could result in adverse effects, such as impaired cognitive function and memory consolidation [47]. In a study conducted by Pasca et al. [49] demonstrated that the ketogenic diet may lead to sleep stabilization, as confirmed by actigraphic data. Polysomnographic analysis revealed a slight increase in total sleep time and an improvement in sleep efficiency. Additionally, a reduction in wakefulness during the night was observed, along with a tendency to shorten the duration of stage 1 NREM sleep, while the REM phase was prolonged. These findings suggest that the ketogenic diet may positively impact sleep structure, although changes in the REM phase and the reduction in wakefulness could have a varied effect on cognitive and restorative functions of the body.

The ketogenic diet has also been shown to positively influence brain neuroplasticity, enhancing the mechanisms responsible for neuronal regeneration and adaptation [50]. One of the key mechanisms is the elevated level of Brain-Derived Neurotrophic Factor (BDNF), which plays a critical role in neurogenesis and synaptic plasticity. BDNF facilitates the growth of new neurons and the strengthening of synaptic connections, processes essential for learning, memory, and cognitive resilience. Research suggests that the ketogenic diet may elevate BDNF levels, potentially enhancing brain function, including improved stress adaptation and cognitive performance [51].

This diet influences mitochondrial function, which is integral to intracellular calcium signaling with the endoplasmic reticulum, thereby modulating synaptic transmission and plasticity in astrocytes [52].

By enhancing mitochondrial efficiency, KD supports improved brain function by providing energy stability and protecting neurons from oxidative stress. Additionally, the improvement of mitochondrial biogenesis is crucial for neuroprotection and supports neuroplasticity, which may have a beneficial effect on cognitive adaptation and resilience [53, 54].

Phillips et al. [55] conducted the first randomized study assessing the impact of the ketogenic diet on patients with Alzheimer's disease. The study aimed to determine whether a 12-week modified ketogenic diet could improve cognitive function, daily functioning, and quality of life in these patients. In the study, 26 patients were randomly assigned to either the ketogenic diet group or the control group, which followed a standard diet. The results showed that patients on the ketogenic diet experienced improvements in daily functioning and quality of life, as measured by tools such as ADCS-ADL and QOL-AD, compared to those on the standard diet. Changes in cognitive function were less pronounced but still indicated a potential benefit from the ketogenic diet. This study suggests that the ketogenic diet may be a promising intervention in the treatment of Alzheimer's disease, improving patients' daily functioning and quality of life.

A high-fat, low-carbohydrate diet influences neurotransmitter balance, particularly GABA and glutamate, which are crucial for mental stability and cognitive function. Research indicates that the state of ketosis enhances the glutamine synthetase pathway in astrocytes, facilitating better "buffering" of synaptic glutamate by glial cells. This increases the availability of glutamine for GABAergic neurons, thereby improving GABA synthesis, the primary inhibitory neurotransmitter in the central nervous system. Furthermore, during ketosis, glutamine metabolism is altered, leading to a greater availability of glutamine for GABA synthesis and less conversion to glutamate, thus reducing the risk of excitotoxicity, or neuronal damage caused by excess glutamate. The improvement of this neurotransmitter balance supports neuroplasticity, positively influencing cognitive abilities and brain health [56], [57].

The long-term effects of KD still require further investigation, especially regarding its impact on individuals with chronic health conditions. This underscores the importance of regular health monitoring for those following this dietary regimen to ensure optimal outcomes and prevent potential adverse effects.

## 8. Are testosterone levels influenced by the ketogenic diet?

Testosterone, the primary male sex hormone, plays a crucial role in both physical and cognitive performance[58]. It is vital for muscle development, strength, endurance, and energy levels[59,60]. All of these are essential for athletic performance. Elevated testosterone levels are linked to increased muscle hypertrophy, greater strength, reduced fatigue, and quicker post-exercise recovery [61,62]. Moreover, testosterone influences cognitive factors like motivation and focus, which contribute to improved performance in complex tasks[63], like team sports. The study by Kraemer et al. highlighted the role of testosterone in enhancing muscle strength and size, particularly when combined with resistance training[64]. Testosterone also boosts protein synthesis and muscle recovery, key factors in athletic performance and long-term training success[62].

The ketogenic diet can indirectly impact testosterone production, in particular by promoting weight loss and reducing body fat. Excess fat, especially abdominal fat, converts testosterone into estrogen, so reducing fat through ketosis may help increase or maintain testosterone levels at optimal values. It has been proven that weight loss, irrespective of diet, can improve testosterone levels, however keto's specific effectiveness on abdominal fat loss may be more beneficial[65].

Insulin resistance and chronic inflammation reduce testosterone levels [66]. The ketogenic diet can improve insulin sensitivity, reduce inflammation, and enhance overall endocrine function, which supports higher testosterone levels [10].

It‘s important to realize that long-term adherence to the ketogenic diet, especially when it leads to prolonged low carbohydrate intake, can reduce energy availability, potentially affecting hormonal balance, including testosterone levels [10]. Research on athletes following ketogenic diets presents mixed results. There are studies that present stable testosterone levels, while others suggest declines, which could depend on factors like diet composition, carbohydrate intake and diet duration [67]. The effect of KD on testosterone is complex. For ideal results, a balanced approach via interval ketogenic diet application, could be the solution to the long-term concerns that are caused by insufficient caloric intake.

## 9. Implications for long-term health

Long-term use of KD may provide metabolic benefits, such as improved lipid profile, increased insulin sensitivity, and weight reduction [68]. Studies conducted on humans have shown that KD can lead to a decrease in triglyceride levels and total cholesterol, while simultaneously increasing HDL cholesterol, which promotes metabolic health and may reduce the risk of cardiovascular diseases [69].

Moreover, KD affects the gut microbiota by increasing the production of beneficial short-chain fatty acids, such as butyrate, which alleviates inflammation in adipose tissue and regulates appetite and energy metabolism, which is particularly important for individuals with obesity and type 2 diabetes [69,70].

A. Valenzano et al. conducted a study involving quantitative monitoring of obesity parameters and profiling of orexin-A in serum over a period of 8 weeks using a very low calorie ketogenic diet (VLCKD) in 10 men and 10 women aged 20-60 years with obesity. The use of VLCKD positively influenced the reduction of visceral adipose tissue (VAT), and the level of orexin-A in serum increased. This suggests the usefulness of short-term KD in promoting weight reduction in individuals burdened by this condition [71].

Limiting carbohydrates in the KD is associated with a potential reduction in inflammation, which may support recovery after intense training and decrease muscle soreness, which is particularly important for athletes training at high intensity. Studies suggest that KD may reduce levels of inflammatory markers, such as pro-inflammatory cytokines (e.g., TNF-α, IL-6) and C-reactive protein (CRP), contributing to the alleviation of the inflammatory response after physical exertion [68,69,72].

Despite its benefits, KD raises certain concerns, especially with long-term use. There is a risk of lipid disorders, which may increase cardiovascular risk, as well as deficiencies in certain vitamins and minerals, such as B vitamins, vitamin D, calcium, and magnesium [68,69].

Long-term use of a KD may be a potential cause of hormonal changes, especially regarding cortisol, which can lead to menstrual cycle disorders and affect bone health. Ketosis and carbohydrate restriction can induce a state of energy deficiency, known in sports as RED-S (Relative Energy Deficiency in Sport). Such deficiencies can lead to elevated cortisol levels and decreased estrogen, which critically impact bone mineralization and the proper menstrual cycle [73].

The lack of estrogen and chronically high cortisol levels can increase the risk of osteopenia and osteoporosis in active women who follow a ketogenic dietary approach for an extended period, particularly if it is associated with reduced energy availability and low intake of vitamin D and calcium, which support bone health [74,73]. Furthermore, long-term use of the KD, due to increased acidity in the body, may have an additional impact on bone health. Bones act as an alkaline buffer, and a diet high in fat and protein and low in carbohydrates may exacerbate calcium excretion in urine, further increasing the risk of weakening their structure [74]. The long-term effects of KD still require research, particularly in the context of the health of patients with chronic diseases, highlighting the need for regular health monitoring in individuals on this diet [70,74].

## CONCLUSIONS

The ketogenic diet provides potential advantages for endurance sports and activities of low to moderate intensity by enhancing fat oxidation and maintaining steady energy levels. Its effectiveness in high-intensity, glycogen-dependent sports is less clear due to the limited availability of glycogen. However, implementing strategies like TKD or CKD and tracking performance can assist athletes in optimizing their outcomes.

Future research could focus on better understanding individual responses to the ketogenic diet across various sports disciplines, particularly regarding endurance and recovery. Additionally, it would be valuable to further investigate the long-term effects of the ketogenic diet on hormonal health, including testosterone levels, as well as its impact on mental health and sleep quality.

**Authors' Contributions Statement:**

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- **Data Curation:** Ł.S.P., B.Z., K.K., T.M., A.S., P.H., J.S., P.M., J.D., M.Ł.
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- **Investigation:** Ł.S.P., B.Z., K.K., T.M., A.S., P.H., J.S., P.M., J.D., M.Ł.
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*All authors have reviewed and consented to the publication of the final version of the manuscript.*

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