Ketogenic Diet

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1. Introduction

The ketogenic diet, initially introduced in the early nineteenth century, refers to a diet pattern that is low in carbohydrates and high in fat with a moderate proportion of protein (1.2–1.5 g/kg) [1][2]. The ketogenic diet increases the oxidation of fatty acids and ketone bodies production—creating a state of ketosis and mild acidosis [3][4]. A ketogenic diet leads to glycolysis inhibition, inhibits glutamatergic synaptic transmission, and assists in weight loss [5][6], making it popular not only for patients with obesity or metabolic syndrome, but even for athletes, both professional and amateur [7]. Ketone bodies (acetate, aceto-acetate, and beta-hydroxybutyrate) have been shown to prevent recurrent seizures [8][9][10], hence are prescribed for children with intractable seizures. However, the mechanism of the anti-seizure effects of ketone bodies is not well understood. The ketogenic diet may also have a protective effect against cognitive impairment [11] and malignancy [12]. Indications for the ketogenic diet have been extended to include glucose-1 transporter deficiency syndrome and pyruvate dehydrogenase deficiency disorders [13][14].

Multiple formulations of the ketogenic diet are currently available, including the classic keto diet, low glycemic index diet (LGID), medium-chain triglyceride diet (MCT), and modified Atkins diet. These diets differ in the proportions of lipid, carbohydrate, and protein contents [10][13][14][15]. Despite potential advantages, the ketogenic diet has multiple adverse effects. During the first four-week period, nausea, vomiting, and diarrhea are particularly common with the medium-chain triglyceride diet [16][17][18], posing a risk for acute kidney injury, hyponatremia, hypomagnesemia, hypercalciuria, hyperuricemia, and metabolic acidosis [19][20][21]. Long-term adverse effects of the ketogenic diet, including osteopenia, risk of bone fractures, alterations in vitamin D levels, are well reported [22][23][24]. Increased risk for kidney stones is well described in patients using the ketogenic diet for over a 2 year period [17][20][25][26], with complications such as obstructive uropathy, acute kidney injury, and chronic kidney disease [27][28][29].

The incidence of kidney stones among patients on the ketogenic diet ranges from 3% to 10% [20][30][31], compared to one in several thousand in the general population [17][24]. We performed a meta-analysis on the incidence and characteristics of kidney stones in patients on the ketogenic diet to better understand the kidney stones' burden and pathophysiology in this population.

2. Incidence and Characteristics of Kidney Stones in Patients on Ketogenic Diet

A pooled incidence of kidney stones at 5.6% in patients treated with a ketogenic diet after four years. The incidence of nephrolithiasis in the general population is reported at 0.3% per year in men and 0.25% per year in women [32].

Uric acid stones are the most common stones in patients receiving the ketogenic diet, followed by calcium-based stones and uric acid–calcium mixed stones. In contrast, calcium oxalate stones are the most common stones in the general population [32]. The exact mechanism of nephrolithiasis following the ketogenic diet is unclear. However, it is likely related to hypocitraturia and acidosis, common in people consuming a high-protein and low-alkali diet [20]. Acidosis contributes to significant reabsorption of citrate in the proximal tubule, further contributing to hypocitraturia [25][33][34][35][36][37][38]. A more generous amount of free calcium is available for stone formation in a low-citrate environment [33][39]. Chronic acidosis also leads to demineralization of the bone and increased calcium excretion [17][20]. Hypercalciuria, immobilization, anti-epileptic drugs, and fat malabsorption further precipitate urinary calcium. Moreover, the low urine pH seen in patients with a low-alkali diet contributes to uric acid crystals [33]. Obesity, insulin resistance, and an animal-protein diet are associated with

low urine pH [40]. The uric acid stone may act as a nidus for calcium-based nephrolithiasis formation [33]. Furthermore, fluid intake restriction is traditionally applied to children receiving the ketogenic diet, making them susceptible to stone formation [33].

Potential benefits of urine alkalization with oral potassium citrate in children with a urine calcium to creatinine ratio of >0.20 mg/mg to prevent kidney stone formation is well reported [20][25][35][38]. Genetic polymorphisms in transporters, such as renal sodium citrate cotransporter, is a known risk factor in recurrent stone formers [41][42]. McNally et al. reported that the empiric use of oral citrate in children treated with a classic ketogenic diet led to a reduction in the incidence of kidney stones from 6.75% to 0.9% without an increase in adverse effects [43]. The international ketogenic diet study group agreed that oral citrates appear to prevent kidney stones; however, there was mixed opinion on its empiric use (class III) [9]. The consensus statement is unchanged since 2009 due to the lack of new evidence. Hence, we need a well-designed study to analyze the empiric use of urine alkalization therapy. A ketogenic diet is generally prescribed for weight loss in adults, who require a shorter duration of therapy; the empiric use of oral citrates may not be necessary. However, this remains to be elucidated by future studies.

Purine-rich foods (red meat, fish, poultry, beer, and legumes) increase the uric acid load [40]. The digestion of animal protein produces a transient acidic environment, which results in a lower urine pH, promoting the precipitation of uric stones [40]. Since uric stones are the most common stones in patients receiving a ketogenic diet, switching from animal proteins to plant-based proteins results in lower uric acid excretion, but, sequentially, lower uric acid stone formation is unclear. Siener et al. reported that patients consuming a balanced diet of vegetables and animal proteins had higher urine pH and urine uric acid concentration than those on a typical western diet [44]. It is also recommended that patients with symptomatic hypercalcemia, hyperuricosuric calcium urolithiasis, and urate nephropathy should be prescribed a urate-lowering agent [40]. However, empiric use of xanthine oxidase inhibitors in patients on a ketogenic diet requires further investigation.

Other measures to mitigate the risk of renal stones include liberalizing fluid intake and avoiding the initial fasting phase at the start of ketogenic diets [45][46]. Modification of the diet regimen to allow small, frequent meals might help decrease gastrointestinal side effects and avoid volume depletion [47]. Screening for underlying metabolic disorders should be considered before initiation of a ketogenic diet to help avoid substantial acidosis [48]. Considering the long-term risk of bone fractures and osteopenia, the 2018 international ketogenic diet group recommended periodic DEXA scan screening for evaluation of bone mineral density [9]. Epidemiological studies have shown a temporal relationship between idiopathic osteoporosis and kidney stones. In addition, changing dietary patterns, including the ketogenic diet, could possibly be an important environmental trigger in the association, as well [49]. Bone health should be monitored closely in patients on the ketogenic diet and more clinical trials are needed to further define the negative impacts on bone health [50]. Although prophylactic calcium and vitamin D is recommended in all people on the ketogenic diet for bone health [23][24], athletes with dermal calcium loss during exercise/sweating and obese subjects restricting dairy are at further risk of worsening bone health if not on adequate calcium supplements [7][50]. However, given the reported risk of nephrolithiasis from hypercalciuria, supplementation remains a challenge [20][25]. Periodic urine chemistry analyses to measure the calcium to creatinine ratio, calcium, citrate, and oxalate can help identify patients at risk for kidney stone formation, and timely referral to a nephrologist should be considered. Patients with a family history of nephrolithiasis should be screened before starting a ketogenic diet due to their higher risk for stone formation. In the era of precision medicine, further studies are needed to understand the use of genetic variants to further personalize management, even in the dietary therapy field [51].

3. Conclusions

In conclusion, the estimated incidence of kidney stones in patients on ketogenic diets is 5.6%, which is comparable among adults and children. Uric acid stones are the most prevalent kidney stones in patients treated with ketogenic diets, followed by calcium-based stones. These findings may impact the prevention and management of kidney stones in patients treated with ketogenic diets.

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