How might Low Carb and Ketogenic Diets affect the Progression of Chronic Kidney Disease?

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ABSTRACT

Background: Obesity, an ever-increasing cause for deaths in the American population, often leads to complications such as Type II Diabetes Mellitus. Both obesity and diabetes predispose to renal disease, which can be ameliorated by treatment of both disorders. Ketogenic and Low Carb diets (KD/LCD) can lower blood sugar of T2DM patients and accelerate weight loss. Diet is a potential factor in slowing the rate of decline in kidney function. Yet, high diet acid loads, as from keto acid, may promote renal damage. Here, we evaluate existing studies on the benefits or harms of KD/LCD on factors associated with renal disease progression.

Methods: Reviews and analysis of existing studies on chronic kidney disease and Ketogenic diets. We analyzed eGFR, the measure of the rate of change in decline of renal function to infer the effects of Ketogenic and Low Carb diets.

Results: Nine of the 22 papers reviewed were analyzed. Studies included from 18 to 1797 participants and included healthy subjects, those with diabetes and /or obesity, and those with normal renal function or moderate kidney failure (eGRF ranged from 94 ± 12 mL/min/ to 40 ml/min/1.73m^2). Study duration ranged from 5 weeks to 6 years. Several studies demonstrated improvements, including decreases in serum creatinine, urinary albumin, weight loss, and eGFR.

***Conclusions*:** Renal function improved in shorter studies of diabetics who demonstrated weight loss. Longer studies or those in nondiabetics demonstrated no change in renal function.

Introduction

The Ketogenic Diet (KD) is a low-carbohydrate, high-fat diet known for improving a variety of conditions including seizures in children resistant to anticonvulsant drugs, blood glucose levels, and lipid profiles in obese diabetics. Examples of foods in a KD are given in Figure 1. Today, diabetes and obesity are pandemic, with more than 90% of type 2 diabetics (T2DM) being obese or overweight [1]. Studies have shown that the KD can expedite weight loss in obesity as well as improved metabolic control in T2DM [2]. Moreover, both diabetes and obesity are risk factors for chronic kidney disease (CKD) [3]. Many studies have evaluated the effect of a KD/LCD on obesity and diabetes control. In this paper, we will briefly discuss the physiology of ketosis, and review the effects of a KD/LCD on both obesity and DM. However, while KD is known to aid weight loss in T2DM and obesity, it's also known that high diet acid loads, which include the keto acids generated from fat metabolism, may be damaging to the kidney [4]. We will therefore review the literature on the potential effects of KD/LCD on the progression of renal disease, particularly in those with T2DM and obesity.

Physiology of the Ketosis

Oxidative cellular energy uses adenosine triphosphate (ATP) mainly produced from glucose metabolism. A diet such as the KD severely limits carbohydrate intake (often to less than 50 grams a day [5]), so that the body enters a catabolic state where fats are metabolized instead of carbohydrates, such as glucose.

Ketogenesis

Ketogenesis, the process by which fatty acids are converted into ketones, takes place in mitochondria of liver cells [6]. Ketone bodies substitute for glucose as the body's source of energy. Fatty acids can be metabolized into Acetyl CoA, an integral aspect of the Krebs Cycle for the production of ATP [7]. of the two-carbon Acetyl CoA combines with the four carbon oxaloacetate, to produce the six carbon citric acid, a key component of the cycle. Pyruvate and oxaloacetic acid both come from the breakdown of glucose. If glucose supply is decreased, or if oxaloacetic acid is not available, the acetyl CoA is broken down to ketone bodies; these include acetoacetic acid, beta hydroxybutyric acid and acetone. (see Figure 2).

Ketones and Keto acids

Ketone bodies are molecules produced by the liver and used when the body lacks glucose. [38] Ketone bodies can be utilized as fuel in the heart, brain and muscle, but not the liver. because the liver lacks the enzyme thiophorase (β-ketoacyl-CoA transferase). After strict fasting for 3 days, the brain gets 25% of its energy from ketone bodies [8]. After about 24 days, ketone bodies become the major fuel of the brain, making up to two-thirds of brain fuel consumption [9]. With normal renal function, ketones can accumulate in the body under fasting conditions, or with low carbohydrate intake as in the KD. This is not the same process as that seen with inadequate insulin production in uncontrolled type 1 diabetes mellitus, where excessive production of ketones is associated with diabetic ketoacidosis (DKA), and the treatment is insulin [10].

Obesity and T2DM

As of 2018, more than 42% adults in the US are obese according to CDC [11] (Figure 3). Obesity is a factor for many diseases, but most notably a precedent for T2DM. Excess calories accumulate as adipose tissue, leading to elevated levels of fatty acids; hormones; and proinflammatory cytokines., Release of proinflammatory cytokines can lead to chronic inflammation. Studies suggest that abdominal visceral fat induces production of proinflammatory cytokines, making the body desensitized to insulin action, causing insulin resistance, the root of T2DM [12].

Obesity, Type 2 Diabetes, and the Keto Diet

Diet and exercise have been shown to reverse some of the metabolic effects in DM as well as increase weight loss in both obesity and DM. Patients on a KD with a caloric restriction have been shown to lose weight effectively, decrease glycated hemoglobin (HgA1c), and improve their lipid profile [13]. Caloric deficits are often important for weight loss with these diets, as fats contain nine calories per gram. Thus, having a fat-based diet while keeping the same caloric intake may not further weight loss. KD helps decrease HgA1c, as formation of ketone bodies results from less glucose metabolism.

For example, in the 2005 study by Yancy, et al [14] seeking to identify the relationship between KD and T2D, twenty-eight overweight participants between 35-75 years with normal renal function underwent a keto diet for four

months. Over the course of the study, the average HgA1c decreased from 7.5 ± 1.4%to 6.3 ± 1.0% (normal <6.0%). Seven of the 21 participants became medication independent, while only 4 of the 21 participants had no improvement.

Chronic Kidney Disease

Young adult humans have a glomerular filtration rate of about 140 mL/min. Over a lifetime, this decreases on average at 1 mL/min/year. GFR is used as the main indicator for the progression of renal damage. Chronic kidney disease (CKD) is defined as a condition which cannot be reversed, in general due to a combination of glomerular sclerosis, tubular atrophy and interstitial fibrosis. In Western countries, diabetes, high blood pressure, and obesity are the main contributors to the development of ESRD [16].An estimated GFR (eGFR) of > 90 with >30 mg/dL of albumin indicates stage 1 CKD, i.e., almost normal kidney function with some kidney damage; eGFR of 89-60 (stage 2 CKD) represents minor loss of kidney function; GFR from 59-30 (Stage 3 CKD) indicates moderate loss of kidney function; eGFR of 29-15 (Stage 4) indicates severe loss of kidney function, and a eGFR of <15 (Stage 5) represents end stage renal disease (ESRD) [15] and requires dialysis therapy to keep one alive.

Measures of Renal Function

There are two main indicators that are used to assess potential damage to the kidneys: 1) an estimate of renal perfusion, such as GFR, and 2) urine protein excretion. To measure GFR, one needs a marker whose excretion is constant over time; one such marker is creatinine. One can measure creatinine in the serum, in a 24-hour urine collection, or one can use a formula that estimates GFR from the serum creatinine, age, gender and race. There are several formulas in use, all of which were derived empirically, that is, by matching the best regression equation to a very large dataset. In the urine, one can measure albumin excretion, or total protein excretion, which includes albumin, alpha-, beta-, and gamma-globulins. Normal glomerular basement membranes (GBM) do not allow these proteins to pass through them.

Obesity and Kidney Disease

Obesity is common in CKD patients. Obesity can lead to atherosclerotic damage to the blood vessels as well as damage to the GBMs. Obesity itself causes increasing amounts of protein to be filtered through the membranes, damaging the filtration system in kidneys, leading to focal and segmental glomerular sclerosis (FSGS). As with other protein-losing syndromes, FSGS can cause diffuse edema from low serum albumin as well as elevations in both cholesterol and triglycerides [17]. Higher body mass indices (BMIs) are also associated with nephrolithiasis, and both elevated blood lipid levels and renal stones are associated with progressive loss of renal function [18].

Diabetes and Kidney Disease

Diabetes is common in CKD patients, especially T2DM in older people. Twenty to thirty percent of diabetics will develop kidney disease, a condition known as diabetic nephropathy [19]. Elevated blood sugar levels lead to damage in many organ systems, due to inflammation, to elevated levels of advanced glycation end products, to diffuse vascular damage and in the kidney, to hyperfiltration that leads initially to increases in kidney size, and then over the next 5-10 years leads to sufficient damage to the GBM, and to progressive renal functional decline.

Keto Diet and Kidneys

If KD can improve glucose control and help with weight loss, they could potentially help slow the damage to the kidneys seen with DM and obesity. Figure 4 demonstrates the methodology for our literature review. Table 1 is a composite review of the few articles found on the use of low carbohydrate/KD in which renal function was also assessed.

Methodologies

Literature searches were retrieved from Pubmed, Google, and ScienceDirect. In addition, we reviewed all of the references in the studies we found for further potential study data. Search terms included diabetes, diabetes mellitus, geriatrics, weight loss, low carbohydrate diet, ketogenic diet, renal failure, chronic kidney disease, obesity, high protein diet, Atkins diet.

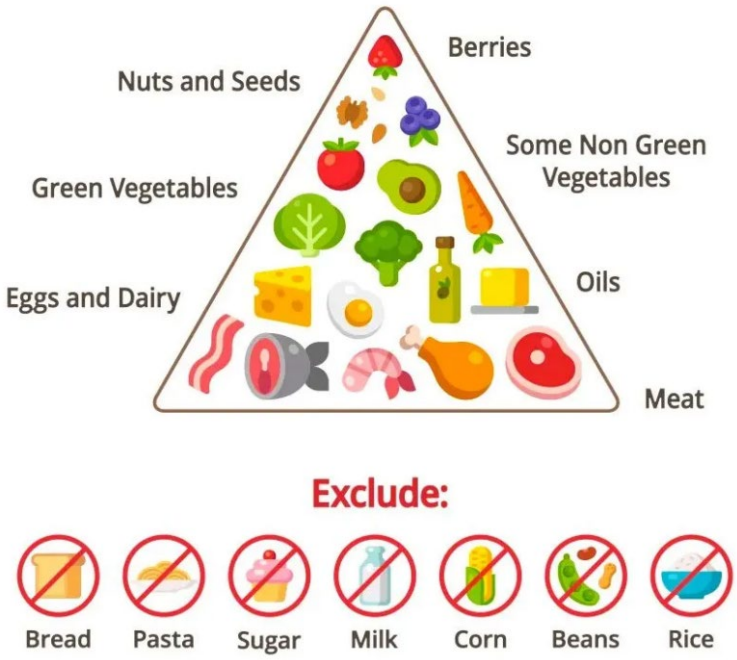

Figure 1. Keto/Low Carb Diet Pyramid

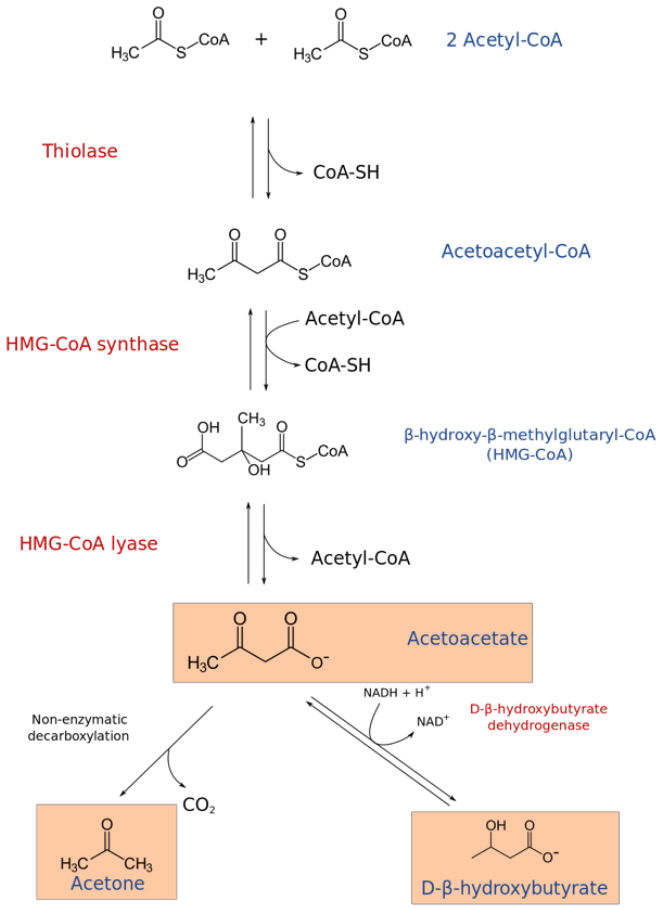

Figure 2. The Biochemistry of Ketone Bodies

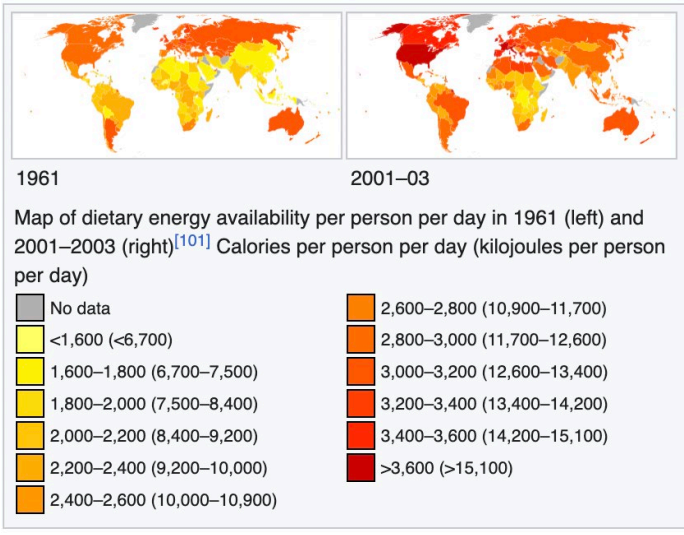

Figure 3. Increasing World-wide Incidence of Diabetes and Obesity

Table 1. Table of Research Papers

Author (reference)	Year Published	Length of Study	Number of Participants	Random (Y/N)	Definition and level GFR of participants	Results
Friedman et al. (31)	2012	2-years conducted between 2003 and 2007.	307 obese adults without serious medical illnesses	N	CrCl, mean 134±38 mL/min	Compared with the low-fat diet, LC/HP consumption was associated with: • reductions in serum creatinine (relative difference, 24.2%, p<0.01) and cystatin C (28.4%, p<0.01) at 3 months • increases in creatinine clearance at 3 (16 ml/min, p<0.01) and 12 (21 ml/min, p<0.01) months; serum urea at 3 (13%), 12 (14%), and 24 (9%) months (all p<0.01); and • 24-hour urinary volume at 12 (438 ml) and 24 (268 ml) months, (both p<0.05) Urinary calcium excretion increased at 3 (36.1%) and 12 (35.7%) months (both p<0.01), with no changes in bone density or new kidney stones. • No significant change in albuminuria in either group.
Kostogrys et al. (20)	2015	2 months	18 rats randomized to control, WD, LC/HP diets	Y	normal at baseline	Compared to the control and WC diets: • LC/HP rats ate less and had lowest weight (p<0.05) • LC/HP rats had greater kidney weight (p<0.05) and a trend towards higher serum Cr Serum homocysteine concentration decreased in both rats fed WD and LC/HP diets (p<0.05 for both).
Tay et al. (29)	2015	1 year, weight loss diet	115 adults with T2DM	Y	eGFR* 94±12 mL/min/1.73 m^2	a hypocaloric LC diet and an energy-matched traditional HC diet had similar effects on markers of renal function in

Author (reference)	Year Published	Length of Study	Number of Participants	Random (Y/N)	Definition and level GFR of participants	Results
		combined with exercise One hour 3x a week			BMI 34.6±4.3 kg/m^2, HbA 1c:7.3±1.1% ,	people with T2DM without DKD consumption of an LC weight loss diet does not adversely affect renal function in such populations. • Longer-term follow-up studies are required to determine
Farhadnejad et al. (30)	2018	Approx 6 years	cohort study 1797 Iranian participants, aged ≥20 yrs, LC/HP diet calculated as tertiles	N	No renal disease: eGFR**>60 mL/minute/1.73m^2 Renal disease: eGFR**< 60 mL/minute/1.73m^2	Subjects with highest LC/HP diet score at baseline were smore likely to be female, younger, had lower eGFR, SBP, DBP, and triglyceride levels compared with the lowest diet score (p<0.05) After adjusting for age, sex, smoking status, physical activity, total calorie intake, body mass index, diabetes, hypertension, and baseline eGFR: o participants in the highest tertile of LC/HP diet had greater risk of incident CKD (odds ratio: 1.48; 95% confidence interval: 1.03-2.15), in comparison to those in the lowest one (P for trend 0.027).
Tirosh et al. (32)	2013	2 years	318 adults; 86% men; BMI, 31 kg/m^2	Y	Average baseline eGFR§: 70.5mL/min/1.73m^2 Breakdown: 31% CKD 3 69% CKD 1/2	• Significant (p<0.05 within groups) improvements in eGFR were achieved in low carbohydrate (+5.3% [95% CI 2.1–8.5]), Mediterranean (+5.2% [3.0–7.4]), and low- fat diets (+4.0% [0.9–7.1]) with similar magnitude (p>0.05) across diet groups. eGFR increased in participants with (+6.7%) or without

Author (reference)	Year Published	Length of Study	Number of Participants	Random (Y/N)	Definition and level GFR of participants	Results
						(+4.5%) T2DM, and those with lower baseline eGFR (<60 mL/min/1.73 m2 (+7.1%) vs higher baseline eGFR (>60 mL/min/1.73 m2 (+3.7%). • In a multivariable model adjusted for age, sex, diet group, T2DM, use of ACE inhibitors, 2-year weight loss, and change in protein intake, only a decrease in fasting insulin (β = -0.211; p = 0.004) and systolic BP (β = -0.25; p=0.001) independently associated with increased eGFR. • The urine microalbumin-to-creatinine ratio improved similarly across the diets, particularly among participants with sex-adjusted microalbuminuria at baseline, with a mean change of -24.8 (p<0.05).
Friedman et al. (34)	2013	12 weeks	6 obese individuals with diabetic nephropathy	N	• eGFR[$]: 40 ml/min/1.73m^2 urine albumin excretion <30 mg/d	With median weight loss of 14 kg (p<0.05), median improvements were observed in markers of: • glomerular filtration, eGFR 21->22, p<0.05 - sCr 3.54->3.13, p<0.05 - cysC 2.79->2.46, p<0.05 • diabetes status, - fasting glucose 116->131, p<0.05 - fasting insulin, 26.9->10.4, p<0.05 • QOL measures (physical function, general health), p=0.04

Author (reference)	Year Published	Length of Study	Number of Participants	Random (Y/N)	Definition and level GFR of participants	Results
						Other factors of borderline significance: • Albuminuria (mg/d) 2124->1366, p=0.08 • Lean body mass (%) 57.6->64, p=0.11
Bruci et al. (33)	January 2020	3 months	92 overweight or obese adults	N	• eGFR*: 38 had mild kidney failure and • 54 (control) had no renal conditions	Safety markers including kidney function were unchanged throughout the study and not differentially affected by intervention in the two groups, with efficacy outcomes confirming those of previous studies and—most likely—not depending on kidney function. VLCD is a safe and effective dietary intervention in patients with obesity affected by mild CKD when conducted under medical supervision in a real-life setting, Caution should be taken in screening for a lack of micronutrients and for altered bone metabolism, as well as in accurately monitoring protein consumption at all times.
Obayu et al. (38)	2016	6-24 months	1687 adults 861 LCD 826 control	Y	eGFR** >60 ml/min/1.73m3 at baseline	The mean change in eGFR: • LCD group, −4·7 to 24·0 ml/min/1·73m2 • control diet, −4·1 to 10·8 ml/min per 1·73m2. The mean change in eGFR in the LCD vs. control diet, +0·13 ml/min/1·73m2; 95% CI 0·00, 0·26, p=0.02

Author (reference)	Year Published	Length of Study	Number of Participants	Random (Y/N)	Definition and level GFR of participants	Results
Suyoto et al. (36)	2018	5wk -12 months	942 adults 500 LCD 442 control	Y	eGFR* >70 ml/min/1.73 m2 CrCl >90 ml/min	No significant changes in: • serum creatinine • eGFR • urinary albumin excretion • creatinine clearance

Abbreviations used:

BP-blood pressure
CKD – chronic kidney disease
CrCl – 24-hour urine creatinine clearance
DKD – diabetic kidney disease
eGFR – estimated glomerular filtration rate: * CKD-EPI; ** NKF, $ MDRD;
HC – high carbohydrate
HP – high protein
LC(D) – low carbohydrate (diet)
T2DM – type 2 diabetes mellitus
VLCD – very low carbohydrate diet
WD – Western Diet

Discussion

Of the nine research papers with sufficient data to analyze, four [20, 27, 29,36] concluded that the diet does not cause significant renal changes, one conveyed increased risk of CKD [30], and four [31-34] demonstrated improvements, including decreases in serum creatinine, urinary albumin, weight loss, and increase in eGFR. Participants in three studies had preexisting T2DM, four studied recruited obese (BMI > 30) patients as subjects, and some studies subjects were both obese and diabetic. Kostogrys, et al. [20] studied observations of renal and other organ function of rats, whereas eight papers observed changes in renal function in human participants. In human studies, the number or participants in studies ranged from 18 to 1797. Five studies included participants with normal renal function, of which two included participants both with and without renal diseases, and four studied only participants with lower eGFRs. The participants across the nine studies varied from 20 to 75 years of age. Four of the nine studies were randomized and five were not. The duration of studies ranged from 3 months to 6 years.

While KD may aid weight loss and lower blood glucose levels, KD is not suitable for those with a GFR of less than 30 mL/min, who already have difficulties excreting metabolic acids, or those who have kidney stones that form in high acid urines regardless of GFR [21]. KD is also an unsafe option for those with pancreas, liver, and thyroid conditions [37]. Due to severely restricted carbohydrate intake, diets like KD may cause low blood pressures, kidney stones, and nutrient deficiencies [21].

Metabolic acidosis, defined as a serum bicarbonate < 22 mmol/L, is a common complication of advanced CKD [22]. Metabolic acidosis in patients can accelerate the progression of kidney disease. Among other adverse effects of acidosis in CKD are bone breakdown, muscle wasting, and inflammation [23].

The EPIC study [24] analyzed the relationship between dietary acid load and risk of T2DM. 66,485 women participated and were followed for up to14 years. Two scores were utilized to examine results: PRAL (Potential Renal Acid Load) and NEAP (net endogenous acid production). Positive PRAL and higher NEAP scores represent potential acid formation whereas a negative or low score represents potential base formation (base here, clinically means the opposite of acid). Over the 14 years, 1,372 cases of T2DM were discovered. For the highest PRAL quartile and NEAP score, greater acid forming potential leads to notable increase in risk of T2DM compared to the first quartile and low NEAP score (with base forming potential).

High acid diets may also promote the production of kidney stones that form in high acid urine (calcium oxalate and uric acid stones) [25]. This is particularly true in diabetics, who have higher net acid excretion and are predisposed to uric acid stones [26]. Renal stone formation is associated with more rapid progression of CKD.

Conclusions

We separated studies into two groups based on outcome: group 1 saw no improvements in eGFR, and group 2 saw improvements in eGFR. Group 2 consisted of studies ranging from 5 months to 2 years and focused on diabetic participants with researchers seeing improvements in eGFR and weight loss. Group 1 studies ranged from 6 months to 6 years, utilizing participants both diabetic and nondiabetic, thus disproving study length or initial health as confounding variables.

Limitations

Some limitations in this analysis include differing study durations, how low carbohydrate diets were defined, study endpoints, as well as the potential sample bias inherent in all clinical trials where subjects must agree to participate. The longest study in this table was only 6 years, while renal disease typically progresses over decades; longer study lengths might help determine the long term potential of KD.

Another factor was what kind of low carbohydrate diets were used. In Kostoryos's study on rats [20], LCHP diet consisted of 21% fat and 52.4% protein. In the 6-year Iranian study food frequency questionnaires were used for individual's food intake. Comparisons were noted through calculating their LCHP diet scores by dividing participants into quintiles of carbohydrate with those receiving highest points indicating best adherence to LCHP diet.[31] In other studies, participants were given the food, ate around 800 kcals a day, and were limited to 20-60 grams of carbohydrate intake a day.

An additional factor was the varying methodologies used to calculate renal function. The eGFR using the MDRD equation was calculated empirically from populations with greater degrees of renal dysfunction than the CKD-epi equation. Different equations will produce higher or lower GFR results, depending on which equation is used [27].

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