

The Ketogenic Diet and Dermatology: A Primer on Current Literature

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PRACTICE POINTS

- The ketogenic diet has been employed since antiquity for varying ailments and has a good safety and efficacy profile if administered by a knowledgeable provider.
- New literature is showing promising potential roles for the ketogenic diet as an adjunctive therapy, particularly in the realm of inflammatory disorders, metabolic diseases, and malignancy.
- The dermatologist should be aware of this diet because it is gaining popularity with physicians and patients alike. Dermatologists also should know how it can potentially benefit a number of patients with dermatologic diseases based on small clinical trials, population studies, and basic science research.

The ketogenic diet has been therapeutically employed from antiquity and is still utilized today in many disease states. With the boom of the complementary and alternative health movement over the last 2 decades, the lay population has grown more interested in disease prevention and treatment via dietary and lifestyle changes and enhancing health and human performance. The ketogenic diet, whether exclusive or intermittent, has been purported by health care professionals and laypersons alike to meet these demands. In this review article, we look to the current literature for proven and possible mechanisms by which ketones and a ketogenic diet may be utilized in the field of dermatology and direct our readers to pursue further research for this promising potential treatment option.

Cutis. 2020;105:40-43.

The ketogenic diet has been therapeutically employed by physicians since the times of Hippocrates, primarily for its effect on the nervous system.¹ The neurologic literature is inundated with the uses of this medicinal diet for applications in the treatment of epilepsy, neurodegenerative disease, malignancy, and enzyme deficiencies, among others.² In recent years, physicians and scientists have moved to study the application of a ketogenic diet in the realms of cardiovascular disease,³ autoimmune disease,⁴ management of diabetes mellitus (DM) and obesity,^{3,5} and enhancement of sports and combat performance,⁶ all with promising results. Increased interest in alternative therapies among the lay population and the efficacy purported by many adherents has spurred intrigue by health care professionals. Over the last decade, there has been a boom in so-called holistic approaches to health; included are the Paleo Diet, Primal Blueprint Diet, Bulletproof Diet, and the ketogenic/low-carbohydrate, high-fat diet. The benefits of ketones in these diets—through intermittent fasting or cyclical ketosis—for cognitive enhancement, overall well-being, amelioration of chronic disease states, and increased health span have been promulgated to the lay population. But to date, there is a large gap in the literature on the applications of ketones as well as the ketogenic diet in dermatology and skin health and disease.

The aim of this article is not to summarize the uses of ketones and the ketogenic diet in dermatologic applications (because, unfortunately, those studies have not been undertaken) but to provide evidence from all available

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The authors report no conflict of interest.

The views expressed in this article are that of the authors and do not represent the Department of Defense, the Department of the Army, or Department of the Navy.

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literature to support the need for targeted research and to encourage dermatologists to investigate ketones and their role in treating skin disease, primarily in an adjunctive manner. In doing so, a clearly medicinal diet may gain a foothold in the disease-treatment repertoire and among health-promoting agents of the dermatologist. Given the amount of capital being spent on health care, there is an ever-increasing need for low-cost, safe, and tolerable treatments that can be used for multiple disease processes and to promote health. We believe the ketogenic diet is such an adjunctive therapeutic option, as it has clearly been proven to be tolerable, safe, and efficacious for many people over the last millennia.

We conducted a PubMed search of articles indexed for MEDLINE using varying combinations of the terms *ketones*, *ketogenic*, *skin*, *inflammation*, *metabolic*, *oxidation*, *dermatology*, and *dermatologic* and found 12 articles. Herein, we summarize the relevant articles and the works cited by those articles.

Adverse Effects of the Ketogenic Diet

As with all medical therapies, the ketogenic diet is not without risk of adverse effects, which should be communicated at the outset of this article and with patients in the clinic. The only known absolute contraindications to a ketogenic diet are porphyria and pyruvate carboxylase deficiency secondary to underlying metabolic derangements.⁷ Certain metabolic cytopathies and carnitine deficiency are relative contraindications, and patients with these conditions should be cautiously placed on this diet and closely monitored. Dehydration, acidosis, lethargy, hypoglycemia, dyslipidemia, electrolyte imbalances, prurigo pigmentosa, and gastrointestinal distress may be an acute issue, but these effects are transient and can be managed. Chronic adverse effects are nephrolithiasis (there are recommended screening procedures for those at risk and prophylactic therapies, which is beyond the scope of this article) and weight loss.⁷

NLRP3 Inflammasome Suppression

Youm et al⁸ reported their findings in *Nature Medicine* that β -hydroxybutyrate, a ketone body that naturally circulates in the human body, specifically suppresses activity of the NLRP3 inflammasome. The NLRP3 inflammasome serves as the activating platform for IL-1 β .⁸ Aberrant and elevated IL-1 β levels cause or are associated with a number of dermatologic diseases—namely, the autoinflammatory syndromes (familial cold autoinflammatory syndrome, Muckle-Wells syndrome, neonatal-onset multisystemic disease/chronic infantile neurological cutaneous articular syndrome), hyperimmunoglobulinemia D with periodic fever syndrome, tumor necrosis factor-receptor associated periodic syndrome, juvenile idiopathic arthritis, relapsing polychondritis, Schnitzler syndrome, Sweet syndrome, Behçet disease, gout, sunburn and contact hypersensitivity, hidradenitis

suppurativa, and metastatic melanoma.⁷ Clearly, the ketogenic diet may be employed in a therapeutic manner (though to what degree, we need further study) for these dermatologic conditions based on the interaction with the NLRP3 inflammasome and IL-1 β .

Acne

A link between acne and diet has long been suspected, but a lack of well-controlled studies has caused only speculation to remain. Recent literature suggests that the effects of insulin may be a notable driver of acne through effects on sex hormones and subsequent effects on sebum production and inflammation. Cordain et al⁹ discuss the mechanism by which insulin can worsen acne in a valuable article, which Paoli et al¹⁰ later corroborated. Essentially, insulin propagates acne by 2 known mechanisms. First, an increase in serum insulin causes a rise in insulinlike growth factor 1 levels and a decrease in insulinlike growth factor binding protein 3 levels, which directly influences keratinocyte proliferation and reduces retinoic acid receptor/retinoid X receptor activity in the skin, causing hyperkeratinization and concomitant abnormal desquamation of the follicular epithelium.^{9,10} Second, this increase in insulinlike growth factor 1 and insulin causes a decrease in sex hormone-binding globulin and leads to increased androgen production and circulation in the skin, which causes an increase in sebum production. These factors combined with skin that is colonized with *Cutibacterium acnes* lead to an inflammatory response and the disease known as acne vulgaris.^{9,10} A ketogenic diet could help ameliorate acne because it results in very little insulin secretion, unlike the typical Western diet, which causes frequent large spikes in insulin levels. Furthermore, the anti-inflammatory effects of ketones would benefit the inflammatory nature of this disease.

DM and Diabetic Skin Disease

Diabetes mellitus carries with it the risk for skin diseases specific to the diabetic disease process, such as increased risk for bacterial and fungal infections, venous stasis, pruritus (secondary to poor circulation), acanthosis nigricans, diabetic dermopathy, necrobiosis lipoidica diabetorum, digital sclerosis, and bullosis diabetorum.¹¹ It is well established that better control of DM results in better disease state outcomes.¹² The ketogenic diet has shown itself to be a formidable and successful treatment in the diseases of carbohydrate intolerance (eg, metabolic syndrome, insulin resistance, type 2 DM) because of several known mechanisms, including less glucose entering the body and thus less fat deposition, end-product glycation, and free-radical production (discussed below); enhanced fat loss and metabolic efficiency; increased insulin sensitivity; and decreased inflammation.¹³ Lowering a patient's insulin resistance through a ketogenic diet may help prevent or treat diabetic skin disease.

Dermatologic Malignancy

A ketogenic diet has been of interest in oncology research as an adjunctive therapy for several reasons: anti-inflammatory effects, antioxidation effects, possible effects on mammalian target of rapamycin (mTOR) regulation,⁷ and exploitation of the Warburg effect.¹⁴ One article discusses how mTOR, a cell-cycle regulator of particular importance in cancer biology, can be influenced by ketones both directly and indirectly through modulating the inflammatory response.⁷ It has been shown that suppressing mTOR activity limits and slows tumor growth and spread. Ketones also may prove to be a unique method of metabolically exploiting cancer physiology. The Warburg effect, which earned Otto Warburg the Nobel Prize in Physiology or Medicine in 1931, is the observation that cancerous cells produce adenosine triphosphate solely through aerobic glycolysis followed by lactic acid fermentation.¹⁴ This phenomenon is the basis of the positron emission tomography scan. There are several small studies of the effects of ketogenic diets on malignancy, and although none of these studies are of substantial size or control, they show that a ketogenic diet can halt or even reverse tumor growth.¹⁵ The hypothesis is that because cancer cells cannot metabolize ketones (but normal cells can), the Warburg effect can be taken advantage of through a ketogenic diet to aid in the treatment of malignant disease.¹⁴ If further studies find it a formidable treatment, it most certainly would be helpful for the dermatologist involved in the treatment of cutaneous cancers.

Oxidative Stress

Oxidative stress, a state brought about when reactive oxygen species (ROS) production exceeds the antioxidant capacity of the cell and causes damage, is known to be a central part of certain skin diseases (eg, acne, psoriasis, cutaneous malignancy, varicose ulcers, cutaneous allergic reactions, and drug-induced skin photosensitivity).⁷ There are 2 proven mechanisms by which a ketogenic diet can augment the body's innate antioxidation capacity. First, ketones activate a potent antioxidant upregulating protein known as NRF2, which is bound in cytosol and remains inactive until activated by certain stimuli (ie, ketones).¹⁶ Migration to the nucleus causes transcriptional changes in DNA to upregulate, via a myriad of pathways, antioxidant production in the cell; most notably, it results in increased glutathione levels.¹⁷ NRF2 also targets several genes involved in chronic inflammatory skin diseases that cause an increase in the antioxidant capacity.¹⁸ As an aside, several foods encouraged on a ketogenic diet also activate NRF2 independently of ketones (eg, coffee, broccoli).¹⁹ Second, a ketogenic diet results in fewer produced ROS and an increase in the nicotinamide adenine dinucleotide ratio produced by the mitochondria; in short, it is a more efficient way of producing cellular energy while enhancing mitochondrial function. When fewer ROS are produced, there is less

oxidative stress that needs to be attended to by the cell and less cellular damage. Feichtinger et al¹⁹ point out that mitochondrial inefficiency and dysfunction often are overlooked components in several skin diseases, and based on the studies discussed above, these diseases may be aided with a ketogenic diet.

Patient Applications

Clearly, a ketogenic diet is therapeutic, and there are many promising potential roles it may play in the treatment of a wide variety of health and disease states through hormonal normalization, antioxidant effects, anti-inflammatory effects, and improvement of metabolic risk factors. However, there are vast limitations to what is known about the ketogenic diet and how it might be employed, particularly by the dermatologist. First, the ketogenic diet lacks a firm definition. Although processed inflammatory vegetable oils and meats are low in carbohydrates and high in fat by definition, it is impossible to argue that they are healthy options for consumption and disease prevention and treatment. Second, nutrigenomics dictates that there must be an individual role in how the diet is employed (eg, patients who are lactose intolerant will need to stay away from dairy). Third, there are no clear proven clinical results from the ketogenic diet in the realm of dermatology. Fourth, as with everything, there are potential detrimental side effects of the ketogenic diet that must be considered for patients (though there are established screening procedures and prophylactic therapies that are beyond the scope of this article). Further, other diets have shown benefit for many other disease states and health promotion purposes (eg, the Mediterranean diet).²⁰ We do not know yet if the avoidance of certain dietary factors such as processed carbohydrates and fats are more beneficial than adopting a state of ketosis at this time, and therefore we are not claiming superiority of one dietary approach over others that are proven to promote health.

Because there are no large-scale studies of the ketogenic diet, there is no verified standardization of initiating and monitoring it, though certain academic centers do have published methods of doing so.²¹ There are ample anecdotal methods of initiating, maintaining, and monitoring the ketogenic diet.²² In short, drastic restriction of carbohydrate intake and increased fat consumption are the staples of initiating the diet. Medium-chain triglyceride oil supplementation, coffee consumption, intermittent fasting, and low-level aerobic activity also are thought to aid in transition to a ketogenic state. As a result, a dermatologist may recommend that patients interested in this option begin by focusing on fat, fiber, and protein consumption while greatly reducing the amount of carbohydrates in the diet. Morning walks or more intense workouts for fitter patients should be encouraged. Consumption of serum ketone-enhancing foods (eg, coffee, medium-chain triglyceride oil, coconut products) also should be encouraged. A popular beverage

known as Bulletproof coffee also may be of interest.²³ A blood ketone meter can be used for biofeedback to reinforce these behaviors by aiming for proper β -hydroxybutyrate levels. Numerous companies and websites exist for supporting those patients wishing to pursue a ketogenic state, some hosted by physicians/researchers with others hosted by laypeople with an interest in the topic; discretion should be used as to the clinical and scientific accuracy of these sites. The dermatologist in particular can follow these patients and assess for changes in severity of skin disease, subjective well-being, need for medications and adjunctive therapies, and status of comorbid conditions.

For more information on the ketogenic diet, consider reading the works of the following physicians and researchers who all have been involved with or are currently conducting research in the medical use of ketones and ketogenic diets: David Perlmutter, MD; Thomas Seyfried, PhD; Dominic D'Agostino, PhD; Terry Wahls, MD; Jeff Volek, PhD; and Peter Attia, MD.

Conclusion

Based on the available data, there is potential for use of the ketogenic diet in an adjunctive manner for dermatologic applications, and studies should be undertaken to establish the efficacy or inefficacy of this diet as a preventive measure or treatment of skin disease. With the large push for complementary and alternative therapies over the last decade, particularly for skin disease, the time for research on the ketogenic diet is ripe. Over the coming years, it is our hope that larger clinical, randomized, controlled trials will be conducted for the benefit of dermatology patients worldwide.

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