Ketones, the ketogenic diet, and the skin: a review of where we are and where we should go

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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 two decades, an interest in the lay population has grown in regard to dietary and lifestyle means of preventing and treating disease and enhancing health and human performance. The ketogenic diet, whether exclusive or intermittent, has been purported by health professional and lay person 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 dermatology and direct our readers to pursue further research for this promising potential treatment option.

Key Words: *Ketones; Ketogenic; Diet; Inflammation; Skin; Dermatology*

The ketogenic diet has been therapeutically employed by physicians since the times of Hippocrates primarily for its effect on the nervous system (1); indeed, the neurological literature is becoming 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 and obesity (3,5), and enhancement of sports and combat performance (6), all with promising results. Perhaps spurring the intrigue by healthcare professionals is the large growth of interest in alternative therapies that the lay population has expressed, and the efficacy purported by many adherents. The last decade has seen a boom in the so-called holistic approaches to health; included are the Paleo diet, Crossfit community, Primal and Ancestral Diets, Bulletproof diet, and the Keto/Low-Carb High-Fat diet. While these communities, with the exception of the ketogenic/low-carb high-fat diet, may not promulgate an exclusive ketogenic diet, they do assert the benefits of ketones in one way or another, be it through intermittent fasting, cyclical ketosis, etc., for cognitive enhancement, overall well-being, amelioration of chronic disease states, and increase in length of health-span. But to date, there is a large gap in the literature when it comes to the applications of ketones and the ketogenic diet in dermatology and skin health and disease. The aim of this paper 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 literature to support the need for targeted research and to pique the interest of our colleagues and peers so that those studies may gain support and come underway. In so doing, a clearly medicinal diet may gain a foothold in the disease-treatment repertoire and health-promoting agents of the dermatologist. The health-care horizon is always being investigated for a low-cost, safe, and tolerable treatment which can be used for multiple disease processes and to promote health. The aim of this paper is to argue that the ketogenic diet is such a therapeutic option as it has clearly been proven to be tolerable, safe, and efficacious for many over the past millennia.

METHODS AND MATERIALS

A PubMed search was done with the search criteria of "ketones," "ketogenic," "skin," "dermatology," and "dermatologic." Below are the summaries of the relevant papers which turned up in our search.

Nlrp3 inflammasome suppression

Youm et. al reported their findings in Nature Medicine that beta-hydroxy butyrate, a ketone body which naturally circulates in the human body, specifically suppresses activity of the NLRP3 inflammasome (7). NLRP3 inflammasome serves as the activating platform for the interleukin IL-1B (7). Abberant and elevated IL-1B 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 Neurologic Cutaneous Articular Syndrome), Hyper IgD with periodic fever syndrome, TNF-receptor associated periodic syndrome, Juvenile Idopathic Arthritis, Relapsing Polychondritis, Schnitzler's Syndrome, Sweet Syndrome, Behcet's Disease, gout, sunburn and contact hypersensitivity, hidradenitis suppurativa, and metastatic melanoma (8). 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 NRLP3 inflammasome and IL-1B.

Acne

A link between acne and diet has long been suspected, but lack of well-controlled studies has caused only speculation to remain. Recent literature suggests that the effects of insulin may be a significant driver of acne through effects on sex hormones and subsequent effects on sebum production and inflammation. Cordain et al. (9) discuss this in an extremely valuable paper, which was later corroborated by Paoli et al. (10). Essentially, insulin propagates acne by two known mechanisms. First, an increase in serum insulin causes a rise in Insulin-like Growth Factor-1 (IGF-1) levels and decrease in Insulin-like Growth Factor Binding Protein-3 (IGFBP-3) levels. This 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 IGF-1 and Insulin causes a decrease in Sex Hormone Binding Globulin (SHBG) and leads to increased androgen production and circulation which, in the skin, causes an increase in sebum production (9,10). These together with skin that is colonized with P. acnes leads to an inflammatory response and the disease known as Acne Vulgaris (9,10). A ketogenic diet could help acne in that it results in very little insulin secretion, unlike the typical Western diet which causes frequent large spikes in insulin levels. Further, as discussed previously, the anti-inflammatory effects of ketones would benefit the inflammatory nature of this disease.

Diabetes and diabetic skin disease

Diabetes carries with it the risk for skin diseases specific to the diabetic disease process such as increased risk of bacterial and fungal infections, venous stasis, pruritus (secondary to poor circulation), acanthosis nigricans, diabetic dermopathy, necrobiosis lipoidica diabeticorum, digital sclerosis and bullosis diabeticorum (11). It is well established that better control of diabetes results in better disease state outcomes (12). The ketogenic diet has

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shown itself to be a formidable and successful treatment in the diseases of carbohydrate intolerance (metabolic syndrome, insulin resistance and type 2 diabetes) due to several known mechanisms: 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, an increase in insulin sensitivity, and decreased inflammation (13). Lowering the resistance to insulin in a patient 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: the anti-inflammatory effects (discussed previously), the anti-oxidation effects (discussed below), possible effects on Mammalian Target of Rapamycin (mTOR) regulation (8) and exploitation of the Warburg effect (14). Fomin et al. (8) present in another paper how mTOR, a cell-cycle regulator and important in cancer biology, can be influenced by ketones both directly and indirectly through modulating the inflammatory response. It has been shown that suppressing mTOR activity limits and slows tumor growth and spread (8). As well, ketones may prove to be a unique method of metabolically exploiting cancer physiology. The Warburg Effect, which earned Otto Warburg the Nobel Prize, is the observation that cancer cells produce ATP solely through aerobic glycolysis followed by lactic acid fermentation (14). This phenomenon is the basis of the PET scan. There are several small studies which have employed ketogenic diets to combat malignancy, though nothing of substantial size or control, which show that a ketogenic diet can halt or even reverse tumor growth (15). The hypothesis is that since cancer cells cannot metabolize ketones but normal cells can, the Warburg Effect can be taken advantage of through the means of a ketogenic diet in order to aid in the treatment of malignant disease (14). If further studies find this a formidable treatment, this would most certainly 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 cause damage, is known to be a central part of certain skin diseases; for example, acne, psoriasis, cutaneous malignancy, varicose ulcers, cutaneous allergic reactions, and drug-induced skin photosensitivity (8). There are two proven mechanisms by which a ketogenic diet can augment the body's innate antioxidation capacity. First, ketones activate a potent antioxidant up-regulating protein known as Nrf2. Nrf2 is bound in cytosol and remains inactive until activated by certain stimuli (i.e., ketones) (16). Migration to the nucleus causes transcriptional changes in DNA to up-regulate, via a myriad of pathways, antioxidant production in the cell; most notably, it results in increased glutathione levels (17). Nrf2 also targets several genes that cause an increase in the antioxidant capacity that are involved in chronic inflammatory skin diseases (8). As an aside, several foods encouraged on a ketogenic diet also activate Nrf2, independently of ketones (i.e., coffee, broccoli) (18). Second, a ketogenic diet results in fewer produced ROS and an increase in the NAD+/NADH ratio produced by the mitochondria (in short, it is a more efficient way of producing cellular energy while enhancing mitochondrial function). Fewer ROS produced leads to less oxidative stress which needs to be attended to by the cell and leads to less cellular damage. Indeed, Feichtinger et al. (19) point out that mitochondrial inefficiency and dysfunction is an often overlooked component in several skin diseases, and based on the studies discussed above; these diseases may be aided with a ketogenic diet (19-22).

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