To B or Not to B? The B Vitamins and Their Influence on the Body's Largest Organ

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Within the human diet, there are thirteen essential vitamins (Calderón‐Ospina & Nava‐Mesa, 2019). Out of the thirteen vitamins, eight are categorized as B vitamins. The B vitamins are essential because they must be acquired through the diet and cannot be synthesized by the body. These vitamins help the body maintain health, homeostasis, and function. The B vitamins include thiamine (B1), riboflavin (B2), niacin (B3), pantothenic acid (B5), pyridoxine (B6), biotin (B7), folate (B9), and cobalamin (B12). The B vitamins are a group because they often occur in the same foods, however, they do not have the same or even similar biochemical makeups (Calderón‐Ospina & Nava‐Mesa, 2019). Due to the nature of these vitamins as being water-soluble, daily ingestion is needed. These vitamins are not stored in large amounts within the bodily tissues and excess consumption most often leads to excretion through the kidneys. This allows for toxicity to be rare, although not impossible (DiBaise & Tarleton, 2019). The B vitamins have many roles within the human body, especially regarding organ function. Within the role of promoting organ function, the B vitamins play significant roles in maintaining the health and function of the skin, which is the largest sensory organ in the human body. This literature review aims to explore the relationship between the various functions of the B vitamins and skin health.

The skin is the most exposed organ of the human body, as well as the largest in surface area, averaging around 20 square feet (Hoffman, n.d.; Williams et al., 2011). Due to the skin being a barrier between the inside of the body and the environment, it is constantly in contact with external stressors, such as sun exposure, pollution, and adverse weather conditions. In addition, the skin serves as a permeability barrier and antimicrobial barrier, limiting the movement of water and electrolytes, while also protecting against bacteria and microorganisms (Feingold, 2009). The skin barrier also provides mechanical protection by maintaining skin

temperature through sweat and allowing for sensory exploration of the world through vibration and touch. Hence, the skin functions as a barrier against physical, chemical, and immune irritants and compounds such as fragrances and pollen, which is crucial for the health and survival of the body (Swaney & Kalan, 2021).

The outer appearance of the skin gives a visual insight into the health and wellbeing of the body (Boo, 2021; Schagen et al., 2012). The fascination and obsession with the skin is partially due to the attempt that humans make to appear youthful as long as possible. The beauty and youthfulness of human skin does not just come from the outside with the range of cosmetic products that are available. Beauty of the skin is generally seen as hydrated skin that is free of blemishes and lesions. In contrast, beauty is also influenced by internal health and what is being put into the human body, such as nutrients like the B vitamins (Schagen et al., 2012). The skin is one of the few organs that is visible and susceptible to the external environment. From an aesthetic viewpoint, the fact that the skin is visible to others means that the health of this organ is important to how individuals view themselves and others (Boo, 2021).

The structure of the skin primarily consists of the dermis and epidermis (Chen & Lyga, 2014; Williams et al., 2011). The epidermis has four types of cells: keratinocytes, melanocytes, Langerhans cells, and Merkel cells, each of which are responsible for their own role in skin structure, pigmentation, immune function, and sensory touch (Williams et al., 2011). One unique feature of the skin is that its epithelial cells are constantly renewing themselves by regenerating from the epidermis every 28 days (“What is a skin cycle?”, n.d.). The keratinocytes within the epidermis, which help to restore the epithelial barrier by carrying out the epithelialization process, continually develop, travel to the surface and then are shed. The layer at the very surface of the skin is known as the stratum corneum and those cells are both flat and deceased (Chen &

Lyga, 2014). The stratum corneum functions as the outermost barrier to protect water from leaving and unwanted materials and organisms from entering the body (Menon et al., 2012). Lipids in the stratum corneum are used to develop and preserve the barriers of the skin. The stratum corneum has an extracellular lipid matrix that is composed of fatty acids, cholesterol, and ceramides, as well as sphinogo- and phospholipids. Free fatty acids have been shown to have antimicrobial activity, promoting the skin's ability to be a barrier against microorganisms (Feingold, 2009).

Below the epidermis is the dermis, which is made up of fibroblasts and extracellular matrix (Chen & Lyga, 2014). The dermis is primarily made up of fibroblasts that are abundant in collagen (Williams et al., 2011). The third and final layer of the skin is the hypodermis. The hypodermis is made of fat and connective tissue, which acts to insulate the body and helps store energy (Hoffman, n.d.).

Collagen is a protein found in the skin that is also an important part of the integrity and tensile strength of dermal structure (Lakshmi et al., 1990). There are 28 different types of collagen that exist, although only seven are relevant for the health of the human body. Type I and III collagen are the two of the seven collagen types that play a big role in the skin, especially within wound healing ("What are the different types of collagen? and which types of collagen will benefit you most?", n.d.). The major type of collagen within the skin is Type 1 collagen which provides structure and weight to the skin. Normal, healthy skin is made up of 80-90% Type I collagen. Type III collagen is also seen within skin tissue in lesser amounts, found in higher amounts of fetal skin compared to those of older age. Within the beginning of wound healing, type III collagen is produced first by mesenchymal cells and then is later followed by production of type I collagen by fibroblasts. Throughout the healing process, the type III

collagen that was originally produced in high amounts, is slowly replaced with type I (Alvarez & Gilbreath, 1982).

An important part of the skin and its health is the microbiome of the skin (Byrd et al., 2018). The skin has colonies of microorganisms that are beneficial to the health of the skin. It is home to *staphylococcus*, *dermabacter*, *brevibacterium*, and many more microorganisms (DermNet NZ, n.d.).These beneficial microorganisms take part in a commensal relationship with the skin. The bacteria on the skin use nutrient sources within sweat, sebum, and stratum corneum. Sebum provides a lipid source, while sweat provides salt and stratum corneum has proteins available within the sloughed skin (Flowers & Grice, 2020). Production of free fatty acids can promote good nutrient stores for the beneficial bacteria of our skin. So while inhibiting sebum production through the use of dermatologic medications like androgen inhibitors may potentially reduce acne, the skin will suffer slightly due to bacteria not receiving adequate nutrients (Byrd et al., 2018). Secondary to these properties, the skin has been found to be useful in the prevention of pathogen infiltration into the body as it serves as a barrier to the external environment.

Skin health is partially maintained through the interactions and relationship between the skin, microorganisms, and the human body's immune system (Swaney & Kalan, 2021). This microbiome can be disrupted with pathogens or gaps in the skin barrier. These can all change and negatively impact the way that the skin functions (Swaney & Kalan, 2021). The microbiota on the skin play a role in a healthy skin barrier. The microbiota that live on the skin have adapted to be able to thrive in that environment, which is an environment that is extremely inhospitable for living microorganisms (Swaney & Kalan, 2021). The health of the gut microbiome will also

somewhat influence the body's supply of B vitamins, as certain B vitamins can be synthesized by bacteria in the gut (Yoshii et al., 2019).

As individuals age, so do their organs and the skin is no different (Boo, 2021; Dalens & Prikhnenko, 2015). Skin aging can occur secondary to a malfunction in the dermal fibroblasts and a lowered biosynthetic activity. Skin aging is characterized by reduced elasticity, decreased moisture, uneven surface texture, skin marks and pigmentation, as well as wrinkles, also known as rhytids (Dalens & Prikhnenko, 2015). Wrinkles/rhytids are lines, creases, or folds in the skin ("Wrinkles", n.d.). Chronological aging logically affects the skin at the same rate and pattern as the other organs in our bodies, since the skin itself is an organ. Chronological aging of the skin is seen with aging due to UV exposure as well as internal factors. There is a decrease in collagen and the skin is seen to have an impaired texture, as well as wrinkles, dryness, and thinning (Boo, 2021). Extrinsic skin aging is due to external factors and the environment (Schagen et al., 2012). Intrinsic skin aging is characterized as dry, brittle and thin skin which occurs over time (Mohsen et al., 2015). The aging of skin plays a role in the health and outward appearance of the human body.

Even though the skin has an amazing ability to constantly replace itself, this ability begins to take more and more time with aging ("Micronutrients in human development – part 3", 2013). Aged skin is thinner than younger skin due to slowed collagen production, and has less water stored within its cells, resulting in more easily dehydrated skin. Exposure to UV radiation can speed up the breakdown of collagen and cause damage to skin cells and their DNA through oxygen exposure ("Micronutrients in human development – part 3", 2013).

Certain dermatological approaches to treat skin issues include meso preparations which are used to inject vitamins, enzymes, and plant extracts in order to decrease and repair any

aging-related skin issues (Dalens & Prikhnenko, 2015). Healthy skin needs adequate intake of essential nutrients. Studies have shown that it is possible to delay or prevent skin aging by supplementing with nutrients (Dalens & Prikhnenko, 2015; Mohsen et al., 2015).

Many skin issues are seen within humans and other animals (Alvarez & Gilbreath, 1982; Cibrian et al., 2020; Williams et al., 2011). Some of these skin issues are due to skin aging, while others are caused by other factors. These include impaired collagen production, problems related to wound healing, texture abnormalities, sun damage, and inflammation, as well as other factors. Wound healing is also dependent on the body's ability to produce adenosine triphosphate (ATP) at sufficient levels to heal wounds and synthesize collagen (Alvarez & Gilbreath, 1982). Longer term, repeated damage to DNA can lead to skin damage as severe as skin cancer, as well as impair the responses of the immune system to regulate the presence of damaged cells within the skin (Williams et al., 2011). Skin diseases characterized by inflammation are often linked with impaired regulation of the immune system of the skin and the skin barrier. Chronic inflammation in skin diseases is often caused by an abnormally quick increase in keratinocytes and inflammatory cells that grow larger in size, indicating there is an increased need within the cell for more nutrients (Cibrian et al., 2020).

Research has shown that the brain and skin have a two way connection and influence on each other (Minich, 2018). Research has also presented evidence calling for the skin to be classified as a neuroendocrine organ (Minich, 2018). The cells in the skin, especially the keratinocytes, can secrete stress hormones, neurotrophins, and neurotransmitters. Certain neurotransmitters and hormones have specific functions within the skin, such as estrogen, progesterone, and testosterone. Acetylcholine promotes the homeostasis of skin cells. Dopamine has a possible role in nerve signal promotion. Endocannabinoids help to prevent inflammation

and tumor creation and growth. It also promotes the secretion of other transmitters and hormones that maintain the homeostasis of the skin, as well as reduce itching sensations. Histamine helps to promote keratinocyte function, as well as the function of other cells in the skin. Histamine also plays a role in promoting melanin synthesis, antimicrobial peptide activity, and immune responses by T helper 2 cells which are integral in allergy inflammation. Melatonin is used as an antioxidant and can regulate skin pigmentation. Serotonin affects the blood vessels to promote dilation or constriction (Minich, 2018). These neurotransmitters and hormones each play a part in the health of the skin.

The skin is connected to the body and responds to stress via a stress response that involves both epinephrine and the hypothalamic-pituitary-adrenal axis (HPA) (Chen & Lyga, 2014; Minich, 2018). The HPA axis helps regulate the body's bodily processes and reaction to stress (Sheng et al., 2021). When stress occurs, the hypothalamus will secrete epinephrine and then will activate the HPA axis once the surge of epinephrine lulls (Harvard, 2020). Epinephrine can lead to inflammation and less blood flow in the skin. Within the HPA axis, stress stimulates the secretion of corticotropin-releasing hormone (CRH) from the hypothalamus which then promotes the secretion of adrenocorticotropin. CRH is the main regulator of the HPA axis. Adrenocorticotropic hormone (ACTH) is also released in response to stress and promotes cortisol and corticosterone production and secretion. Stress hormones like cortisol and corticosterone can negatively impact the skin by decreasing its ability to function as a barrier to the external environment and microorganisms (Minich, 2018). Cortisol suppresses the immune system and corticosterone helps to regulate energy metabolism and the body's reaction to stress (Emmanuel Konstantakos, n.d.; ScienceDirect Topics, n.d.). The skin also has its own HPA axis and all of the neurotransmitters and receptors are produced within the skin as well as the brain.

CRH can increase the permeability of the skin blood vessels, potentially leading to inflammation (Chen & Lyga, 2014). The skin's inflammation increases with CRH secretion likely due to mast cells. Mast cells are cellular sensors that release proinflammatory cytokines in response to triggers (National Cancer Institute, n.d.). Psychological stressors, such as unwanted changes and death of close relatives, and skin ailments, such as acne and wrinkles, have been linked in clinical observations. Stress can be seen within the skin by promoting wrinkles, lowered function of the skin barrier, and less water retention, as well as inflammation and a reduced ability for the skin to heal (Chen & Lyga, 2014).

The skin is integral for the health and wellbeing of the human body (Swaney & Kalan, 2021). However, the organ itself also needs to remain healthy. The skin can remain healthy through proper nutrient intake, avoidance of stressors, and evading damage. Nevertheless, the skin's ability to protect against nutrient loss, stress, and damage all decreases over time with skin aging. All of the essential nutrients for humans will be helpful for healthy skin, but the B vitamins have an abundance of research providing an argument that the proper intake of the B vitamins could be the key to long-lasting health for the skin (Alvarez & Gilbreath, 1982; Boo, 2021; Byrd et al., 2018; Chen & Lyga, 2014; Cibrian et al., 2020;Dalens & Prikhnenko, 2015; Feingold, 2009; “Micronutrients in human development – part 3”, 2013; Minich, 2018; Mohsen et al., 2015; Swaney & Kalan, 2021; Williams et al., 2011; Yoshii et al., 2019).

B1 overview - thiamine

Vitamin B1 goes by many names, including thiamine and aneurin (Priyadharsini, 2016). Of interest, thiamine was the first vitamin to be identified (“Vitamin B1 thiamine deficiency”, n.d.). It is chemically made of a pyrimidine ring with a methylene bond attaching it to a thiazole

ring. With the help of ATP in which to add a double phosphate to its structure, thiamine is transformed into its coenzyme: thiamine pyrophosphate (TPP) (Priyadharsini, 2016). Food sources of thiamine include nuts and dried beans, whole grain cereals, liver, eggs, and pork products. The recommended daily allowance (RDA) for thiamine for adults is 1.0-1.5 mg/2000-3000 calories (Priyadharsini, 2016).

Thiamine is absorbed predominantly within the first part of the small intestine in the jejunum and ileum (Priyadharsini, 2016). At lower concentration, thiamine is absorbed by active transport via thiamine transporter 1 (ThTr1). At higher concentrations, thiamine is absorbed by passive diffusion. However, beyond a certain point, absorption decreases as the ingested amount increases (Priyadharsini, 2016). Ingested thiamine is not the only source of thiamine within the human body. Bacteria in the intestines are able to produce some thiamine (Sriram et al., 2012). Once absorbed, thiamine is transported by the bloodstream to the liver where it is then transported to other areas of the body or excreted. Although thiamine is a water soluble vitamin, it is stored in small amounts within the human body. In fact, roughly 30 milligrams of thiamine is stored in various places. Approximately 15 milligrams of that is within the skeletal muscles, with the other 15 milligrams stored within other organs and tissues (Priyadharsini, 2016). Thiamine is transported across cell membranes by human thiamine transporter-1 and human thiamine transporter-2 (Sriram et al., 2012).

Thiamine has various influences on the human body, such as assisting in metabolism and regulating lactic acid levels (“Office of dietary supplements - pantothenic acid”, n.d.; Sriram et al., 2012). Starting at the basic level of metabolism, thiamine helps with glucose metabolism by functioning as a cofactor for the production of energy. It is required in the synthesis of adenosine triphosphate (ATP), deoxyribonucleic acid (DNA), and ribonucleic acid (RNA) due to its use in

producing ribose from glucose (“Office of dietary supplements - pantothenic acid”, n.d.). Within the form of TPP, thiamine participates in pyruvate dehydrogenase by promoting the conversion of pyruvate to acetyl CoA. TPP is also used in the conversion of alpha-ketoglutarate to succinyl CoA (Priyadharsini, 2016). Thiamine is involved in the energy pathway for carbohydrates and the synthesis of DNA and RNA from glucose. In addition, it is responsible for assisting cells deal with metabolic acidosis by promoting the removal of a carboxyl group from alpha-keto acids, thus causing the release of CO2 (Dalens & Prikhnenko, 2015). Thiamine is also important in regulation of lactic acid levels as lactic acid will build up in its absence since thiamine is required for the conversion of lactate to pyruvate (Sriram et al., 2012). In the view of these vital metabolic functions, thiamine is influential to human health.

Thiamine is important in the central nervous system (Libretexts, 2020). It is essential for myelin production and production of neurotransmitters such as amino acids, serotonin, and acetylcholine. TPP plays a role in the maintenance of the myelin sheath and promoting nerve impulses (“Vitamin B1 thiamine deficiency”, n.d.). Due to its role in energy metabolism, thiamine helps to provide nerve cells with energy. Research has also been done to show that thiamine can prevent cellular damage through its antioxidative abilities. It was also reported that a deficiency of thiamine may result in increased susceptibility of cells to oxidative stress (Calderón‐Ospina & Nava‐Mesa, 2019). The brain is adversely affected as a result of thiamine deficiency (Libretexts, 2020).

Thiamine deficiency is referred to as beriberi and it can be split into two categories: wet and dry (“Office of dietary supplements - pantothenic acid”, n.d.). Wet beriberi involves symptoms such as failure of the heart and fluid within the body tissues involving edema or swelling. Dry beriberi can cause the muscles to waste (Libretexts, 2020). The symptoms of

beriberi are related to oxidative stress and inflammation in the body. In fact, research on mice with a thiamine deficiency found that tumor necrosis factor alpha (TNFα) and monocyte chemoattractant protein-1 (MCP-1) levels were significantly higher within the mice consuming a thiamine deficient diet. TNFα is an early indicator of inflammatory response as it is an inflammatory cytokine. MCP-1 helps to regulate monocytes and macrophages. Deficiency of thiamine could lead to higher oxidative stress and inflammation (de Andrade et al., 2014).

Thiamine's main function within the skin is to promote wound healing through its role in energy and collagen metabolism, which can be adversely affected by a deficiency (Alvarez & Gilbreath, 1982). When thiamine levels are deficient, there is a reduction in collagen metabolism and production, which could impact wound healing and tensile strength in the skin. In an animal model study with rats, the weight of wound areas were taken and revealed that the thiamine deficient rats had wound areas that weighed less than the thiamine supplemented and control rats (Alvarez & Gilbreath, 1982). The weight difference reflects lower collagen concentrations within the rats that were deficient. The deficient rats also showed a lower activity for lysyl oxidase than the other two groups of rats. Lysyl oxidase initiates collagen crosslinking to form the structure of collagen and plays a role in its tensile strength. The type III to type I collagen ratio in the rats was 62% less in the rats that were thiamine deficient (Alvarez & Gilbreath, 1982). Compared to the control, thiamine-deficient rats had lower type III collagen levels within their wound chambers. This is significant because the deficient synthesis of type III collagen may result in insufficient amount of Type I collagen and improper Type I collagen development (Alvarez & Gilbreath, 1982).

Thiamine is also important in the wound healing process due to its influence on energy metabolism (Alvarez & Gilbreath, 1982). Due to the increased activity within the cells during

healing, an increased requirement of energy is needed. Within thiamine deficiency, the ability of cells to produce enough ATP to meet the energy needs of repairing tissues is likely to be insufficient (Alvarez & Gilbreath, 1982).

Thiamine also has other effects, such as increasing circulation and promoting wrinkles, within the skin (Alvarez & Gilbreath, 1982; Cosgrove et al., 2007). However, there has been limited research regarding these additional functions. This vitamin also has shown potential for improving circulation, which may lead to a more vibrant, glowing skin (Mohsen et al., 2015). On the other hand, mucocutaneous symptoms of thiamine deficiency present as changes in the skin and cheilosis, which is seen as inflammation and cracking in the corner of the mouth (Sriram et al., 2012). Although deficiency of thiamine exhibits mucocutaneous symptoms based on the role of thiamine in cellular metabolic pathways, excessive intakes of thiamine also have some mucocutaneous symptoms. One study found that thiamine intakes were associated with wrinkles, in which a higher intake leads to a higher likelihood that wrinkles would form (Cosgrove et al., 2007). To have a better understanding, more research needs to be conducted on the effects of thiamine deficiency, excess, and normal levels on the skin.

B2 overview - riboflavin

Vitamin B2 is also known as riboflavin, lactoflavin, hepatoflavin, and Vitamin H (Priyadharsini, 2016). Riboflavin was first discovered by English chemist Alexander Blyth in 1872. The discovery was characterized by milk and the yellow pigmentation found within it. Riboflavin's chemical structure is a flavin isoalloxazine ring that has a side chain of a sugar attached to it. The chemical formula for riboflavin is 7,8-dimethyl-10-ribityl-isoalloxazine. Riboflavin is naturally a fluorescent, yellow-green pigment and also exists as an orange-yellow

crystal in food. Riboflavin is sensitive to light, but stable when exposed to oxidation, acid, and heat (Ahgilan et al., 2015). When exposed to sunlight, riboflavin is converted to lumichrome or lumiflavin depending on the acidity or alkalinity of the solution (Ahgilan et al., 2015). The RDA is 1.3 mg for adult males and 1.1 mg for females that are not pregnant (DiBaise & Tarleton, 2019). Dietary sources of riboflavin include dairy products, almonds, fortified grains, meat, eggs, and green leafy vegetables (Priyadharsini, 2016).

Riboflavin is absorbed predominantly in the first part of the small intestine in the duodenum, which is the first part of the small intestine, by a transport system that increases in speed and efficiency up until approximately 27 milligrams of riboflavin (Priyadharsini, 2016). After absorption, riboflavin is metabolized by the liver (DiBaise & Tarleton, 2019). Then, riboflavin is transported in the blood bound to albumin and globulins/immunoglobulins. At normal concentrations, riboflavin is taken up into cells by a carrier, but higher concentrations of riboflavin require diffusion for uptake (Priyadharsini, 2016). Upon entering the cytoplasm of cells in the small intestine, heart, kidney, and liver, riboflavin is converted to its coenzymes. The first step of conversion is dependent on ATP and flavokinase, which is an enzyme in the cytosol. The second conversion step is also ATP dependent and requires flavin adenine dinucleotide (FAD) synthetase. FAD is essential for conversion of xanthine to uric acid, succinate to fumarate and pyruvate to acetyl CoA (Priyadharsini, 2016). While riboflavin can be obtained through the diet, lactic acid bacteria in the colon have been shown to have the ability to produce riboflavin (DiBaise & Tarleton, 2019).

Riboflavin has many influences within the human body (Dalens & Prikhnenko, 2015; Libretexts, 2020). Riboflavin and its derivatives (FAD and flavin mononucleotide [FMN]) help to transfer and distribute energy to cells from the metabolism of fat and carbohydrates.

Additionally, riboflavin participates in activating vitamins B6 and 9 as well as assisting in the redox metabolism that occurs at the cellular level (Dalens & Prikhnenko, 2015). Riboflavin's deficiency, known as ariboflavinosis, is characterized by sores, skin dehydration, as well as textual issues of the skin such as a scaly texture (Libretexts, 2020).

Riboflavin functions as both an antioxidant and anti-inflammasome (Ahn & Lee, 2020). It impedes the activation of "nod-like" receptor protein-3 (NLRP3) inflammasome in order to reduce inflammatory responses (Ahn & Lee, 2020). Riboflavin exhibits anti-inflammatory properties through the following potential mechanisms: Pro-inflammatory transcription nuclear factor kappa B (NF-κB) is turned on by the breakdown of inhibitory kappa B (IκB). The breakdown of IκB initiates the transport of NF-κB to the nucleus and promotes its binding to regions that subsequently promote the coding for proteins that are pro-inflammatory. Within lipopolysaccharide stimulated inflammation and its pathways, proteasomes are used to regulate the pathways. Riboflavin as a proteasome inhibitor could potentially lead to the down-regulation of the inflammatory pathway activation caused by reactive oxygen species (ROS) (Suwannasom et al., 2020). Riboflavin supplementation has shown potential as an antioxidant and lowers ROS concentrations within keratoconus. This occurs because FAD is used to promote the conversion of glutathione disulfide (GSSG) to glutathione (GSH) (Suwannasom et al., 2020). FMN and FAD both serve as coenzymes for redox reactions and have potential uses for reducing oxidative stress by inhibiting the peroxidation of lipids (Suwannasom et al., 2020).

Riboflavin has been found to be a photosensitizer, generating oxidative damage to the skin that is exposed to light (Suwannasom et al., 2020). This damage is due to the light results in a triplet-excitation state of riboflavin. This triplet-excitation state is advantageous because it means that riboflavin could be used in conjunction with long-wave UV radiation to disable

pathogens (Suwannasom et al., 2020). Riboflavin when exposed to UVA irradiation has been shown to display antimicrobial activity. Through exposure to UVA light, riboflavin was shown to inhibit pathogens in stand alone solutions through the disc diffusion method (Ahgilan et al., 2015). The pathogens studied were both gram positive and negative, as well as fungi. It stands to reason that riboflavin could effectively be used on pathogens that commonly infect wounds and blood.

Riboflavin has shown additional biological benefits, such as promoting cellular respiration and limiting pain responses, however, there is limited evidence-based research regarding this (Ahgilan et al., 2015; Suwannasom et al., 2020). Riboflavin supplementation has been used for jaundice treatment in neonatal conditions, benefiting infants and reversing jaundice (Ahgilan et al., 2015). Riboflavin has been found to help cells effectively use oxygen through its role in cellular respiration (Ahgilan et al., 2015). A study found that oral supplementation of riboflavin decreased detection of painful stimuli from the sensory nerves which are part of the peripheral nervous system (Suwannasom et al., 2020). These sensory nerves detect sensations from touch, pain, and temperature and send them to the brain ("Riboflavin transporter deficiency", 2019). Riboflavin supplementation increases the function of macrophages. Additionally within macrophages that are infected with Staphylococcus aureus, riboflavin supplementation lowered the inflammatory response factors of the microorganism (Dey & Bishayi, 2016). All of these roles that riboflavin plays in the human body need further research.

When riboflavin is not consumed in adequate amounts everyday, deficiency can occur (Lee et al., 2021; Suwannasom et al., 2020). Riboflavin's deficiency can lead to inflammation, dehydrated skin, lesions and other skin-related issues, including itching sensations (Lee et al., 2021). Additionally, the deficiency can lead to scaly rashes, pigmentation, and cheilitis

(Suwannasom et al., 2020). Consuming adequate amounts of riboflavin daily will help to prevent these adverse effects within the skin.

Animal studies of both riboflavin supplementation and deficiency have shown some skin influences of the vitamin (Flieger et al., 2016; Lee et al., 2021). Within mice, riboflavin deficiency can cause scratching behaviors induced by histidine that were significantly reduced through oral intake of riboflavin. Riboflavin does this by inhibiting the regulation of the activity of transient receptor potential cation channel subfamily member V 1 (TRPV1) (Lee et al., 2021). In bats, riboflavin can be overproduced when the body is exposed to fungal pathogens and the overproduction causes large amounts of riboflavin to interact with skin tissue (Flieger et al., 2016). This interaction can lead to skin becoming more susceptible to infection or large amounts of cell death (Flieger et al., 2016).

Riboflavin deficient rats display both qualitative and quantitative changes in maturation and creation of skin collagen within clinical research done over three groups of male weanling rats (Lakshmi et al., 1989). Epithelization, where epithelial cells help to heal a wounded area, was found to take four to five days longer in rats that were deficient in riboflavin, as compared to rats that had adequate levels. Additionally, the rate of wound contraction, which slowly decreases the size of the wound, takes four days longer in the rats that were riboflavin deficient. The rats that were deficient also had significantly less scar tissue collagen than the controls. It appears that crosslinking and the amount of collagen within a wound is important because it increases tensile strength, preventing wound dehiscence. Mature, crosslinked collagen, which means it has stable cross-linking, is vital for the skin to heal and for platelets to adhere to each other in order to heal a wound (Lakshmi et al., 1989). Due to a decrease in both crosslinking and collagen amount within riboflavin deficiency, it stands to reason that the explanation for decreased

incision wound tensile strength is those with the deficiency (Lakshmi et al., 1989). Due to riboflavin's connection with collagen and its promotion of the maturity of skin collagen, mucocutaneous lesions are seen within the deficiency of riboflavin (Lakshmi, 1998).

Riboflavin deficiency has been found to lead to a thickening of the outermost layer of skin in rats, as well as a faster cellular rate of reproduction in the skin, often leading to cancer (Wynder & Chan, 1970). Within one study involving rats, the rats were separated into four groups and fed riboflavin-deficient diets before returning to normal diets after 4 weeks (Wynder & Chan, 1970). The control group remained consuming a normal diet, while the treatment groups were once again put on a deficiency diet. While rats deficient in riboflavin had higher tumor counts within the study, riboflavin supplementation in the deficient rats did not significantly reduce the number of tumors (Wynder & Chan, 1970). In this study, the tumors formed within riboflavin deficiency were not reversible with a return to adequate riboflavin levels. Although useful for possible prevention of skin cancer, the study shows evidence that riboflavin may not be helpful to treat skin cancer.

Riboflavin supplementation has been investigated as a treatment for acne in humans (Ahgilan et al., 2015). Photodynamic therapy with alpha-lipoic acid (ALA) and photodynamic therapy (PDT) gel containing riboflavin and tryptophan was used on subjects with facial acne (Wangsuwan & Meephansan, 2019). The PDT with riboflavin gel had significantly better improvements in comedone acne at the third week of treatment. When blue light and riboflavin interact, radicals are created and reactive oxygen species (ROS) are generated, which lowers acne production and synthesis of sebum (Wangsuwan & Meephansan, 2019).

Riboflavin has potential as a photosensitizer (Wangsuwan & Meephansan, 2019). Photosensitizers take light and transfer them to nearby molecules. This transfer promotes an

excited singlet state that then becomes an excited triplet state. This triplet state is more stable than the single state (Wikipedia Foundation, 2022). In a double-blind, split face research study, patients with facial acne that was considered mild to moderate in severity had a riboflavin-tryptophan gel applied to half their face and an ALA gel applied to the other side (Wangsuwan & Meephansan, 2019). Then, the subject's faces were exposed to radiation through the use of a blue light for 20 minutes. Over a 4-week period, the 37 subjects underwent four different sessions for the treatment. At the end of the treatments, the intensity and amount of acne lesions were evaluated. Additional components related to acne were also assessed, such as pore size and secretion of sebum. The results found that the photodynamic treatment of the blue light paired with the use of the riboflavin-tryptophan gel appeared to promote significant results in the reduction of acne lesions, sebum production, and the severity of the lesions themselves. There were also improvements in the size of the subject's facial pores and the texture of the skin, however these improvements were not statistically significant. The riboflavin-tryptophan (RT) gel, although it produced significant results from baseline, did not produce significantly better results from the 5-aminolevulinic acid gel treatment. New acne treatments need to be explored because current products can have side effects including bacterial resistance and irritation of the skin. Photodynamic therapy utilizes a photosensitizer and light to catalyze a reaction, as shown by previous studies over how the combination of riboflavin and pulsed light can significantly reduce bacteria on the skin without causing damage to the organ itself. It is also important to note that the RT gel had trace amounts of niacinamide and glycolic acid, which may have had effects on acne themselves. Additionally, the study only lasted 7 weeks, meaning that the length of the study was not long enough to determine if the results are significant long-term (Wangsuwan & Meephansan, 2019).

In summary, riboflavin has shown to play a role in many processes within the human body (Priyadharsini, 2016). Current research has indicated the possible use of riboflavin for treatment and prevention of many different skin conditions, such as cancer, acne, and wound healing. More research needs to be conducted regarding both oral and topical use of vitamin B3, especially research involving human subjects. Studies of longer duration and sample size may lead to a better understanding of riboflavin effects on the human body.

B3 overview - niacin

Vitamin B3 is known by multiple names, such as nicotinic acid, niacin, and nicotinamide (Priyadharsini, 2016). Chemically, niacin is a pyridine-3-carboxylic acid (Priyadharsini, 2016). Nicotinic acid is found in plants and is known to be a provitamin (Prousky et al., 2011). Niacin is a part of coenzymes nicotinamide adenine dinucleotide (NAD) and nicotinamide adenine dinucleotide phosphate (NADPH). These coenzymes are involved in the breakdown and synthesis of carbohydrates, lipids, and proteins, as well as ATP production. NAD is necessary for the conversion of pyruvate to acetyl CoA (Priyadharsini, 2016). NADPH is integral in the synthesis of fatty acids and cholesterol (“Office of dietary supplements - pantothenic acid”, n.d.). Niacin is also unique in that the body can convert something else to get niacin. In fact, 60 mg of tryptophan can produce 1 mg of niacin in the body (Benavente et al., 2009). In the skin, a deficiency of niacin results in an irritation referred to as pellagra dermatitis (DiBaise & Tarleton, 2019). Of interest, vitamin B3 is also the only vitamin approved by the United States Food and Drug Administration (FDA) in order to prevent heart attacks (“Study paints clearer picture of 'nasty' side effects from well-known heart drug”, 2017). Niacin is found in both animal products and plant sources. Within animal sources, niacin is found in meat, liver, kidney, and fish. Plant

sources include yeast, nuts, legumes, germ and bran, tea, and coffee. The RDA for adults is 6.6 mg per 1000 calories consumed (Priyadharsini, 2016).

Niacin absorption occurs in the upper part of the small intestine and metabolism occurs in the liver (Priyadharsini, 2016). Niacinamide is a form of niacin that involves an amide that is absorbed in the small intestine and partially in the stomach. It can also be absorbed by the skin with topical use ("Office of dietary supplements - niacin", n.d.). When in lower concentrations, nicotinic acid is absorbed via sodium-dependent diffusion. At high concentrations, it is transferred by way of passive diffusion. Most transported and stored vitamin B3 is in the form of niacinamide (Priyadharsini, 2016). Nicotinamide is stored in the liver in the form of NAD and can be excreted by the kidneys. It can also be synthesized through the conversion of tryptophan to nicotinamide in the liver (Bains et al., 2018). Tryptophan conversion occurs in the liver and requires the presence of pyridoxine (DiBaise & Tarleton, 2019).

Biologically, niacin has many different influences on the human body, such in cellular metabolism and oxidative processes (Dalens & Prikhnenko, 2015; Prousky et al., 2011). Nicotinamide is a part of two coenzymes that are common within the cellular metabolism pathways, namely nicotinamide adenine dinucleotide (NAD) and nicotinamide adenine dinucleotide phosphate (NADP). These coenzymes are crucial for the production of ATP from the macronutrients and help promote the synthesis and production of fatty acids (Dalens & Prikhnenko, 2015). Similarly, nicotinic acid is transformed into NAD and then plays a part in redox reactions, in which the oxygen state of atoms changes, and metabolism. NAD is used in oxidative pathways for the production of energy from macronutrients and NADP is used in anabolic pathways for oxidative defense and the production of fatty acids (Prousky et al., 2011).

Niacin has anti-inflammatory and antioxidant features (Pietrzak et al., 2009; Si et al., 2014). Niacin prevents inflammation within the blood vessels. For example, in the human aorta, it has the ability to repress the adherence of the macrophages and monocytes, as well as the growth of them. Macrophages are white blood cells that stimulate the immune system and kill microorganisms ("NCI Dictionary of Cancer terms", n.d.). Monocytes are white blood cells that transform into macrophages when pathogens are detected in the body ("Monocytes: A type of white blood cell - what are normal ranges?", n.d.). Niacin also has been shown to suppress the creation of reactive oxygen species and oxidation of low-density lipoproteins in vitro (Si et al., 2014). Low-density lipoproteins (LDL) are one type of cholesterol in the body associated with increased heart disease and stroke risk (Centers for Disease Control and Prevention, 2020). Niacinamide has anti-inflammatory properties through its ability to reduce the synthesis of interleukins 1, 6, and 8 as well as tumor necrosis factor α which are all proinflammatory cytokines (Pietrzak et al., 2009).

Niacin works to lower the amount of triglycerides being synthesized, thus influencing the metabolism of lipoproteins in the body (Kamanna et al., 2009). In the body's adipocytes or fat cells, niacin prevents the breakdown of triacylglycerols, which are the storage form of fat in adipose tissue, as well as preventing the movement of free fatty acids from the cells into the plasma. This is important in the body's production of triglycerides because the liver makes triglycerides through the use of free fatty acids in the plasma (Kamanna et al., 2009).

Other various influences of niacin include prevention of pellagra and anti-microbial properties (Bains et al., 2018; Xing et al., 2019). Pellagra can occur in deficiency due to interference with the tryptophan to niacin conversion (DiBaise & Tarleton, 2019). Nicotinamide is also known as vitamin PP, due to niacin deficiency being presented as pellagra. Pellagra is

categorized by the 4 Ds, with one of those Ds being dermatitis, which can lead to scaling on the skin and patchy redness (Bains et al., 2018). Oral supplementation of nicotinamide has been used to treat pellagra, with doses of 100-300 mg in three to four doses daily. Nicotinamide is the preferred treatment for vitamin B3 deficiency as it does not cause the flushing symptoms associated with niacin supplementation (Bains et al., 2018). Niacinamide also has antifungal properties, especially against Candida albicans, which is an opportunistic pathogen within the human gut (Xing et al., 2019). Niacinamide works to prevent infections from these pathogens and can protect the body from illnesses associated with microorganisms, such as Candida albicans. Hence, both niacin and niacinamide protect the body from a variety of disease states, including pellagra and microorganism infections.

In the skin, niacin deficiency is seen primarily in areas exposed to the sun as the symptoms are generally triggered by photosensitivity (Sugita et al., 2013). Pigmented and scaly portions of the skin occur in niacin deficiency, as well as erythema and rashes (Priyadharsini, 2016). Within deficiency, the skin can present a condition beginning like a sunburn, later progressing to a condition of thickened and flaky skin. In addition, itching and blisters may be associated with the condition, as well as a color difference in the skin, causing the skin to resemble a shade that is more brown-blue in color (Ashkani Esfahani et al., 2015).

Niacin shows important benefits for the skin (Benavente et al., 2009; Hakozaki et al., 2002; Scatozza et al., 2020). It is involved in NAD which is important for both DNA repair and the synthesis of energy. These help to improve the integrity of the skin barrier and immune function. These properties of DNA repair and synthesis of energy allow for niacin to be beneficial in the treatment of rosacea, photodamage, acne vulgaris, dermatitis, skin cancer, and actinic keratosis, which is rough and scaly patches of skin (Benavente et al., 2009). Rosacea is

flushing of the skin caused by dilation of blood vessels in the skin (Mayo Foundation for Medical Education and Research, 2021). Niacinamide inhibits inflammatory responses in acne cases and has been known to heighten the production of lipids within the cells, allowing for potential benefits for skin cells and the skin barrier (Hakozaki et al., 2002). It also has the potential ability to decrease dehydration in the skin barrier, leading to the treatment of acne, rosacea, and dermatitis (Scatozza et al., 2020). Niacin is able to lower hypersensitivity responses in the skin due to its influence on the function of dendritic cells, which are antigen-presenting cells that play a role in the immune system (Ingersoll et al., 2012). Common uses for niacinamide include the treatment of hyperpigmentation, sallowing or yellowish appearance, texture issues, enlarged pores, rubor or redness, wrinkles and lines, and sebum production (Farris, 2014). These skin conditions are influenced by niacin.

It is hypothesized that nicotinamide regulates the status of oxidation states for the cells in order to suggest its role in the homeostasis of the skin (Boo, 2021). Within a meta-analysis of eight randomized-controlled trials with nicotinamide containing moisturizers, serums, or lotions and placebos, all of the studies found improvement in the treatment group receiving nicotinamide and noted an decrease in hyperpigmentation, sallowing of the skin, wrinkles, texture, and blotchiness in the skin (Boo, 2021). Some of the trials also noted a reduction in the size and appearance of facial pores while others described improved skin barrier with moisture and elasticity improvements (Boo, 2021). Supplementation of nicotinamide has been shown to replenish the supply of NAD in the cells, as well as reduce oxidative stress and inflammation, improve the integrity of the extracellular matrix and barrier of the skin, and block the pigmentation process within the skin (Boo, 2021).

Topical nicotinamide is able to penetrate the skin well, allowing it to be a good candidate for topical use (Ashkani Esfahani et al., 2015). Topical niacinamide has many functions and has been shown in research to prevent carcinogenesis and immunosuppression caused by light exposure (Bissett et al., 2006). It has also shown to reduce the severity of acne lesions, better skin outcomes related to bullous pemphigoid, which are by fluid-filled blisters on the skin, and improve the skin's reaction to photoaging by averting a reduction of collagen in the dermis (Bissett et al., 2006). When applied topically, nicotinamide can help reduce transepidermal water loss which increases the moisture content of the skin, helping with the health of the epidermal barrier. Through its use on protein synthesis, more keratinocytes can be produced, allowing for the skin to have more cells for the stratum corneum to replace itself with. Nicotinamide also helps to increase the amount of NADP and can increase the production of ceramide, which is important for maintaining skin moisture. The structure of the skin, as well as wrinkles, can be improved through nicotinamide application. Other potential functions of topical nicotinamide include a reduction in acne severity and amounts, rosacea, and irritation secondary to the anti-inflammatory properties of nicotinamide (Bissett et al., 2006).

Topical niacinamide has been found to limit the production of sebum which can lead to reduction in acne and the size of pores, as well as benefit the texture of the skin (Farris, 2014). Within a clinical study done on Caucasian subjects, a significant reduction of sebum and inflammation occurred after four weeks of treatment (Farris, 2014). This helps in preventing rubor and benefiting the appearance of rosacea. After 4 weeks, niacinamide treatment demonstrated a potential in limiting hyperpigmentation by preventing the transfer of melanosomes to keratinocytes. There was also a stimulation of the synthesis of collagen, promoting less wrinkles that was significant after 12 weeks of treatment (Farris, 2014).

Niacinamide is able to protect the skin barrier from water loss and loss of integrity, allowing for a lower incidence of photoaging (Bissett et al., 2004). In addition, it can prevent photoaging side effects of collagen loss from the dermis and help decrease the appearance of aging caused by light exposure. The skin barrier has also improved with topical niacinamide as well. In a double-blind clinical trial, 50 Caucasian female subjects were given either a control moisturizer or the same moisturizer except with 5% niacinamide added in. At 8 and 12 weeks of using topical 5% niacinamide moisturizer, facial images indicated a significant reduction in sallowing of the skin, preventing a yellow hue to the skin that is a sign of photoaging (Bissett et al., 2004).

Nicotinamide could be useful for acne, according to a review of current literature (Mohsen et al., 2015; Walocko et al., 2017). Nicotinamide provides skin with plenty of oxygen and may prevent acne (Mohsen et al., 2015). Since nicotinamide can provide anti-inflammatory benefits without potential risks of antibiotic resistance like other acne treatments, it is a promising contender. This review, published in *Dermatologic Therapy*, involved individuals with mild acne given nicotinamide in some form or combination. The review found that, out of 10 studies that met the review criteria on PubMed, eight studies found a reduction in acne severity and amount (Walocko et al., 2017). Six of those studies were over topical application of nicotinamide and two were over oral supplementation. One topical study found that sebum excretion and levels were reduced in 21.3% of the 130 male and female Japanese and Caucasian subjects over a four week period. Based on this reduction, it appears that topical nicotinamide may aid in protecting the barrier of the skin thus preventing infection. Both oral studies showed a reduction in acne, but were ingested in combination with other ingredients, negating any ability to determine if the benefit was due to the nicotinamide (Walocko et al., 2017). A different

clinical study of 198 subjects found that acne, as well as rosacea may also be treated effectively with niacinamide orally at a dose of 750 mg (Prousky et al., 2011). Hence, more research is indicated to better understand the effects of oral supplementation of vitamin B3 on acne.

Most of the research investigating niacinamide's influence on acne has been topical use (Ashkani Esfahani et al., 2015; Bains et al., 2018). Topical niacinamide could be utilized for acne treatment as it has shown a suppressive effect on sebum production. Nicotinamide has anti-inflammatory and sebostatic properties which is important because acne can occur due to production of too much sebum or inflammation (Bains et al., 2018). Nicotinamide works to inhibit activator protein 1 which is involved in the inflammatory processes associated with acne (Bains et al., 2018). Furthermore, a 4% niacinamide treatment was used on human subjects and showed a significant reduction in inflammatory papules (Ashkani Esfahani et al., 2015). The anti-inflammation effects of nicotinamide were also shown in cases of rosacea, where horny layer moisture was improved and was paired with a decreased red color of the skin (Ashkani Esfahani et al., 2015).

The common strength of topical niacinamide treatments for acne within the current research was 4% (Bains et al., 2018; Byrd et al., 2018; Hakozaki et al., 2002). A 4% niacinamide gel lowered the amount and severity of acne within subjects (Prousky et al., 2011). A different study from 1995 indicated that topical niacinamide, at a strength of 4%, could be used twice a day for eight weeks to treat acne effectively (Hakozaki et al., 2002). In a group of 160 adult subjects, both male and female, given nicotinamide or erythromycin gel at 4% two times a day for 8 weeks, there was no significant difference between the two for reduction in acne lesions themselves. However, the subjects who received the nicotinamide treatment had significantly less oil production (Bains et al., 2018). This same sebum reduction was found in a randomized

trial that showed a significant sebum production reduction in those using a nicotinamide moisturizer compared to a placebo (Bains et al., 2018). Topical use of 4% niacinamide has shown evidence to be useful in the treatment of acne.

Nicotinamide also has shown anti-inflammatory properties (Scatozza et al., 2020). Nicotinamide works by inhibiting nuclear PARP-1 enzymes and inhibiting the production of IL-12, TNF-alpha/gamma, and IL-1 by controlling NFkB-mediated transcription. B3 suppresses cytokine-mediated induction of nitric oxide synthase and inhibits leukocyte chemotaxis and the release of lysomal enzyme, all of which work to prevent inflammation (Bains et al., 2018).

Niacinamide has wound healing potential (Ashkani Esfahani et al., 2015; Weinreich et al., 2010). Utilizing oral nicotinamide, one study showed a reduction in wound healing time from 15-17 days to 7-10 days compared to the control (Ashkani Esfahani et al., 2015). Parenteral administration of niacin showed an increase in the vitality of the skin and better wound healing significantly (Ashkani Esfahani et al., 2015). In a study done with rats, niacin performed significantly better than isoniazid for healing wounds (Weinreich et al., 2010). Niacin was able to decrease the wound area more effectively than the body was able to heal wounds without it(Weinreich et al., 2010).

When exposed to UVA radiation, nicotinamide has shown the ability to increase the numbers of collagen, fibrillin, and elastin while lowering matrix metalloproteinase (MMP) within fibroblasts in the dermis (Boo, 2021; Scatozza et al., 2020). Nicotinamide increased in vitro wound healing due to its association with increased collagen synthesis (Boo, 2021). It also has shown an ability to heighten the amount of NAD+ and energy in the form of ATP within cells in the skin (Scatozza et al., 2020). This is important for wound healing and proper skin cell

function. Just as with niacin's ability to cause vasodilation to induce flushing of the skin, this same property could be used to accelerate wound healing as well (Weinreich et al., 2010).

Nicotinamide has anti-aging effects by amplifying the production of collagen in the skin and decreasing the higher amount of glycoaminoglycosides in the dermis of the skin when the skin is damaged by solar irradiation (Bains et al., 2018). Niacinamide also influences aging skin by increasing the production of keratin and proteins, as well as promoting the creation of ceramide. By doing so, this can lead to improvement in structure and texture of the skin (Priyadharsini, 2016). Through the use of a 5% nicotinamide cream in 30 Japanese women, results showed a significant reduction in rough texture of skin and wrinkles as compared to the "vehicle only cosmetic" (Bains et al., 2018). In addition, a study of a topical nicotinamide emulsion of 2.5% demonstrated an ability to reverse age-related damage in the skin with regards to surface structure and texture (Ashkani Esfahani et al., 2015).

As one ages, the NAD and NADP supply in cells depletes (Ashkani Esfahani et al., 2015; Boo, 2021). Treating cells of older adults with nicotinamide appeared to restore cellular function of the mitochondria and expression of genes to levels seen in younger adults (Boo, 2021). In cell cultures, niacinamide returned levels of NADP in aging cells to levels of youthful cells. NAD and NADP are also useful in the synthesis of collagen. Additionally, niacinamide increased the growth of both epidermal and dermal cells, suggesting the possibility of niacinamide as treatment for some age-related changes in the skin (Ashkani Esfahani et al., 2015).

Another portion of aging skin that niacin could potentially treat is wrinkles (Bissett et al., 2006). The mechanisms proposed for wrinkle reduction associated with niacinamide include a boost in the synthesis of collagen and lower dermal glycosaminoglycan (GAG) levels (Bissett et al., 2006). In a double-blinded, placebo controlled, split-face study, subjects were healthy

females, aged 35-60 years old, Caucasian in race, and were not pregnant (Bissett et al., 2006). All subjects had baseline wrinkle grades of 2.0 or higher, meaning there was a presence of wrinkles even if they were only shallow, and textured skin on the cheeks. The study began with a washout period that lasted two weeks in which all subjects used the same facial products. The cleanser that was used in the washout period remained a part of the subject's facial routine throughout the 12-week study. However, the moisturizer was switched for all subjects, half receiving a placebo and half receiving a moisturizer with niacinamide in it. After 8 weeks of treatment, subjects undergoing the niacinamide treatment had a significant reduction in hyperpigmented spots and their intensity. At the same point in time, the treatment group also noticed a reduction in wrinkle appearance that was significant compared to the placebo. In addition, the treatment group saw a depletion in the blotchiness of the face accompanied by red color throughout the treatment, but the depletion was only significant at the 12th week. The treatment group also saw significant prevention in sallowing of the skin. Viscoelastic properties and elastic recovery both improved throughout the study for niacinamide subjects with the improvement being significant at week 12. This could potentially be due to niacinamide's ability to enhance remodeling of the dermis through its influence on skin collagen and avoidance of glycation within the dermal matrix (Bissett et al., 2006).

Niacin can cause skin toxicity, leading to flushing and irritation of the skin (Dunbar & Gelfand, 2010). The skin is important in regulating body temperature and is also the largest of our organs that are a part of the immune system. As a part of the skin toxicity components of niacin, disruption of the immune portion of the skin and its ability to regulate temperature are seen. Swelling, pain, warmth, and redness are all seen with both deficiency and excessive amounts of niacin supplementation. Niacin deficiency is seen as dermatitis. When niacin is

consumed in excess as seen with supplementation, the symptoms that are exhibited could be likened to hypersensitivity. The exposure to niacin has also been noted to cause itching. The entire combination of these symptoms has been described with the word flushing, mainly due to the most common symptom of redness (Dunbar & Gelfand, 2010). Niacin flushing and all its components of vasodilation, rubor, swelling, and increase in skin temperature are due to niacin's ability to bind to receptors within immune cells ("Study paints clearer picture of 'nasty' side effects from well-known heart drug", 2017).

The flushing caused by niacin is seen mostly as a red color in the skin known as rubor, as well as increased skin temperature with the vasodilation of the blood vessels, bringing warm blood to the skin's surface (Kamanna et al., 2009). Tingle or itch sensations are also common. Within 12-45 minutes post niacin treatment, PGD2, PGE2, PGI2 and metabolites all have been shown to increase in amount. These prostaglandins are responsible for the vasodilation following niacin treatment. The receptors of these prostaglandins also play a role in niacin flushing by promoting blood vessel relaxation. GPR109A, known as G protein-coupled receptor 109A, elevates the levels of prostaglandins and arachidonic acid. These elevated levels turn on the prostaglandin E receptor 4, as well as prostaglandin D2 and E2 receptors. These receptors are located in the capillaries and promote the dilation of blood vessels in the skin. Niacin plays a role in this process by its interaction with the dermal Langerhans cell that activate GPR109A (Kamanna et al., 2009).

In addition to flushing, niacin can influence other areas of skin color (Bains et al., 2018). Sallowing of the skin, which is the loss of color in which skin becomes more yellow or brown in color, is prevented by nicotinamide. It is caused whenever there is glycation between a protein and glucose, resulting in the emergence of products which are cross linked and give the skin a

yellow color. Nicotinamide is said to have anti-glycation properties since it is a precursor to NADPH (Bains et al., 2018). Thus, nicotinamide's effects can include regulating the color of the skin.

In addition to prevention of sallow skin, nicotinamide may improve hyperpigmented spots over time (Boo, 2021). In a study of 18 women of Japanese descent, the subjects had nicotinamide-containing moisturizer applied to half of their face while a placebo was applied to the other half of their face (Boo, 2021). Side-by-side comparisons of the treatment at 4 and 8 weeks showed a significantly lower number of hyperpigmented spots in the side that received the nicotinamide treatment. Similar results were found in a subsequent study with 79 women of Japanese descent (Boo, 2021). Within studies done on the topical utilization of nicotinamide, it was also shown that nicotinamide has skin lightening abilities within a concentration of 4-5% (Boo, 2021). More research can be done to show if other concentrations of nicotinamide are also effective in the treatment of hyperpigmentation.

Research has reported that niacinamide may inhibit the transfer of melanosomes to keratinocytes within research (Bains et al., 2018; Hakozaki et al., 2002). This reduction in transfer was seen at 35-68% reduction. Within the same experiment, the side of the subjects' faces that were treated with niacinamide showed a significant reduction in hyperpigmentation than the vehicle side after 4 weeks. The significance remained present even at week 8 of the study. Within the study results, the subjects themselves perceived the niacinamide treatment to have a greater efficacy in hyperpigmentation treatment than the vehicle. The study also found that groups in which the subjects used moisturizer daily with niacinamide added had a lighter basal skin color and less hyperpigmentation (Hakozaki et al., 2002). Likewise, in a double-blinded randomized controlled trial of 202 subjects, there was a significant reduction in

visible pigmentation and spots on the subjects face that used the nicotinamide formula (Bains et al., 2018). Nicotinamide may also be used to lighten the skin against tanning due to its ability to prevent the transfer of melanin to keratinocytes (Bains et al., 2018). It appears that nicotinamide has the potential of inhibiting the transfer of melanosomes from melanocytes into keratinocytes (Bains et al., 2018). This is the mechanism proposed by researchers for how niacinamide influences skin pigmentation.

When looking at cultured skin cells, nicotinamide has shown an ability to improve different parts of the skin barrier, such as in improving production of components like ceramides and free fatty acids (Boo, 2021). Some mechanisms exist to explain these benefits. NADPH is part of the production of fatty acids and ceramides, which is essential for the skin barrier, while NADH hinders enzymes that help produce glycosaminoglycans. Just like with niacin's influence on other portions of the skin barrier, niacin is able to promote the skin barrier's health through the production of proteins. Niacin plays a role in protein synthesis for structure of the skin barrier and collagen. In addition, nicotinamide can promote ceramide synthesis by activating the mRNA expression of serine palmitoyl transferase, the key enzyme for the synthesis of sphingolipids. Niacinamide also can stabilize mast cells by impeding cAMP phosphodiesterase, preventing nitric oxide synthase activity, and subduing antigen-induced lymphocyte transformation. Additionally, B3 is a precursor of NAD. Therefore, it prevents the depletion of energy from the cells (Bains et al., 2018). Through all of these activities, vitamin B3 is able to help maintain a healthy skin barrier.

The integrity of the stratum corneum, as well as elasticity and moisture of the skin have all been found to improve within studies regarding topical application of niacinamide (Farris, 2014). In a study over dry skin, also known as xerosis, in the winter, subjects were given topical

niacinamide to use. The results of its use were an improvement in the barrier of the epidermis and prevented the loss of water from the epidermis with improved moisture of the horny layer also present (Gehring, 2014). Moisturizers that contain nicotinamide have also been shown in studies to effectively treat atopic dermatitis. Atopic dermatitis results in lower levels of ceramides and a higher level of transepidermal water loss, thus resulting in a weaker barrier function of the skin.These studies reported that there was a 2-3 times increase in the presence of free fatty acids due to nicotinamide use, which would be of benefit to the skin barrier (Bains et al., 2018). In a randomized, controlled observational study with 50 subjects with rosacea, a nicotinamide containing moisturizer helped enhance the barrier of their skin (Boo, 2021).

The horny layer within the epidermal barrier is made up of lipids, free fatty acids, ceramides, and cholesterol (Ashkani Esfahani et al., 2015). Nicotinamide has demonstrated that topically it increases the synthesis of the lipids within the horny layer, thus improving the moisture of the epidermal barrier (Ashkani Esfahani et al., 2015). A study conducted on 292 subjects compared the consumption of nicotinamide with a placebo on transepithelial water loss. After 500 mg twice a day for 12 months, the nicotinamide group had a water loss reduction of 6 -7% compared to the placebo group (Bains et al., 2018). As one ages, the NAD+ supply in cells depletes. In another study, treating cells of older adults with nicotinamide showed a restoration in function of the mitochondria and expression of genes to levels similar to younger adults (Boo, 2021). Overall, topical use of nicotinamide can help with the health and moisture level of the skin.

Nicotinamide has shown to be protective against skin damage due to UV radiation, along with decreasing the speed of the development of a precancerous condition called actinic keratosis (Chen et al., 2015). It appears that nicotinamide has an ability to lead to the healing of DNA that

has been damaged by UV irradiation. This supports nicotinamide's ability to be chemoprotective (Scatozza et al., 2020). Niacinamide has also been shown to improve the skin's reaction to retinoids and increase their effectiveness when treating photodamage (Farris, 2014).

The mechanisms involved within this skin cancer prevention point to niacin's ability to increase the levels of NAD in the skin and prevent both photocarcinogenesis and photo-immunosuppression (Gensler et al., 1999). Low levels of niacin negatively influence DNA repair processes, including expression of p53 and poly(ADP-ribose) polymerase (PARP) activity but subsequently encourages malignant transformation. Both p53 and PARP are needed within the cells to respond to DNA damage caused by UV irradiation (Gensler et al., 1999). Due to being a precursor to NAD, niacin could help prevent skin cancer by preventing p53 and PARP activity (Gensler et al., 1999).

Cell deterioration, cancer, and aging are all influenced by niacinamide (Bains et al., 2018). Niacinamide works to inhibit the enzyme PARP-1, which promotes said conditions (Bains et al., 2018). UV rays excessively activate PARP-1 enzyme which in turn further depletes NAD in cells which leads to premature cell death (Bains et al., 2018). Nicotinamide helps to restore energy in the cells due to its role as a precursor to NAD and NADPH. It also averts the overactivation of the enzyme PARP-1 by way of a negative feedback loop. In addition, nicotinamide has the potential to shield cells against immunosuppression due to UVA and UVB rays (Bains et al., 2018). This points to niacin's potential role in the prevention of skin cancer.

Niacin additionally acts as an antioxidant and thus protects against oxidative damage to DNA (Gensler et al., 1999; Walocko et al., 2017). It has been reported that niacin may prevent photocarcinogenesis and photo immunosuppression in mice. Consumption of niacin leads to higher levels of NAD in skin, even if the skin has been exposed to UV radiation repeatedly.

These results suggest that prevention of skin carcinogenesis by supplemental niacin may be due to the blockage of UV-induced immunosuppression and cutaneous NAD depletion. Maintenance of NAD levels in skin with consequent PARP enhancement of base excision repair of UV-induced oxidative DNA damage likely contributes to the skin cancer prevention capacity of supplemental niacin (Gensler et al., 1999). Nicotinamide could be a potentially helpful part of repairing UV radiation damage since NAD supplies a substrate needed by nuclear enzyme poly-ADP-ribose polymerase which helps heal damage caused by genotoxic stress (Walocko et al., 2017).

Deficiency in niacin can lead to the skin being sensitive to the sun, as seen in studies done over niacin deficiency and skin cancer in animals (Benavente et al., 2009). Through its deficiency, models of cell cultures have shown that early skin cancer development is characterized by signaling events that are dependent on NAD. Reactive oxygen species are found in higher concentrations within the deficiency of niacin. Skin cells that are deficient in vitamin B3 are more susceptible to damage from UV radiation due to the lack of NAD+ (Benavente et al., 2009). Within mice, nicotinamide supplementation was used to impede the development of photo-carcinogens (Ashkani Esfahani et al., 2015). Oral supplementation of nicotinamide reduced the oxidative damage to the skin of rats due to UV radiation, as well as reducing the inflammation and restoring antioxidants to the skin in the process (Boo, 2021).

Oral supplementation showed a beneficial role in the partial prevention of skin cancer within mice exposed to ultraviolet light (Prousky et al., 2011). Groups of mice were fed diets supplemented with niacin at 0.1%, 0.5%, and 1.0%, as well as having a control group. The beginning incidence of skin cancer within the control group was 68%. The supplementation groups led to a decrease in skin cancer incidence by 60%, 48%, and 28% respectively after 26.5

weeks of ultraviolet therapy. The tumor incidence was significantly reduced within mice fed the 0.5% and 1.0% niacin supplements as opposed to the 0.1% supplementation group and the control group. The total number of tumors within each mouse was significantly lower in mice fed the 0.5% or 1.0% supplementation diet. Although there was a reduction in the incidence of tumors on the supplementation diets, it must be kept in mind that even the highest supplementation group of 1.0% did not completely prevent the development of tumors within mice that were exposed to ultraviolet radiation (Gensler et al., 1999). Within rats, deficiency of niacin appears to make rats more inclined towards instability within their genomes and more likely to experience skin cancer (Prousky et al., 2011). Supplemental niacin potentially has the ability to partially prevent this genome instability.

Niacin supplementation appears to lower skin cancer rates within mice and has been found to prevent immunosuppression due to light exposure within humans (Prousky et al., 2011). Topical niacin has been found to be able to make the barrier of the skin thicker and function better (Prousky et al., 2011). A phase 3, double-blinded, randomized, controlled trial study involving 386 subjects, studied the results of each subject using either 500 mg of topical niacinamide treatment or 500 mg of a placebo for 12 months. The subjects each had at least two incidences of nonmelanoma skin cancer within the past five years. At the end of the study, the nicotinamide receiving group displayed a decreased rate in nonmelanoma skin cancer by 23% compared to the placebo group (Chen et al., 2015). In the third phase of this clinical trial, two doses of 500 mg of nicotinamide a day had a significant reduction in nonmelanoma skin cancer cases, as well as cases of actinic keratosis cases. It is important to note that the effect of those dosages stopped six months after the doses stopped, indicating that those with high sun exposure may be benefitted from niacin supplementation (Bains et al., 2018).

In an in vitro study, nicotinamide worked to lower the incidence of melanoma cell counts by almost 90% (Scatozza et al., 2020). The use of nicotinamide in vitro caused an increase in cell death, or apoptosis. Additionally niacinamide was able to increase the time that cells spent in G1 phase and limit time spent in S and G2 phases. This limits the time cells are able to replicate and grow. However, nicotinamide showed significant results in the growth of tumors when studied in vivo, suggesting that nicotinamide's ability to protect the body might be limited within subjects with skin cancer (Scatozza et al., 2020).

Although the mechanisms for niacin's influence on the skin have been extensively researched, other influences have a limited amount of human studies (Bains et al., 2018). It has been noted that niacin may have an anti-psoriatic effect as an anti-inflammatory agent, having the ability to prevent the expression of ICAM-1 and MHC-II, and inhibiting the production of IL-12, TNF-alpha/gamma, and IL-1 (Bains et al., 2018). Research has shown that antimicrobial effects of niacinamide may be due to the mechanism that nicotinamide inhibits nuclear PARP enzymes, hence preventing the integration of proviral DNA. Niacinamide has also been reported to inhibit Propionibacterium acnes and mycobacterium tuberculosis by acting on Sir2 enzymes which are NAD dependent deacetylases (Bains et al., 2018). Research indicates that vitamin B3 can influence the skin in many ways, both good and bad.

B5 overview - pantothenic acid

Vitamin B5 is also known as filtrate factor, calcium pantothenate, and pantothenic acid (Priyadharsini, 2016). It has also been referred to as the anti-stress vitamin. Chemically, pantothenic acid consists of a beta-alanine linked to pantoic acid. Pantothenic acid is important for liver detoxification and it is sensitive to heat (Gheita et al., 2019). It is found in certain fish,

egg yolk, milk, yeat, meat, liver and kidney, molasses, cereals, legumes, sweet potatoes, and is highest in royal jelly. The RDA is 6-9 mg per day for adults (Priyadharsini, 2016).

Pantothenic acid is absorbed into the intestines by a saturable process and by simple diffusion during low and high concentrations respectively ("Office of dietary supplements - pantothenic acid", n.d.). It is useful in many metabolic capacities due to its connection with acetyl CoA. Pantothenic acid is crucial to the creation of coenzyme A, which is used especially when synthesizing within the creation of fatty acids and oxidizing pyruvate within the tricarboxylic acid cycle, as well as cholesterol and acetylcholine synthesis ("Office of dietary supplements - pantothenic acid", n.d.). Pantothenic acid is an especially vital nutrient involved in energy production from the metabolism of the macronutrients (Dalens & Prikhnenko, 2015).

Pantothenic acid has many uses within the dermatology field (Gheita et al., 2019; "Micronutrients in human development – part 3", 2013; "Vitamin B5 (pantothenic acid)", n.d.). Some of the current research examines the use of pantothenic acid derivatives and its helpfulness in treating atopic dermatitis. Studies found that pantothenic acid has the ability to help treat and manage mild to moderate cases of childhood atopic dermatitis ("Vitamin B5 (pantothenic acid)", n.d.). Other studies found pantothenic acid creams are beneficial in treating the side effects of isotretinoin use ("Vitamin B5 (pantothenic acid)", n.d.). Pantothenic acid also enhances the skin barrier and moisturizes the skin, improving the ability of the skin barrier to retain moisture. Additionally, these both have a positive effect on wound healing (Gheita et al., 2019). Panthenol, a B5 precursor, improves the moisture supply within the skin. It can be applied topically and upon absorption will then be converted to pantothenic acid, which is transported to deeper skin tissues to improve moisture and water binding. Panthenol has also been found to help UV radiation exposed skin when applied topically. Research has conveyed that it may prevent

inflammation and rubor, however it can also have some negative effects on the skin ("Micronutrients in human development – part 3", 2013). Common side effects of vitamin B5 topical use include hypersensitivity presenting as rashes, swelling, hives, and itching as well as jaundice ("Vitamin B5 (pantothenic acid)*",* n.d.).

Pantothenic acid has shown to have beneficial impacts on acne (Yang et al., 2014). Adults with mild to moderate acne were participants in a randomized double-blinded, placebo-controlled study. The subjects were given either an oral pantothenic acid supplement or a placebo for the 12 weeks of the study. Results showed that the supplement was safe and tolerated by the subjects, as well as effective in significantly decreasing the number of acne lesions on the face after the 12 weeks of treatments had concluded (p=.02). The counts of the lesions reduced significantly in the supplement group by 68.21% compared to the placebo. The supplement also reduced the inflammatory lesions significantly (Yang et al., 2014). Oral pantothenic acid supplementation shows potential for treatment of acne.

Pantothenic acid is involved in CoA metabolism and thus has an influence on the function and integrity of the barrier of the epidermis and differentiation of keratinocytes that is essential in protecting the stratum corneum (Yang et al., 2014). Clinical trials have shown the ability of topical pantothenic acid to soften the skin. This, paired with the antibacterial property of pantothenic acid, may play a role in the ability of the vitamin to reduce acne (Yang et al., 2014). Limitations of the research included insufficient time and lack of severity of the acne, leading to the possibility that the acne improved on its own without outside help. The long-term effects of this treatment were not studied, meaning the significant improvement may not be present further down the road. In an 8 week study, oral pantothenic acid decreased acne lesions on the face (Yang et al., 2014). A randomized placebo controlled trial that was double blinded

also found that pantothenic acid supplementation improved acne on the face (Yoshii et al., 2019). This improvement was thought to be due to vitamin B5 and the connection to coenzyme A. CoA is converted back to pantothenic acid or converted to cysteamine when B5 deficiency occurs. The conversion to cysteamine can result in inflammation because it inhibits signaling of PPAR γ (Yoshii et al., 2019).

Dexpanthenol creams can be used effectively to treat superficial wounds of the skin, as seen in a small study of 20 adult subjects, both male and female (Proksch & Nissen, 2002). Dexpanthenol is converted to pantothenic acid in the tissues. Pantothenic acid is used for CoA which is involved in the production of fatty acids and sphingolipids. Fatty acids and sphingolipids are parts of the stratum corneum and help maintain the integrity of the cell membrane (Proksch & Nissen, 2002). When compared to a placebo and a control, dexpanthenol containing creams accelerated wound healing significantly (Proksch & Nissen, 2002). Hydration of the stratum corneum and skin roughness were also improved more in the dexpanthenol cream than the other two. It significantly lowered the inflammation of the skin seen through reduced red pigmentation (Proksch & Nissen, 2002). During wound healing, keratinocytes need to be replaced. Coenzyme A needs to increase during this time to synthesize more fatty acids and sphingolipids. Pantothenic acid works to help with coenzyme A synthesis (Proksch & Nissen, 2002). However, pantothenic acid is unstable and is not able to be topically applied, which is why the form of dexpanthenol is used in topical products. It poses no downside due to its ability to be easily converted to pantothenic acid within the tissues ((Proksch & Nissen, 2002).

Pantothenic acid has shown beneficial roles within the skin (Gheita et al., 2019; “Micronutrients in human development – part 3”, 2013; “Office of dietary supplements - pantothenic acid”, n.d.; Proksch & Nissen, 2002; “Vitamin B5 (pantothenic acid)”, n.d.; Yang et

al., 2014; Yoshii et al., 2019). Current research points to pantothenic acid's ability to be used for acne and wound healing within the future. Further research over topical and oral supplementation is warranted to expand the knowledge and evidence surrounding pantothenic acid's ability to influence the skin.

B6 overview - pyridoxine

Vitamin B6, known as pyridoxine or pyridoxal, is found in three forms naturally (Priyadharsini, 2016). These forms are pyridoxine, pyridoxal, and pyridoxamine. Chemically, these essentially are a combination of an alcohol, aldehyde, and amino acid respectively. They are used to form pyridoxine-5'-phosphate (PNP), pyridoxal phosphate (PLP), and pyridoxamine-5'-phosphate (PMP) (Priyadharsini, 2016). Toxicity only has been seen within superdoses of the vitamin from supplements ("Vitamin B6 toxicity", n.d.). Pyridoxine is involved in the synthesis and breakdown of amino acids. Deficiency can cause dermatitis ("Office of dietary supplements - pantothenic acid", n.d.). Pyridoxine is found predominantly in liver, milk, fish, egg yolk, fortified cereal products, starchy vegetables such as potatoes, legumes, whole grains, avocados, and bananas. The adult RDA is 1.5-2.5 mg per day (Priyadharsini, 2016).

Pyridoxine absorption occurs in the jejunum and metabolism occurs in the liver(DiBaise & Tarleton, 2019). Pyridoxine is easily absorbed by mucosal cells through passive diffusion. It is transported through the bloodstream and excess vitamin is excreted by the kidneys through the urine (DiBaise & Tarleton, 2019). Pyridoxine is involved in over 100 reactions in the human body within its role as a cofactor. These reactions include the metabolism of the macronutrients and as a coenzyme in the metabolism of amino acids (Kato, 2012; "Vitamin B6 deficiency", n.d.). Pyridoxine deficiency is linked to higher levels of homocysteine and cystathionine since

these amino acids are metabolized using a cofactor of pyridoxine phosphate, which pyridoxine is a precursor for (Lakshmi et al., 1990).

Pyridoxine serves as a radical scavenger (antioxidant), and has antiglycation and anti-inflammatory properties (Kato, 2012). It is used in production of neurotransmitters, metabolism of lipids, amino acids, and glucose, as well as the expression of genes and the production of hemoglobin ("Vitamin B6 toxicity", n.d.). Pyridoxine can inhibit the peroxidation of lipids and is involved within the first portion of the production of porphyrin (Kato, 2012; "Vitamin B6 deficiency", n.d.). It is also involved in amino acid decarboxylation, cysteine metabolism, production of heme and niacin, glycogenolysis, and transamination. Within the skin, pyridoxine deficiency is seen as erythema, dermatitis, pellagra, and intertrigo (Priyadharsini, 2016).

Properties of pyridoxine include that of anti-oxidative, glycation, inflammation, and angiogenesis (Kato, 2012). It also has anti-dermatitis factors. When consumed in large doses, pyridoxine may have phototoxic activity when exposed to UV radiation (Kato, 2012). When being exposed to the sun, high doses of pyridoxine should be avoided (Kato, 2012). Lower levels of pyridoxine have been found to promote inflammation, as noted in studies regarding how pyridoxine influences cardiovascular health (Kato, 2012). Pyridoxine deficiency can be linked to inflammation. Research has found that low circulation of PLP is linked with inflammatory markers and the presence of inflammatory disease. However, there is no permitted causal inference between the low concentration of PLP and inflammation due to the cross-sectional study design (Morris et al., 2009). Despite that, the study reported that high levels of pyridoxine protected against inflammation, as well as a higher need for pyridoxine when inflammation is present (Morris et al., 2009).

Pyridoxine is important for the growth and development of skin, but also for the maintenance of its health (Kato, 2012). Pyridoxine deficiency has demonstrated negative cutaneous influences. Pyridoxine deficiency is correlated with dermatitis potentially due to its deficiency impairing the biosynthesis of collagen (Kato, 2012). This deficiency has been associated with itchy rashes and cheilitis ("Vitamin B6 deficiency", n.d.). In rats the very first manifestation reported related to pyridoxine deficiency was skin lesions. In humans, one of the first reports was its connection to seborrheic dermatitis (Coburn et al., 2003).

Pyridoxine excess has also shown cutaneous manifestations (Kato, 2012; Rezakovic et al., 2015; "Vitamin B6 deficiency", n.d.). Toxicity of pyridoxine has been seen with manifestations of sensitivity of the skin to light and painful cutaneous eruptions. Toxicity can also alter the sensory nerves in the skin to the feelings of vibrations, temperature, and toughness ("Vitamin B6 deficiency", n.d.). It has been found that pyridoxine excess can also cause dermatitis just like deficiency, as well as increase sensitivity to light and UV rays. Within normal levels, pyridoxine can help mediate photosensitivity and has been found to prevent the growth of melanoma both in vivo and in vitro (Coburn et al., 2003). High consumption of pyridoxine can intensify skin tumorigenesis induced by UV rays (Kato, 2012). The use of pyridoxine topically has been shown, through studies, to exacerbate phototoxicity in the skin due to the UV rays (Kato, 2012). There also is potentially a relationship between UV-radiation and pyridoxine, leading to increased presence of cancer in the skin (Kato, 2012). In mice, the groups were exposed to the same amount of UV-radiation after different amounts of pyridoxine treatments for 18 weeks. The highest treatment with 35 mg pyridoxine hydrochloride (PN HCL)/kg had the highest number of skin tumors per mouse from week 14 onward. The lowest treatment of 1 mg PN HCL/kg had the lowest incidence of tumors all throughout the study (Kato, 2012). In

amounts high above the recommended daily values, pyridoxine can be a risk factor for rosacea, as evidenced by a case study assessing rosacea development in a patient consuming 25 milligrams of pyridoxine for pulmonary tuberculosis treatment along with isoniazid (Rezakovic et al., 2015).

Pyridoxine has many roles and functions within the human body (Kato, 2012; Lakshmi et al., 1990; Morris et al., 2009; Rezakovic et al., 2015; "Vitamin B6 deficiency", n.d.). Pyridoxine and its functions as an antioxidant and anti-inflammatory agent make it beneficial for the hea;th of the skin and treatment and prevention of certain skin conditions. However, excess amounts of pyridoxine have also been shown to cause skin manifestations.

B7 overview - biotin

Vitamin B7 is called biotin, vitamin H, and coenzyme R (Priyadharsini, 2016). The H in vitamin H stands for the word "haut" meaning skin in German ("Biotin responsive dermatoses", n.d.). Chemically, biotin is a heterocyclic carboxylic acid that also contains sulfur (Priyadharsini, 2016). Biotin acts as a cofactor for enzymes involved in carboxylase synthetase. These enzymes are involved in the production of fatty acids as well as the TCA cycle and other pathways ("Biotin responsive dermatoses", n.d.). Deficiency is seen as dermatitis and could lead to rashes on the face ("Office of dietary supplements - pantothenic acid", n.d.). Rich food sources of biotin include chocolate, milk, mushrooms, liver, eggs, and peanuts. The RDA for biotin is 30 micrograms for all non-lactating adults above the age of 19 years (Priyadharsini, 2016).

Biotin absorption occurs in the small intestine (DiBaise & Tarleton, 2019). Bacteria in the gut are also able to produce biotin. Excess of the vitamin that is in the gut is excreted in the feces while excess serum biotin is excreted in the urine by the kidneys (DiBaise & Tarleton, 2019).

Biotin is utilized to help regulate metabolism pathways of the macronutrients through the carboxylase enzymes that it is associated with. These enzymes are: pyruvate carboxylase, beta-methylcrotonyl-CoA carboxylase, propionyl-CoA carboxylase, and Acetyl-CoA carboxylase (“ The function of biotin”, n.d.). Biotin is also involved in the transformation of proteins and amino acids (Dalens & Prikhnenko, 2015). Beyond macronutrient pathways, biotin has other influences on the body. Biotin also is helpful for the health of the human scalp through its prevention of seborrheic dermatitis, along with regulating oxidative stress in cells. Furthermore, biotin is important for the function of human NK lymphocytes, immune cells, and production of cytotoxic T lymphocytes (Agrawal et al., 2016). T lymphocytes are a part of the immune system that help to protect against infections and cancer (https://www.cancer.gov/publications/dictionaries/cancer-terms/def/t-lymphocyte) Additionally, biotin starvation is linked to increased synthesis of ROS (Agrawal et al., 2016).

Though rare, biotin deficiency results in scaly dermatitis, as well as various other conditions (“Biotin responsive dermatoses”, n.d.;Brown, n.d.; Priyadharsini, 2016). Biotin deficiency has also been shown to show itself as skin that is vibrant red in color and scaly in texture (Brown, n.d.). It is present most commonly on the face and around the genitals (“Biotin responsive dermatoses”, n.d.). Deficiency of biotin is additionally seen in the skin as xerosis and pallor (Priyadharsini, 2016). Cutaneous manifestations of biotin deficiency usually resolve within weeks of restoration of biotin levels with as little as 10 mg of biotin supplementation per day (“Biotin responsive dermatoses”, n.d.). Biotin plays a role in cell division, which is essential for skin renewal. However, a deficiency of biotin will negatively impact the skin's ability to renew itself (“Micronutrients in human development – part 3”, 2013).

Biotin deficiency could impair dendritic cells by preventing them from being activated (Agrawal et al., 2016). Dendritic cells that are biotin-deficient enhance T helper type 1/T helper type 17 (Th1/Th17) cells which subsequently increases inflammation. This is caused by the production of proinflammatory cytokines within biotin deficiency. Th17 has been found within genome-wide studies in humans to play a role in inflammation within the mucosal tissues like the skin. The IL-23/Th17 pathway can lead to skin conditions such as atopic dermatitis and psoriasis. Biotin deficient dendritic cells also have increased inflammation due to lowered activation of AMP-activated protein kinase (AMPK) as AMPK helps to regulate inflammation (Agrawal et al., 2016).

Animal studies involving mice have shown associations between biotin and skin (Agrawal et al., 2016; Proud et al., 1990). With mice that are biotin deficient, research has reported that inflammation is increased. Suggested mechanisms included diminished ability to activate AMP kinase when dendritic cells are in biotin deficient medium (Agrawal et al., 2016). Interestingly, biotin deficient rat biopsies found abnormal keratinization. In fact, the fatty acid content of the skin was 30% less than the controls (Proud et al., 1990). This lowered content of fatty acids can lead to less skin moisture and negatively impact the skin barrier.

Biotin also displays similar side effects on the skin in its deficiency as does zinc deficiency (Ogawa et al., 2019). Zinc deficiency, known as acrodermatitis enteropathica, is seen most commonly as lesions and contact dermatitis. The connection was shown within a study conducted on mice where the mice that were biotin deficient also showed low serum zinc levels. Other findings were lower counts of Langerhans cells in the epidermis, increased production of ATP in the skin, and increased contact dermatitis both in severity and time. Biotin deficiency potentially leads to zinc deficiency. After 9 weeks on a biotin deficiency diet, the mice showed

the same serum levels as mice put on a zinc deficient diet at 7 weeks (Ogawa et al., 2019). The lesions seen in biotin and zinc deficiency are thought to be due to the accumulation of ATP within the skin due to its enlistment of neutrophils. It was concluded in the study that biotin is essential for zinc equilibrium within the skin (Ogawa et al., 2019).

Human research has also shown connections between biotin and skin (Brown, n.d.). In infants, there were three observed cases of biotin deficiency. All three infants presented with scaly dermatitis and patchy skin on the face. In two of the cases, crystalline biotin administration was used to promote recovery within three to four weeks. The other case was lost to follow up. Administering a biotin supplement relieved symptoms within five days. When put on a hospital diet sufficient in biotin, the patients showed improvement in symptoms (Brown, n.d.).

Topical supplementation of biotin could improve skin texture (Kalman & Hewlings, 2021). The ingredient complex studied topically in a randomized double-blind study was a mixture of biotin and silicon called Lustriva. The high dose had 10 mg of biotin and 10 mg of silicon, while the low dose had 3 mg of biotin and 10 mg of silicon. Lustriva high dose (LHD) showed a significant reduction in wrinkles on the subject's face versus the placebo. This significant reduction occurred at 12 weeks of treatment. There was no difference between the elasticity of the skin for the LHD, low dose, or placebo groups. LHD showed significant improvement in the texture of the skin, significantly decreasing the roughness of the skin by the third visit (p=.009) (Kalman & Hewlings, 2021).

Biotin can be beneficial for the health of the skin (Agrawal et al., 2016; Brown, n.d.; Kalman & Hewlings, 2021; Ogawa et al., 2019; Proud et al., 1990). Both topical and oral studies have been primarily on biotin supplementation. However, most biotin research has been animal studies. More research should be done between biotin and its connection with human skin.

B9 overview - Folate

Vitamin B9 is also called folacin and vitamin M (Priyadharsini, 2016). Folate is named from the Latin word “folium” meaning leaf (Williams et al., 2011). Chemically, folate is a pteroic acid connected to a glutamic acid. Absorption at low concentrations is by a saturable process and higher concentrations require a non-saturable absorption. Folate is circulated in the body as 5-methyltetrahydrofolate. The metabolism of folate requires B12 as 5-MTHF becomes trapped within cobalamin deficiency. Folic acid is excreted both in the urine and feces. Folate is photoreactive and can be degraded by temperature, light exposure, and acidity (Donnenfeld et al., 2015; Drobnicka-Stepien et al., n.d.). Folic acid is also known as pteroylmonoglutamate and is a stable synthetic compound (Williams et al., 2011). Folic acid's biologically active form is known as folinic acid and results due to a vitamin C-dependent conversion (Priyadharsini, 2016). The most stable form that folic acid is found in is pteroyl-1glutamic acid. This form is used in a majority of folic acid supplements (Drobnicka-Stepien et al., n.d.). In 1998, the US government implemented the requirement for fortification of certain grain products with folate in order to prevent neural tube defects within the population (Williams et al., 2011). Folic acid deficiency is somewhat common because folates that are naturally occurring are vulnerable to oxidative degradation, especially when exposed to heat which makes it more difficult to metabolize (Zablotska et al., 2008). Within the human diet, folate is found in wheat, cauliflower, green vegetables, meat, milk, fish, and yeast. For individuals over the age of 14 that are not pregnant or lactating, the RDA is 400 micrograms per day (Priyadharsini, 2016).

Folate’s main role in the human body is its influence on methionine synthesis (“Office of dietary supplements - pantothenic acid”, n.d.). It is critical in the division of cells because it is able to participate in the transport of the fragments involved in DNA and RNA synthesis that

only have one carbon (Dalens & Prikhnenko, 2015). It also plays a crucial role in the repair and production of DNA (Knott et al., 2007). As an example, it has been reported that folate deficiency appears to decrease the ability of DNA to repair itself when exposed to reactive oxygen species (Williams & Jacobson, 2010). Folate deficiency has been linked to cancer formation within body tissues through an interference in the repair and integrity of DNA, as well as a disruption in methylation of nucleic acid (Donnenfeld et al., 2015). It is needed for the division of cells because one of its derivatives acts as a coenzyme for the one-carbon production of nucleotides. These derivatives function in amino acid metabolism, especially in the conversion of homocysteine to methionine (Drobnicka-Stepien et al., n.d.). There is a possibility that homocysteine and folic acid also play a role in clotting (New et al., 2011).

Folate deficiencies are more likely to appear on the skin due to the organ being one of the last places that folate is transported to in the body (Williams et al., 2011). Within the skin, deficiency is seen as pigmentation issues, as well as dermatitis (Priyadharsini, 2016). Folate is important to healthy skin and maintains that health by promoting cell turnover and repair of DNA (Williams & Jacobson, 2010). Keeping the skin barrier healthy and repairing it requires constant renewal of the epidermal cells and for DNA to go through its synthesis (S) phase within the cell cycle. Folate deficiency can extend the time that DNA is in its S-phase, as well as reduce the ability of the skin cells to renew themselves, allowing for skin cells and DNA to be vulnerable to cancerous mutations (Williams & Jacobson, 2010). Cells are negatively influenced by folate deficiency. Within a study utilizing cell cultures, keratinocytes were grown in a growth medium which promoted deficiency of folate. The cells showed a loss of viability by 20% at day 10 of the experiment. After 10 days, the cells were moved to a growth medium with folate supplementation. The cells regained all viability and returned to pre-treatment levels, showing

that treatment of folate deficiency can be completely reversible. It was also found that the DNA instability in the cells was completely reversed after normal levels of folate were reached again (Williams & Jacobson, 2010).

The folate deficiency found in skin cells after UVR exposure appears to be associated with skin carcinogenesis (Drobnicka-Stepien et al., n.d.; Williams & Jacobson, 2010). This is mostly due to the events that occur when skin is exposed to the sun. When exposed to UV radiation, folate within skin cells is broken down, leading to apoptosis of keratinocytes and a decreased ability of the cells to prevent photo- and oxidative-damage to the DNA. This creates an environment for unpredictability of the genome, promoting the development of skin cancer. The consequences of folate deficiency on the skin cells has been found to be reversible (Williams & Jacobson, 2010). High levels of dietary intake of folate could lead to genetic stability, thus protecting against the initiation of skin cancer development. However, an increase in folate levels could also increase proliferation of skin cells. In normal conditions, this would lead to the replacement of old skin cells with new ones at a faster rate. However, some research in animals found that decreased folate levels in cells that were neoplastic discouraged the growth and development of skin tumors (Donnenfeld et al., 2015). A meta-analysis described a possible association between folate and skin cancer, detailing that an increase in folic acid supplementation led to a decrease in skin cancer risk. However, this meta-analysis consisted of only 3 trials (Donnenfeld et al., 2015). Within a study utilizing 125 Caucasian individuals was made up of 46 healthy subjects and 79 that had a diagnosis of basal cell carcinoma. This study utilizing a Folic Acid Test, found that the individuals with a cancer diagnosis had lower concentrations of folic acid than the healthy subjects (Drobnicka-Stepien et al., n.d.). This lower concentration is potentially due to the fact that serum folate is required to heal DNA damage

secondary to UV radiation, especially cells that are rapidly dividing like those in the skin (Drobnicka-Stepien et al., n.d.).

In order to prevent the breakdown of folate in the skin when exposed to light, the body has adapted to using darker skin pigmentation in the form of melanin as a source of protection (Hasoun et al., 2013). Beyond pigmentation, there are other protective mechanisms in the body that protect the folate supply in the skin. For instance, research has shown that cellular uptake of folic acid within the skin is increased after exposure to UV radiation. It is hypothesized that this is in order to protect the cellular supply of folic acid (Knott et al., 2007).

Chronic arsenic consumption is seen in many countries throughout the world as a result from exposure to contaminated drinking water (Pilsner et al., 2009). The chronic consumption of arsenic can lead to leukomelanosis, keratosis, and some cancers including those of the skin. Leukomelanosis is hypopigmentation of the skin with the presence of black and white spots. The skin lesions seen first from arsenic consumption are considered to be precursors to arsenic-causing skin cancer (Pilsner et al., 2009). Deficiencies of nutrients can increase the risk of arsenic-related skin lesions. In fact, case control studies have found that low intake of folate, among other nutrients, is correlated with development of skin lesions from arsenic exposure (Pilsner et al., 2009). Folate plays a part in one-carbon metabolism which allows for transport of methyl groups to substrates such as arsenic, DNA. and alpha glucosidase (GAA) (Pilsner et al., 2009). As an example, reduced arsenic methylation was found to be associated with deficiency of folate and hyperhomocysteinemia in a study conducted in Araihazar, Bangladesh. In a placebo-controlled, double blind trial characterized by the supplementation of folic acid, the increased intake of folic acid increased arsenic methylation and secretion of arsenic in the urine (Pilsner et al., 2009). This supplementation also showed reduced concentrations in blood arsenic

compared to the placebo (Pilsner et al., 2009). However, the study found no benefit from adequate B12 levels on skin lesions despite its activity to convert homocysteine to methionine. More research needs to be done regarding vitamin B12 and its influence on skin lesions (Pilsner et al., 2009).

B12 overview - cobalamin

Vitamin B12, also referred to as cobalamin, is reddish in color, water soluble, and heat stable (Priyadharsini, 2016). Chemically, cobalamin is a cobalt atom attached to four pyrrole rings and one benzimidazole ring. The sixth position on the ring is either filled by a cyanide, hydroxyl, adenosyl, or methyl group, which determines the different forms of B12. For example, cyanocobalamin has a cyanide group, whereas hydroxocobalamin will have the hydroxyl group. Then, adenosylcobalamin will have an adenosyl group, and methylcobalamin will have the methyl group (Priyadharsini, 2016). B12 is used in the breakdown of lipids and proteins, synthesis of hemoglobin and functionality of the folate coenzyme ("Office of dietary supplements - pantothenic acid", n.d.). Cyanocobalamin is involved in macronutrient metabolism and helps to form coenzymes in order to activate folate (Dalens & Prikhnenko, 2015). Cyanocobalamin is also a nitric oxide scavenger (Guillot et al., 2021). Of interest, cobalamin is the only B vitamin stored in the body. The liver stores enough cobalamin to last several years (Brescoll & Daveluy, 2015). Cobalamin is also the only vitamin to contain a metal ion ("Office of dietary supplements - pantothenic acid", n.d.). Food sources of cobalamin include mainly animal products such as eggs, dairy products, fish, liver, pork, kidney, and chicken. For strict vegetarians, food sources of cobalamin can be obtained from fortified foods, supplements, or

legume nodules in which microorganisms are able to use to produce cobalamin. The RDA for non-pregnant or lactating individuals is 3 micrograms per day (Priyadharsini, 2016).

When cobalamin is ingested orally, the salivary glands produce a substance known as haptocorrin that binds to cobalamin (JJ Medicine, 2017). The complex of haptocorrin and cobalamin enters the stomach via the esophagus. Within the haptocorrin complex, cobalamin is protected from acid degradation. Inside the stomach, parietal cells produce hydrochloric acid and intrinsic factor (IF). As cobalamin passes through the stomach into the duodenum, the pancreas will release proteases that will break apart the haptocorrin complex to release cobalamin. Once released, it binds to IF. This new complex will make its way through the small intestine to the terminal ileum, at which time the complex is separated. Cobalamin will then be absorbed, while IF passes on into the large intestine. Within the bloodstream, cobalamin will attach to both transcobalamin and haptocorrin (JJ Medicine, 2017). Transcoblamins I, II, and III help to transport cobalamin in the bloodstream (Priyadharsini, 2016). Via the portal vein, cobalamin will be transferred to the liver, where some cobalamin will be stored. The remaining cobalamin is transferred to the kidney and goes through glomerular filtration. However, the renal tubules have the receptor megalin, which encourages the reabsorption of cobalamin from the urine. This reabsorption is important since the absorption of cobalamin from the diet is energy consuming, so the body will prefer to not lose unnecessary cobalamin through the urine (JJ Medicine, 2017)

Vitamin B12 has various influences on the human body (Brescoll & Daveluy, 2015; Calderón‐Ospina & Nava‐Mesa, 2019). Cobalamin in the body in the form of methylcobalamin serves to help convert homocysteine to methionine. In the form of adenosylcobalamin, the vitamin will help to achieve the product of succinyl-CoA from methylmalonyl-CoA. These conversion and subsequent end products are essential for the growth and division of cells,

especially those in the skin (“Cyanocobalamin”, n.d.). Adenosylcobalamin is also used to break down fatty acids (Brescoll & Daveluy, 2015). In addition, cobalamin is involved in myelin synthesis and regeneration, which helps to regenerate nerves when they are injured. Cells are more susceptible to oxidative stress in cobalamin deficiency due to its ability to maintain reduced glutathione levels (Calderón‐Ospina & Nava‐Mesa, 2019).

Excessive and deficient cobalamin levels have been known to produce cutaneous side effects (Brescoll & Daveluy, 2015; Cherqaoui et al., 2013; “Cyanocobalamin”, n.d.; Padhi et al., 2016). The side effects include hyperpigmentation of the skin, atopic dermatitis, vitiligo, and acne (Brescoll & Daveluy, 2015) Cobalamin deficiency can manifest as hyperpigmentation of the skin, angular stomatitis, and vitiligo (Padhi et al., 2016). Some manifestations of cobalamin deficiency include macrocytic anemia and hyperpigmentation of the skin which have been linked to each other (Cherqaoui et al., 2013). A form of cobalamin, called cyanocobalamin, is used to help treat B12 deficiency. This form has been linked to the side effect of rashes or itching sensations of the skin (“Cyanocobalamin”, n.d.).

Within individuals treated with B12 injections, reports of acne development were seen (Balta & Ozuguz, 2013; Brescoll & Daveluy, 2015; Kang et al., 2015). However, the acne that developed went away after injections ceased. Existing acne lesions were also seen to be worsened with B12 supplementation (Brescoll & Daveluy, 2015). In a case report of a 37-year old woman, B12 injections induced acne formation on the face, chest, neck, and back that occurred after the second injection. When injections were discontinued, the acne resolved within 2 weeks (Balta & Ozuguz, 2013). Research has found that cobalamin supplementation altered the skin microbiota transcriptome and inhibited cobalamin biosynthesis gene expression within Propionibacterium acnes (P. acnes). This supplementation was also shown to promote

inflammation within acne lesions due to the stimulation of porphyrin synthesis (Kang et al., 2015). Within individuals suffering from acne caused by P. acnes, research has shown a decreased rate of vitamin B12 synthesis, suggesting that B12 levels are lower within the individuals with acne (Kang et al., 2015).

Within the skin, deficiency manifestations are seen mainly as hyperpigmentation (Priyadharsini, 2016). The hypothesis regarding B12 deficiency and hyperpigmentation is: lowered levels of GSH which is important for preventing tyrosine metabolism. Tyrosine plays a role in melanogenesis. The decreased levels of GSH within cobalamin deficiency increase tyrosine activity and thus increase the production of melanin. This hypothesis was proposed by Gilliam and Cox (Vera-Kellet et al., 2015). Another hypothesis proposed by Marks (1985) suggests that cobalamin's role in megaloblastic anemia is the fault. Megaloblastic anemia is found to cause impairment in transporting melanin to keratinocytes (Vera-Kellet et al., 2015). Dr. Bramwell first connected macrocytic anemia to hyperpigmentation of the skin in 1944 (Padhi et al., 2016).

Various case reports have been done over the connection between B12 deficiency and the presence of hyperpigmentation (Aroni et al., 2008; Cherqaoui et al., 2013; Vera-Kellet et al., 2015). Within a case report over a 21-year-old woman of Greek origin who presented with hyperpigmentation and laboratory indications of vitamin B12 deficiency. The dark brown to red hyperpigmentation resembled a large rash and was present on the lateral portion of her legs. The subject was treated with 1 mg intramuscular injections of B12 and was started on vitamin B12 supplementation daily of 1000 micrograms. The subject's hyperpigmentation improved significantly by 3 months post treatment. At 12 months post treatment, the subject's hyperpigmentation was remarkably better and her serum B12 levels were 430 pg/ml. The

proposed mechanism behind the hyperpigmentation was a higher number of blood vessels in the dermis (Aroni et al., 2008).

In a case report of a 40-year-old African American woman, the subject presented with hyperpigmented lesions without itching on both hands and feet, as well as discoloration of the nails on fingers and toes (Cherqaoui et al., 2013). The subject's lab report had signs of B12 deficiency, so intramuscular B12 supplementation was started. However, this subject was lost to follow-up. Nevertheless, other cases and studies have shown that cutaneous deficiency manifestations for B12 are completely reversible with supplementation (Cherqaoui et al., 2013).

A case study involving a 59-year-old woman who had developed skin discolored lesions beginning on her hands and the bottom of her feet that spread to her whole body (Vera-Kellet et al., 2015). The subject presented with thinning of the epidermal layer, high levels of melanocytes in the basal layer, and changes in the keratinocytes. Tests determined that the subject had megaloblastic anemia. B12 supplementation intravenously was started and there was regression of the lesions at 5-months (Vera-Kellet et al., 2015).

A case study of a 13-year-old female presenting with hyperpigmentation of the skin caused by a variant in the LMBRD1 gene (Braz et al., 2021). The hyperpigmentation had been present since birth and found most noticeably on her neck and nails. The pigmentation also darkened after exposure to the sun. After review of lab results, the female subject's blood showed low levels of cyanocobalamin. Her blood contained 179 pg/ml and normal levels range from 130 to 950 pg/ml). Her results also found low levels of homocysteine. Her value of 45.4 nmol/L was drastically lower than the normal range of 5000-15,000 nmol/L. Biopsies of the hyperpigmented skin showed high levels of melanin within the keratinocytes. After supplementation for three weeks, the patient's lab results were both B12 and homocysteine

within normal ranges. Noticeable fading of the hyperpigmented areas was also observed (Braz et al., 2021). Lastly, cobalamin deficiency presented as hyperpigmentation of the skin in a case study involving a 12 year old girl (Brescoll & Daveluy, 2015)

Cobalamin has shown potential ability to heal skin lesions (Padhi et al., 2016). Within one case study, a 34-year-old woman had newly formed, non-pigmented, and non-itching lesions on the skin of her feet. The subjects' cobalamin levels were 113 pmol/L which was lower than the normal range of 132-857 pmol/L. The low serum levels were treated with intramuscular injections of B12 along with a B vitamin complex of B1, B6, and cobalamin. Within 2 weeks of beginning treatment, the lesions improved and the subject attained serum levels of 300 pmol/L (Padhi et al., 2016). A second case involved a 54-year-old woman with lesions on her limbs and neck that had presented 4 months prior to beginning treatment. The lesions were not pigmented and were different shapes and sizes. Subjects B12 serum level was 100 pmol/L. With treatment involving intramuscular injections and B complex supplementation, complete disappearance of skin symptoms was seen in one month after starting treatment. Subject’s ending serum level was 189 pmol/L (Padhi et al., 2016).

A handful of clinical trials have shown promise for cyanocobalamin being used to treat atopic dermatitis, psoriasis, and other inflammatory conditions (Guillot et al., 2021). Psoriasis pathogenesis includes overactivation of the immune system in which IGF-1 and oxidative stress both play a part (Guillot et al., 2021). Eczema and ulcers, as well as erythroderma have been seen in individuals with serum levels of cobalamin above 701 pmol/L (Brescoll & Daveluy, 2015). A case study over a 38-year-old female presenting with erythema and B12 deficiency found that her erythema improved and went away after deficiency was treated (Brescoll & Daveluy, 2015).

Topical cobalamin treatment has shown potential for atopic dermatitis treatment (Brescoll & Daveluy, 2015). forty-nine subjects with atopic dermatitis participated in a study where a cyanocobalamin cream was used on one half of the body and a placebo cream was used on the other half. The treated side of the body saw a significant reduction in erythema, itching, dryness, erosion, infiltration, and lichenification compared to the placebo side. Inflammatory activity within atopic dermatitis may be prevented through B12's role in preventing the synthesis of T lymphocytes (Brescoll & Daveluy, 2015). Eczema also saw improvement with topical B12 treatment. At 2 and 4 weeks, topical cyanocobalamin showed significant improvement in eczema when compared to a placebo (Guillot et al., 2021).

Vitamin B12 has many potential benefits for the skin when consumed in appropriate amounts (Aroni et al., 2008; Braz et al., 2021; Brescoll & Daveluy, 2015; Cherqaoui et al., 2013; Guillot et al., 2021; Padhi et al., 2016; Vera-Kellet et al., 2015). It has the potential to heal skin lesions, prevent hyperpigmentation, and treat certain inflammatory conditions. Cobalamin deficiency most often exhibits cutaneous manifestations such as hyperpigmentation that should be kept in mind when discussing cobalamin and the skin. Although cobalamin may be useful in conditions such as atopic dermatitis and other inflammatory conditions, it may be contraindicated with the condition of acne as cobalamin may make acne worse.

Multiple vitamins

Many of the B vitamins have interrelated roles within the human body that is evident as seen in their similar influences on the skin (Calderón‐Ospina & Nava‐Mesa, 2019; Dalens & Prikhnenko, 2015; Lyon et al., 2020; "Micronutrients in human development – part 3", 2013). Biotin and pantothenic acid are both essential for amino acids that are a part of the health and

function of skin ("Micronutrients in human development – part 3", 2013). Vitamins B1, B6, and B12 are all important for healthy immune function and a healthy nervous system (Calderón‐Ospina & Nava‐Mesa, 2019). Folate and cobalamin both play a crucial role in one-carbon metabolism. One carbon metabolism is influenced by folate and methionine in or to create products of methyl groups for use in the synthesis of DNA, product of antioxidants, and homeostasis of amino acids. Methionine is used for healthy skin function and maintenance (Lyon et al., 2020). Many of the B vitamins are central in cellular functions due to their actions as coenzymes in metabolism and reactions (Dalens & Prikhnenko, 2015). Due to these roles within the body, the B vitamins have many influences on the skin.

Much of the research involving multiple B vitamins in human skin include pyridoxine and cobalamin (Martín et al., 2011; New et al., 2011). Within a case study, large doses of B6 and B12 were seen to initiate rosacea development within a female at the age of 17 (Brescoll & Daveluy, 2015). A case study involving a 38-year old female with rosacea utilized consumption of a vitamin B complex of B12, B6, and B1 for 5 days. After complete removal of supplementation, the rosacea disappeared (Martín et al., 2011). In individuals with a mutation of the methylenetetrahydrofolate reductase (MTHFR) gene, B6, B9, and B12 supplementation helped to heal skin ulcers. The mutation involving the MTHFR gene mainly helps to determine eye and hair color as well as blood type (New et al., 2011).

The consumption of certain B vitamins could help reduce the incidence of skin lesions due to arsenic consumption (Zablotska et al., 2008). As an example, a study in Bangladesh investigated the effect of vitamins on arsenic-related skin lesions. It was found riboflavin, pyridoxine, and folic acid appeared to reduce the risk of said lesions. Arsenic ingestion is common in Bangladesh secondary to contaminated drinking water. Ingesting arsenic has been

linked to cancer. The link to cancer is specifically of importance to the aim of this study which linked skin lesions and arson consumption to each other. The skin lesions were antecedents to another skin condition: nonmelanoma skin cancer. In previous studies, vitamin B12 and folate have both been presented as nutrients that aid in the clearance of arsenic-related toxins. Folate is beneficial for arsenic methylation because methylation of arsenic requires one-carbon metabolism, which is folate-dependent. Additionally, this reaction is catalyzed by an enzyme that is reliant on the presence of vitamin B12. Methylation of arson is important for human health because arson is detoxified to a different form by methylation. Another study has shown that high levels of niacin were linked to the methylation of arson. Those within the study that consumed the B12, folate, and niacin had 46% less negative effects of arsenic ingestion than those that did not consume the vitamins. These doses of vitamins were consumed in higher doses than what is currently recommended for these vitamins (Zablotska et al., 2008).

Within arsenic-consuming individuals, those consuming the highest treatment amounts of the vitamins had the biggest reduction in skin lesions (Zablotska et al., 2008). Consumption of the B vitamins showed an inverse relationship with the development of lesions on the skin, as displayed by a linear trend test. Folic acid, pyridoxine, and riboflavin were all found to modify ingested arson effects, including skin lesions. This study was done with a large population of 11,747 adults. Within Bangladesh, a total of 65,876 individuals utilize the tube wells evaluated in this research, meaning that the study utilized 17% of the population. B12, folic acid, pyridoxine, and riboflavin are all a part of a one-carbon pathway in which S-adenosylmethionine is converted to S-adenosylhomocysteine for the methylation of arsenic. The current study and previous studies indicate that the toxicity of arson may be lessened via the vitamin B-dependent methylation pathway after intake of pyridoxine, riboflavin, and folic acid (Zablotska et al.,

2008). High levels of homocysteine and low levels of folic acid have also been shown in research to lower the rate at which arson is methylated. Part of the reason for this could be related to the need for folate, vitamin B12 and B6 to break down homocysteine in the body (Zablotska et al., 2008).

One study used a B complex supplement with all eight B vitamins (Dalens & Prikhnenko, 2015). Within the study of 50 women, a mesotherapy formulation with all the B vitamins was compared against a formulation with idebenone, a synthetic compound chemically similar to coenzyme Q-10, and hyaluronic acid. The B vitamin mesotherapy formulation also contained minerals, antioxidants, and other components. The mesotherapy improved the appearance of the skin significantly (Dalens & Prikhnenko, 2015). This appears to indicate that topical use of B vitamin complexes may have similar results compared to commonly used dermatologic treatments, such as retinol.

Skin lesions were found to be produced in rats with both riboflavin and pyridoxine deficiency according to one study, but these lesions can be present in humans as well (Lakshmi, 1998). Riboflavin and pyridoxine deficiencies could potentially be linked to each other. FMN-dependent enzymes, including pyridoxine phosphate oxidase, are needed to convert pyridoxine to pyridoxal phosphate. Thus, it can be reasoned that riboflavin deficiency might also lead to pyridoxine deficiency (Lakshmi, 1998). Riboflavin deficiency has been shown to affect the conversion of pyridoxine to PLP in both rats and humans. Within a study involving rats, deficiency of B2 and deficiency of B6 both showed a reduction in the amount of collagen in the skin compared to control groups (Prasad et al., 1983). These results were statically significant. Within deficiency of B2 and B6, skin lesions can occur more easily due to lower amounts of

collagen fibers and weakened collagen. This will diminish the integrity of the epithelial tissues and result in lesions if enough stress is put on those tissues (Prasad et al., 1983).

Similarly, B2 and B6 deficiency can negatively affect collagen (Lakshmi, 1998). Within riboflavin and pyridoxine deficient rats, studies have also shown that there was a negative effect on skin collagen and its ability to mature and crosslink, as well as in the strength and amount of skin collagen. This negative effect on collagen could be the reason that deficiency in riboflavin causes skin lesions. Low collagen levels, or collagen that is weak, could lead to epithelial tissue being vulnerable to stress, friction, and infection. Healing of wounds may also be influenced if collagen is affected. Collagen makes up a component of the new tissue produced in wound healing, as does epithelialization. The delay in epithelialization of wounds has been noted as a symptom of riboflavin deficiency. Within a study on rats with riboflavin deficiency, it appeared that there was a longer period of epithelialization and lower tensile strength in wounds. Riboflavin and pyridoxine deficient rats also may also have elevated homocysteine levels, which may impair collagen maturation (Lakshmi, 1998). This increase in the levels of homocysteine was associated with allysine or hydroxylysine neutralization in collagen and prevention of crosslinking (Lakshmi et al., 1990). Pyridoxine and riboflavin deficiency both weaken collagen within the skin.

Within the context of all B vitamins, one study found a relationship between skin cancer and higher consumptions of all the vitamins (Roe, 1962). Skin cancer caused by benzopyrene was found in a study to occur less often in mice receiving a low B vitamin diet compared to a high B vitamin diet. However, the mice who were given drinking water with only riboflavin saw less lumps in the skin throughout the study. The inhibitory effect was small and had little to no long-term effect within the study (Roe, 1962). Although other research has shown positive

evidence for B vitamin supplementation, this study in rats provides a roadblock for the overarching suggestion of consuming higher levels of B vitamins for skin health.

Although each of the B vitamins have their own individual function and place within our diet and skin, multiple studies have been done utilizing more than one B vitamin for skin research. These studies show that it is not just one vitamin and that pairing them together could either help or hurt the skin. Current research reports that there appears to be both benefits and drawbacks of B vitamin consumption for the skin.

Although much research has been done on the topic of the B vitamins and skin health, there are still gaps in knowledge present. There is much research surrounding niacin and topical use in general, but more needs to be done with supplementation and oral consumption. A majority of the current research available is over niacin and skin, so more research should be done for the other seven B vitamins as well. Many mechanisms still need to be discovered for different interactions between the B vitamins and the skin. More human studies need to be done but this is difficult due to ethical issues encountered when inducing nutrient deficiencies in human subjects. Hence, research must rely on subjects that are already deficient.

The health of our organs, and especially our skin, rely on good nutrition and homeostasis in the body (Zimmerman, 2020). The B vitamins have been shown, through evidence-based research, to influence the skin in a variety of ways. Thiamine appears to play a big role in wound healing of skin. Riboflavin also shows, not only a potential in wound healing, but can also function as a photosensitizer and anti-inflammatory agent. Niacin could be helpful in the prevention of skin cancer and in the maintenance of a healthy skin barrier. Pantothenic acid may help with inflammatory conditions such as atopic dermatitis and acne, as well as protecting the moisture barrier of the skin. Pyridoxine has the potential to function as an anti-inflammatory

agent and help with wound healing, however toxicity may lead to sun-sensitivity in the skin and painful lesions. Biotin deficiency has been associated with scaly dermatitis and inflammation within the skin, while its supplementation may help improve and even out skin texture. Folate deficiency appears to be related to hyperpigmentation and higher incidence of skin cancer. Cobalamin deficiency has been shown to occur with hyperpigmentation as pigmentation and macrocytic anemia have been linked. Additionally, higher cobalamin levels have been associated with acne formation. Each B vitamin has their own influence on the skin, whether in normal intake, deficiency, or excess. In sum, scientific evidence appears to demonstrate that consuming the right amount of each B vitamin could be the key to healthy skin.

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