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Associations Among Acne Vulgaris and Western Diet

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ASSOCIATIONS AMONG ACNE VULGARIS AND WESTERN DIET

by

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ABSTRACT

Acne vulgaris is one of the most common dermatologic conditions, especially among the adolescent population. The pathogenesis of acne is largely multifactorial, with heredity and hormones strongly contributing to one's risk of developing the chronic inflammatory skin condition; it is related to excess sebum production by sebaceous glands, inflammation within comedones, and hyperproliferation of *Propionibacterium acnes*. High prevalence rates of acne in the adolescent population cannot be attributed to heredity alone, but by the influence of Western diet that overstimulates a key conductor of metabolism, the growth factor-sensitive kinase known as mTORC1. Many investigations show associations between acne and Western diet, which is a diet consisting heavily of processed carbohydrates, refined sugars, and dairy products. Both high glycemic load and dairy-rich foods increase the levels of insulin-like growth factors (IGF)-1 and can reduce insulin sensitivity. Increased IGF-1 levels and decreased insulin sensitivity can lead to androgen-mediated increases in sebum production, which in turn attributes to the manifestation of acne vulgaris, as excess sebum is one of the vital mechanisms in the pathophysiology of acne vulgaris.

Keywords: acne vulgaris, Western diet, sebum production, insulin sensitivity, IGF-1

INTRODUCTION

Acne vulgaris, the most common skin ailment in the United States, has become a growing concern in today's population (Mancini, 2008). Not only can the presence of acne cause physical discomfort and scarring to an individual, but it can also cause life-long psychological and emotional scarring, increasing one's risk of depression and in some instances, suicidal ideation. More than 14 million office visits a year are attributed to the diagnosis and treatment of acne vulgaris (Mancini). This inflammatory disease of the sebaceous follicle now affects around 85% of adolescents in Westernized nations (Melnik, 2018). Acne is thought to be a disease of wealthy nations, where an abundance of food, particularly processed food, is readily available; incidence rates of acne are much higher in developed, Westernized countries when compared to developing countries. Non-Westernized populations who live under Paleolithic dietary conditions, where hyperglycemic carbohydrates, milk, and dairy products are constrained, have been found to have low to no cases of inflammatory acne manifestations (Melnik). The pathophysiology of acne vulgaris is largely multifactorial, with heredity and hormones strongly contributing to one's risk of developing the chronic inflammatory skin condition (Mancini). The role of genetic inheritance in the presence of acne has been considered for decades, however, only a small number of genes have been investigated for genetic predisposition or susceptibility in the pathogenesis of acne vulgaris (Szabo & Kemeny, 2011). Researchers seem to believe two major cellular processes that are genetically predisposed, regulation of steroid hormone metabolism and innate immune function of epidermal keratinocytes, are disrupted in patients with acne (Szabo & Kemeny).

However, heredity and hormones alone cannot account for the increase in incidence seen in the United States in the past 25 years (Mahmood & Bowe, 2014).

It is thought that the rise in incidence of acne in the United States may be related to high glycemic load, increased consumption of insulin and insulin-like growth factor 1 (IGF-1) levels, as well as elevated dairy proteins seen in the Western diet (WD), which is a diet consisting heavily of meats, dairy products, and refined sugars (Mahmood & Bowe, 2014). Possible associations among dietary glycemic load and dairy consumption seen in the WD, along with insulin resistance in relation to the pathogenesis of acne need to be further investigated. In addition, current research needs to be evaluated to determine if a physiological link between the high glycemic food and dairy products that compose the typical WD exists. Throughout this scholarly project, the following questions will be posed: Is there an association between the presence of acne vulgaris and the consumption of Western diet? Is there a physiological link connecting high glycemic foods and dairy products and their propensity to cause inflammatory acne?

Within the last decade, several new studies have examined the possible link between high glycemic food and dairy consumption and the incidence of inflammatory acne; the emerging evidence has prompted dermatologists around the nation to reexamine the possibility that certain high glycemic foods and dairy-rich foods can trigger the presence of acne vulgaris.

LITERATURE REVIEW

Methodology

A review of the present literature searching three databases, EBSCOHost, Academic Premier, and primarily, PubMed, from October 30, 2017 to February 12, 2018, yielded numerous high-quality studies relating high glycemic diet and the presence of acne vulgaris in adolescent males and females, as well as dairy-rich diet and the presence of acne in adolescent males and females. Current literature also revealed a possible physiological link between the two core components that make up Western diet, high glycemic load food products and dairy products, with hyperinsulinemia and insulin-like growth factor comprising that link. The following reviewed literature heavily consisted of systematic reviews, as well as a handful of randomized control trials and self-report survey questionnaires. Inclusion process for this literature review included: studies published within the last 20 years, adolescent to young adult participants (between the ages of 12 and 25-years-old), and studies written in the English language.

Main headers used while searching the databases included: *Western diet, WD, Westernized diet, Neolithic diet, American diet, acne, acne vulgaris,* and *inflammatory acne*. The following keywords were used in a variety of combinations while searching the databases: *high-glycemic load, high-glycemic foods, high glycemic index, hyperinsulinemia, insulin like growth factor, IGF-1, dairy-rich diet, high milk diet, dairy diet, dairy products, sebaceous gland disorder, skin inflammation, physiological effects, pathophysiology*.

Pathophysiology of Acne Vulgaris

Acne vulgaris is an extremely common skin condition, accounting for more than 14 million office visits a year, with adolescents comprising the majority of those visits (Mancini, 2008). The pathophysiology of acne is largely multifactorial, beginning with the obstruction of the pilosebaceous unit, which is comprised of the hair follicle, hair shaft, and sebaceous gland (Feldman, Careccia, Barham & Hancox, 2004). Typically, during adolescence, an increase in the production of adrenal androgens occurs, which causes sebaceous glands to increase production of sebum, an oily substance consisting of sterol esters, triglycerides, cholesterol, and inflammation-inducing free fatty acids. This increased production of sebum, along with the accumulation of epithelial cells and keratin, obstructs the hair follicle, causing swelling of the follicle and formation a keratin plug; this process forms the earliest acne lesion known as a microcomedone (Feldman, Careccia, Barhma & Hancox). As the keratin plug enlarges, it causes greater follicular swelling and increases the likelihood that the follicle can become colonized with *Propionibacterium acnes*, which is a normal skin flora, progressing the microcomedone to a visible comedone, or pimple. With the proliferation of *P. acnes*, infiltration of proinflammatory mediators are stimulated, causing a localized inflammatory response that results in a painful papule or pustule depending on the severity of the infiltration (DynamedPlus, 2018). Acne lesions tend to be concentrated to sebaceous gland predominant areas, such as the face, neck, chest, back and upper extremities.

Introduction to Themes

The relationship between acne and diet is somewhat controversial. Specific foods that were once thought to cause acne manifestations (pizza, chocolate, and soda), are no longer

thought to affect the presence of acne. The biochemical counterparts that make up foods are now the topic of interest when studying the relationship between diet and acne vulgaris. Western diet can be broken down into two main counterparts: diet rich in high glycemic foods (processed carbohydrates and refined sugars) and dairy-rich diet, both of which have ties to insulin-like growth factors and the propensity to cause increased insulin resistance. Implications of eating a Western diet and how it affects the manifestation of acne vulgaris will be further evaluated. Furthermore, insulin-like growth factor levels and increased insulin resistance in relation to acne presentation will be investigated.

Theme 1: Associations between High Glycemic Load Diet and Acne Vulgaris

In theme one, possible associations among dietary glycemic index, glycemic load, and insulin resistance, in the pathogenesis of acne vulgaris were examined by a number of researchers.

Cerman et al. investigated associations among dietary glycemic index, glycemic load, insulin-like growth factor 1 (IGF-1), and insulin resistance, in the pathogenesis of acne vulgaris by testing 50 subjects with present acne and 36 healthy control subjects. The patients with acne were further subdivided into the following subsets using the International Consensus Conference on Acne classification system: “mild” (few to several comedones, papules, and pustules; no nodules); “moderate” (several comedones, papules, and pustules; few to several nodules); and “severe” (numerous comedones, papules and pustules; many nodules). Patients who had previously treated their acne using topical or systemic therapies were excluded from the study. The glycemic index values of foods were calculated using white bread as a reference food, based on the patient’s postprandial blood glucose response and blood insulin levels. The participants self-reported food records and dietary patterns over a period of seven days; the Australia-specific

dietary analysis software (Foodworks Xyris Software) was then used to calculate total calorie intake per day, glycemic index and total carbohydrate, protein and lipid breakdown. Both groups were tested for adiponectin enzyme-linked immunosorbent assay (ELISA) kit consisting of 86 test plates. Presence of insulin resistance was also investigated for each participant. Venous blood samples were collected from participants at varying times and analyzed for glycemic factors.

The following results were recovered: for participants with present acne, glycemic index and glycemic load levels were found to be higher (p = .022) when compared to the control group (p = 0.001); however, these differences were not found to be significant. The glycemic index values were significantly higher in patients with moderate to severe acne (p = .035) and there was a positive correlation between acne severity and glycemic index values (p = .014, r = 0.345). The study concluded that diets with high-glycemic loads were positively associated with acne vulgaris (Cerman et al., 2016).

The authors stated that this study had some limitations. First, only young adults were studied. Although the adolescent, young-adult population is of interest in this overall scholarly project, the authors note that their research cannot be extended to other age groups. Second, obese participants were excluded from the study, as obesity was selected as a cofounder; therefore, the results have limited applicability to young, non-obese participants with acne vulgaris. Would similar results have been found if obese participants were included in the study? Obesity has been known to be linked with insulin resistance, which is of great interest in this scholarly project. This raises the following question: is the same construct that is present in the manifestation of acne vulgaris also a link in one's propensity to be obese? This is beyond the scope of the author's study, so it seems wise for the authors to have excluded such participants.

Third, diet recall was limited to a 7-day period, and may not represent participants' long-term diet trend. The time period of participants' food journaling and reliance on participants' self recall of food consumption could have accounted for the present difference in the control group and that of the high-glycemic group. If a longer time frame with daily meal-time journaling were implemented in this study, would a significant difference have been found between the two groups? Overall, this study's conclusion that high-glycemic load diets were positively associated with acne vulgaris is still powerful.

Kaymak, et al. sought to isolate observations suggesting that acne can develop in individuals who have adopted a high glycemic diet. A total of 49 participants who had present acne and 42 healthy control subjects were evaluated in this prospective cohort study. Out of the 49 participants with present acne, 19 were male and 30 were female. Out of the 42 participants in the control group, 16 were male and 36 were female. The International Consensus Conference on Acne Classification was used to grade acne severity and included the following categories: "mild" (few to several comedones, papules and pustules; no nodules) "moderate" (several comedones, papules and pustules; few to several nodules) and "severe" (numerous comedones, papules and pustules; many nodules). Seventeen participants were classified as having mild acne, 27 had moderate acne and 5 participants were classified as having severe acne vulgaris. Glycemic load (calculated as, glycemic index X carbohydrate content / serving size) was implemented in this study in order to assess the potential of a food to increase blood glucose levels. Initial fasting glucose, insulin, insulin-like growth factor (IGF-1), insulin-like growth factor binding protein 3 (IGFBP-3) and leptin were initially measured using participant fasting venous blood samples. Serum glucose measures were calculated using an autoanalyzer and the insulin enzyme-linked immunosorbent assay (ELISA) kit. Serum IGF-1 levels were measured by

DSL-10-2800 nonextraction IGF-1 ELISA test kit, and serum leptin levels were measured using DSL-10-23100i human leptin ELISA. A voluntary self-reported food questionnaire was administered to all participants; participants were also asked how frequently they consumed the specified amounts of foods. Overall glycemic index and dietary glycemic load were then calculated by researchers depending on each participant's response. Each participant was then investigated for the presence of insulin resistance using insulin resistance index (Homa-IR). Insulin resistance index levels above 3 were included as indicators of present insulin resistance (Kaymak et al., 2007).

The study found that no significant difference in serum fasting glucose, insulin, IGF-1, IGFBP-3, and leptin levels of participants with present acne and that of the control group participants ($p > 0.5$). There was no significant difference in insulin resistance levels between the two groups according to the Homa-IR values ($p > 0.5$); none of the participants in either group had insulin resistance. There was found to be no significant differences among participants in the mild, moderate, and severe acne groups according to the overall glycemic index, glycemic loads, fasting serum glucose, insulin, IGF-1, IGFBP-3, and leptin levels ($p > 0.5$). Thus, it was concluded that dietary glycemic index, glycemic load, and insulin levels did not play a role in the pathogenesis of acne in younger patients in this study (Kaymak et al., 2007).

This study was found to have a few limitations. Participant questionnaire responses were collected relying largely on participants' past recollections, possibly skewing the glycemic data. Also, individual laboratory measures were not collected on the actual days of the associated food recollections. With these limitations, the accuracy of the concluded results is questionable. Would a statistically significant difference among acne vulgaris and a high glycemic load diet been found if the participants would have more accurately self-reported their dietary habits?

Smith, Mann, Braue, Makelainen, and Varigos aimed to compare the effects of a low glycemic-load diet with a conventional Western, high glycemic-load diet on clinical, as well as endocrinological aspects of acne vulgaris; they used a randomized, investigator-masked, controlled trial. A total of 43 male participants, ages 15 to 25 years, with mild-moderate present acne completed a 12-week, parallel, dietary intervention study with investigator-masked dermatology assessments. Acne severity was assessed using the Leeds acne grading technique, where a severity grade of greater than 0.25, but less than 2.0 was implemented. Participants taking medications known to affect acne or glucose metabolism were excluded from this study. A washout period free from topical and/or systemic acne therapies of 6 months or more was implemented. Twenty participants per group were randomly assigned to either the low glucose load (LGL) diet group or the control group. The LGL diet group was recommended to consume a diet consisting of energy sources from 25% protein, 45% low glycemic index carbohydrates, and 30% fats. The control group continued to eat their standard Westernized diet. The participants kept track of their food consumption over the course of 12 weeks. Topical therapy, a noncomedogenic cleanser (Cetaphil gentle skin cleanser) was issued to both groups and facial acne was scored at monthly check-in visits at weeks 0, 4, 8, and 12. Changes in lesion count, sex hormone binding globulin (SHBG), free androgen index, and insulin-like growth factor-1 (IGF-1), as well as insulin-like growth factor binding proteins (IGFBP) were the primary outcomes measured in this study. Venous blood samples were collected at the initiation and completion of the 12-week study period in order to assess SHBG, IGF-1, and IGFBP using various ELISA test kits. A masked dermatology registrar assessed facial acne levels at each visit, referring to the Leeds criteria.

In all, 43 participants completed this study per protocol. Seven participants did not complete the study. During the trial period, dietary glycemic load was lower and protein consumption significantly increased in the LGL group when compared to that of the control group ($p < .001$). It was found that at the end of the 12-week dietary intervention, the reduction in total lesion counts was significantly greater in the LGL group than that of the control group ($p = 0.1$). The LGL group was also found to have greater reduction in weight, fat percentage and waist circumference. At the completion of the 12-week trial, the mean change in fasting insulin levels ($p = .03$) and HOMA-IR ($p = .02$) was significantly different between the LGL group and control group, with the LGL group showing improvement in insulin sensitivity and the control group showing increased insulin resistance. Therefore, Smith, Mann, Braue, Makelainen, and Varigos concluded that nutrition-related lifestyle factors seem to play a role in the pathogenesis of acne vulgaris (2007).

This study was found to have some limitations regarding the design and intervention of the study. First, the participants in the LGL group were found to have marked weight loss, however, the change in body mass index (BMI) to the overall treatment effect cannot be excluded. When the data changes in BMI were adjusted for, the effect of the LGL diet on several clinical and endocrine parameters were lost, therefore, the effect of weight loss on acne cannot be concluded. However, the association among acne and weight loss is not of significant interest in this scholarly project. Second, fasting index was used to estimate hyperinsulinemia and insulin resistance; this measure has been proven to be accurate in large studies, but its applicability to smaller studies, such as this one, is uncertain. With that being said, there is a possibility that this index may underestimate or overestimate the relationship between acne and hyperinsulinemia. In this population, this study's conclusion is powerful, overall; implementing a low glycemic diet

seemed to show a significant improvement in insulin sensitivity, and therefore reduced the occurrence of acne manifestations. This study may be on to something; perhaps further research studying the inverse, low glycemic diet, and its association among manifestations of acne vulgaris is warranted.

Theme 2: Associations between Dairy-rich Diet and Acne Vulgaris

In theme two, possible associations among dietary dairy consumption in the pathogenesis of acne vulgaris were investigated by a number of researchers.

Adebamowo et al. examined the association between acne presentation and dietary dairy intake among teenaged boys by using a prospective cohort study of youth and lifestyle factors (Growing Up Today Study) spanning over a two-year period. The Growing Up Study (GUTS) is an ongoing cohort study comprised of 9,039 girls and 7,843 boys between the ages of 9 and 15 years; this group is followed using a yearly questionnaire to ascertain lifestyle factors. 4,273 members of the GUTS were teenaged boys who reported dietary dairy intake on up to 3 food frequency questionnaires. Participants were asked how often they consumed a typical portion of a variety of dairy-rich products over the course of one year. In addition, they were specifically asked about the kind of milk they drank (whole milk, 2% milk, 1% milk, skim/nonfat milk, soy milk, no milk). For study purposes, whole milk and 2% milk were then grouped together, as they retain the most fat. The Spearman correlation coefficients for intake of types of milk at baseline was used to evaluate reproducibility of milk intake during the study time period; these correlations were 0.84 for total milk, 0.67 for whole milk, 0.57 for low-fat milk, and 0.69 for nonfat/skim milk. Two years after the initial dairy questionnaire, the GUTS cohort participants were then asked to rate their acne manifestation level in comparison to other people their age. Possible responses included: “I almost never have any pimples,” “I sometimes get a few

pimples," "I usually have a few pimples," "I sometimes get a lot of pimples," and "I usually get a lot of pimples." The authors then excluded participants who said they had "sometimes a few pimples" and divided the responses between the "almost never" and "usually a few," "sometimes a lot," or "usually a lot" levels in order to clearly distinguish respondents with substantial acne from those without. This left 2,780 boys for analysis. Several variables, including age at baseline, height, and energy intake, were adjusted for and multivariate prevalence ratios for acne, comparing highest milk intake and lowest milk intake were calculated. (Adebamowo et al., 2008).

It was found that a great deal of the study population (45%) drank whole or 2% milk, 23% drank low-fat milk, 29% drank skim/nonfat milk, 0.4% drank soy milk, and 3% did not drink any milk at the time of baseline. A great majority of boys (79%) reported "sometimes having a few pimples" and 21% reported "usually having a few or more pimples." The incidence of acne according to total intake of milk consumption, after adjusting for age at baseline, height, and energy intake, was found to be $p = 0.57$ for less than one serving per week, $p = 0.69$ for 2 to 6 severing per week, $p = 0.73$ for one serving per day, and $p = 0.66$ for two or more servings per day. Therefore, Adebamowo et al. concluded that a positive association between the intake of milk and acne exists, and more specifically, skim/nonfat milk intake was associated with incidence of acne in adolescent boys (2008).

This study was found to have a number of limitations. First, not all members of the initial cohort study responded to the questionnaire; only the boys who responded to the question on acne and provided information about their diet were studied; this could have caused a degree of selection bias. Second, acne assessment was by self-report and boys who had underlying conditions that may have contributed to their acne were not excluded from this study, potentially

decreasing the validity. Third, the questionnaire did not ask the boys to specify the location of their acne. Although it is noted that patients with truncal acne in the absence of facial acne is uncommon, less than 5% of cases, this could have affected the validity of the results as well. In addition, the way the authors grouped the subsets of milk according to fat composition could have affected the results of this study. Whole milk and 2% milk were grouped together and combined into one category representing higher fat content milk. Would further research show a difference between 2% and whole milk? Further research is warranted to deduce if the fat content in milk really affects the presence of acne vulgaris. Overall, the results of the study show a powerful relationship between milk consumption and presence of acne in adolescent males.

LaRosa et al. aimed to investigate the possible association between dairy consumption and acne in the teenage population. By conducting a case-control study among 225 participants, ages 14 to 19 years, the authors tested the hypothesis that teenagers with facial acne will consume more dairy than those without acne. The participants either had moderate presentation of acne or no acne. A total of 120 participants with moderate presentation of facial acne were evaluated by a dermatologist and placed into the acne group; the Global Acne Assessment Scale was used to make this determination. 105 participants, who had no evidence of acne, comprised the control group. Participants currently, or previously taking oral contraceptive pills or isotretinoin within the last 6 months were excluded from the study. Participants then completed three phone interviews, where the 24-hour diet recall technique and the Nutrition Data System for Research Software was utilized. These phone interviews were conducted at random and included both weekday and weekend calls in order to obtain accurate sampling. Specific data concerning milk and dairy product intake, along with nutrient totals, were compared amongst the two groups. Three outcome variables in this study included total daily dairy serving, as well as

total daily servings of full-fat, reduced-fat, and low-fat milk products. The authors then grouped low-fat and skim milk designations together into one, inseparable measurement. Total energy intake and total daily carbohydrate/fat/protein intake were also measured outcome variables. The relationships among the outcome variables and the group variable were examined by linear mixed models for repeated measures (LaRosa et al., 2016).

In all, 50.8% of the acne group was comprised of female participants, whereas the control group was 56.2% female. The average body mass index (BMI) was 22.8 in the acne group, compared to 23.8 in the control group. It was found that the total dairy consumption in the acne group was significantly higher (p = .02) than the control group. No statistically significant differences in the total amount of full-fat dairy products (p = .95) and reduced-fat dairy products (p = .36) was determined between the acne and control groups in this study. It was also found that the total energy in kilocalories did not statistically differ between the two groups (p = .12). Total intake of fat (p = .34), carbohydrates (p = .14), and protein (p = .08) was determined to be similar for both the acne and control groups (LaRosa et al., 2016).

This study was found to have a number of limitations. Due to its design, the study was limited; although this design allows for associations to be made, the case-control design is unable to determine causation of these associations. Relying on participant self-recall is another limitation; self-reported data may cause false associations; therefore, the validity of the dairy intake may be skewed. A third limitation is the unclear parameters defining the acne group. Ambiguous parameters were used to describe the presentation of acne vulgaris without using any of the acne designation scales used in previous studies noted in this scholarly project; participants were simply given the designation of having ‘moderate acne,’ which seems highly subjective.

Ulvestad, Bjertness, Dalgard, and Halvorsen designed a European, longitudinal, questionnaire-based population study that aimed to examine the relationship between high intake of dairy products consumed in early adolescence with moderate to severe acne production occurring later in life. Students attending the 10th grade in Oslo, Norway in 2001 were invited to participate in a self-reported dairy consumption questionnaire. Participants were asked to self-report how many servings of dairy products they consumed, and more specifically, if they consumed full-fat dairy products, semi-skimmed dairy products, or skimmed dairy products. They were asked the following question: 'How much do you usually drink of the following?' and were given the above three varieties. Consumption of dairy products of each fat group were specified to (1) never; (2) one to six glasses per week; (3) one glass daily; (4) two to three glasses daily; (5) four glasses or more daily. For all statistical analyses, dairy product intake alternatives (2) and (3) were combined, corresponding to a medium dairy-product intake, whereas alternatives (4) and (5) were combined, corresponding to a high dairy-product intake. A total of 3,811 students, who were 15 or 16-years-old at the time of the initial questionnaire, participated. Three years later in 2004, these students (now 18-19-years-old) were then asked to self-assess and self-report appearance of acne. The participants were asked one question, 'In the last week, have you had any pimples?' Four possible response options were provided for the students to select: (1) No; (2) Yes, a little; (3) Yes, quite a lot; (4) Yes, very much. Respondent answers (1) and (2) were considered by the authors to be no acne presentation, whereas respondent answer choices (3) and (4) were considered as positive for moderate and severe acne presentation. 2,489 students participated and agreed to the linkage of the data sets. Associations between the incidence of acne and the consumption of dairy products were statically analyzed using a variety of factors. Initially, associations between the incidence of acne and total

consumption of dairy products was examined. Associations between acne prevalence and dairy consumption was then analyzed within the three fat variations, separately. Lastly, the dairy intake data in every fat variety was stratified. Family income, ethnicity, mental distress, and body mass index (BMI) was adjusted for all in logistic regression models (Ulvestad, Bjertness, Dalgard, & Halvorsen, 2017).

In all, 2,489 participants, 1,112 boys and 1,377 girls completed both questionnaires in 2001 and 2004, constituting the study population. The overall prevalence of acne at age 18-19 was 13.9%, more specifically, 14.9% of acne appearing in boys and 13.1% of acne appearing in girls. Semi-skimmed dairy products were the most frequently consumed, with 72.3% of participants consuming them to some degree. 51.5% of participants consumed full-fat dairy products and 21.3% consumed skimmed products. The prevalence of acne was found to be 11.7% in participants who did not consume any dairy products, 13.4% in students with moderate total dairy product intake, and 15.1% in those with high total dairy intake. Ulvestad, Bjertness, Dalgard, and Halvorsen found that when dairy products were examined separately, high-fat dairy products (two or more servings a day) were associated with moderate to severe acne appearance (18.5%, OR 1.55). No associations were found with semi-skimmed or skimmed dairy products, nor with moderate intakes of any variety of dairy products. This study concluded that their hypothesis suggesting dairy consumption as a contributing factor to acne production could be supported; there was an association between high intake of dairy products and acne in the adolescent population (Ulvestad, Bjertness, Dalgard, & Halvorsen, 2017).

This study had a few limitations. First, dairy product intake was self-reported, indicating that a level of recall bias may be present. Self-reported data may also cause false associations, due to the participants' tendency to systemically answer high or low on questions. Second,

appearance of acne was self-reported in this study; without a dermatologist assessing the presence and severity of acne, complete accuracy and validity cannot be attained. Third, the onset of acne and the incidence of acne at age 15-16-years-old is unknown; therefore, it is uncertain if high dairy intakes preceded the development of acne. A final limitation was that this study was a European study conducted in Norway. Although this can be thought of somewhat of a limitation, Norway is, indeed, a Westernized nation that has comparable dietary similarities to that of the United States; thus, the inclusion of this study is within the parameters of this scholarly project.

Theme 3: Associations between Hyperinsulinemia and Acne Vulgaris

In theme three, the role of hyperinsulinemia in relation to acne vulgaris was investigated by a number of researchers.

Cordain et al. sought to investigate the prevalence of acne vulgaris in non-westernized societies, where individuals consume Paleolithic diets that constrain hyperglycemic carbohydrates, milk, and dairy products; these diets are therefore lacking the dietary components that yield high glycemic loads that elevate insulin levels and therefore lead to hyperinsulinemia. Cordain et al. constructed a review article that compiled research from four groups living in unindustrialized societies; the researchers solely focused on two non-westernized groups, the Kitavan Islanders living on the Trobriand Islands near Papua New Guinea and the Ache Hunger-Gatherers living in Paraguay.

The individuals in the Kitavan Islander group consumed their typical diet, which consisted largely of tubers, fish, fruit, and coconut, and consumption of processed carbohydrates like cereals, refined sugars, alcohol, and dairy products was completely non-existent. 1,200 Kitavan Islanders, including 300 who were between the ages of 15 and 25, were observed by a

general practitioner formally trained in dermatologic pathophysiology, as well as the ability to recognize acne presence and varying staging of acne progression. An acne classification scale was used to designate the presence and progression of acne vulgaris using the following parameters: “grade 1” visible open or closed comedones with a few papules present; “grade 2” comedones and papules present with few pustules present; “grade 3” comedones, papules, and pustules present with few nodules present; and “grade 4” comedones, papules, pustules, nodules and cysts all present. The Kitavan subjects had no recorded cases of acne at the beginning of the study; not a single comedone, papule, pustule, nodule or cyst was found on any of the Kitavan subjects. The subjects were followed continuously over a course of 7 weeks and all were found to have maintained their designation of no acne cases (Cordain et al., 2002).

The individuals in the Ache Hunter-Gatherer group consumed a diet consisting of 17% wild game, 69% locally cultivated fruits and vegetables, 3% foraged foods, 3% domestic meat, and 8% Western foods, such as rice, herbal teas and flour, obtained from external sources. 115 subjects, including 15 subjects who were aged 15 to 25 years, were observed by a general practitioner who had extensive training in detection and diagnosis of acne vulgaris using the Acne Classification System. The categories of the Acne Classification System included: “mild,” few to several comedones, papules, and pustules, no nodules; “moderate,” several to many comedones, papules, pustules, few to several nodules; and “severe,” numerous comedones, papules, and pustules, many nodules. The subjects were initially examined by the practitioner and every 6 months thereafter, over the course of 843 days. Not a single case of acne vulgaris in the Ache Hunter-Gatherer group was observed during the observation period (Cordain et al., 2002).

The results from the other two unindustrialized groups yielded similar outcomes, and Cordain et al. concluded that acne incidence rates between westernized and non-westernized societies likely result from environmental factors, like diet (2002).

To dive further into the construct of hyperinsulinemia in relation to the presence of acne vulgaris, Cordain, Eades and Eades conducted research examining the pathophysiology of hyperinsulinemia and insulin resistance in relation to acne vulgaris, among other maladies, denoted as Syndrome X, which includes hypertension, type 2 diabetes, dyslipidemia, coronary artery disease, obesity, abnormal glucose tolerance, among others (2003).

The biochemical breakdown of consumption of high-glycemic load carbohydrates is explained in great detail, suggesting that consuming such high-glycemic-load meals acutely increases hepatic secretion of very low density lipoproteins (VLDL), in turn increasing endocrine and homeostatic changes.

The researchers go further to explain how hyperinsulinemia can cause a shift in the endocrine pathways related to growth, and therefore cause upregulation of insulin growth factors, more specifically IGF-1, which reduces insulin-like growth factor-binding protein 3 (IGFBP-3). Since IGFBP-3 is a ligand for nuclear retinoid X receptor, reduced levels of IGFBP-3 may influence transcription of anti-proliferative genes, thereby causing cellular proliferation and growth in a variety of tissues which promote acne production. Hyperinsulinemia also causes overexpression of the epidermal growth factor receptor (EGF-R) by elevating fatty acids in the plasma, which induces production of transforming growth factor-beta (TGF-beta1). These increased concentrations of both EGF and TGF-beta1 can depress localized keratinocyte synthesis of IGFBP-3, which leads to decreased availability of free IGF-1 to keratinocyte receptor and therefore promotes proliferation of keratinocytes (Cordain, Eades, & Eades).

Another biochemical study published by Melnik, supports associations among Western diet and acne vulgaris by the common link, hyperinsulinemia. It has been well-established that the Western diet staples of high glycemic load foods and milk products have been known to increase insulin and IGF-1. This article provides an additional pathway by which hyperinsulinemia affects the presence and severity of acne vulgaris, with mammalian target of rapamycin complex-1 (mTORC1) comprising that link. mTORC1 is a protein kinase that responds to a range of environmental cues and is the growth factor that is activated by growth hormones, such as insulin and IGF-1 amino acids (Melnik, 2018). Intake of hyperglycemic carbohydrates and milk products both have the propensity to induce postprandial rises of serum insulin levels, which then in turn, signal the activation of mTORC1. Increased expression of mTORC1 kinases in the skin promotes cell growth and proliferation of keratinocytes (Melnik, 2018).

DISCUSSION

Recent studies have suggested that as diets begin to Westernize, prevalence rates of acne vulgaris have increased. The major components of the Western diet, hyperglycemic, processed carbohydrates along with milk and other dairy products, have been identified in the pathogenesis of acne vulgaris.

In theme one, studies have provided a new perspective on nutrient signaling in acne vulgaris by both high glycemic load, increased insulin, IGF-1, and leucine signaling due to dairy protein consumption. In the study conducted by Cerman et al., the dietary glycemic index was much higher in the patients with present acne vulgaris, when compared to individuals in the control group. Furthermore, the glycemic index values were significantly higher in patients with moderate to severe acne presentation when compared to those with mild acne presentation. Thus, Cerman et al. have suggested that "High-glycemic index diets might play a role as a pathogenetic cofactor that triggers the development of acne vulgaris and increases its severity" (2016, p. 159).

Kaymak et al. also discuss the parameters of a Westernized diet, reporting that Turkish dietary attitudes accurately resemble that of the Western population, especially within the last decade with the increase in fast food consumption in Turkey (2007). Therefore, higher incidence rates of acne in the Turkish population could be predicted, due to this recent change in dietary attitudes amongst this population. However, the authors concluded that dietary glycemic index, glycemic load, and insulin levels in patients in the acne vulgaris group were not higher than levels experienced by the control group individuals; this suggests that these factors do not play as large of a role in the pathogenesis of acne vulgaris in the Turkish population.

Smith, Mann, Braue, Makelainen, and Varigos took a contrary approach to studying Western diet; they investigated the independent effects of an experimental low glucose load (LGL) diet in comparison to the standard Westernized diet, high in carbohydrates and refined sugars. Individuals in both groups showed improvement in their present acne, however, the low glucose load group showed significantly greater reductions in the clinical and endocrine assessments of acne. Furthermore, the participants in the LGL diet group also lost weight and decreased measures of adiposity. Conversely, participants in the Westernized diet group did not experience any weight reduction or change in body composition. In accordance with the author's hypothesis, changes in insulin sensitivity correlated moderately with changes in lesion counts, with increased insulin sensitivity showing greater reductions in lesion presentation. Smith, Mann, Braue, Makelainen, and Varigos suggested that, "The therapeutic effect may be a factor of the change in insulin sensitivity, or simply that improved insulin sensitivity is another manifestation of a LGL diet" (2007, p. 254).

By and large, the question of whether or not high glycemic load foods have an effect on the manifestation of acne vulgaris should be addressed. There seems to be conflicting results among the analyzed literature presented in the following studies. Overall, there seems to be a positive relationship between consumption of a high glycemic load diet and acne vulgaris, only when the high glycemic load diet is broken down and insulin sensitivity is specifically studied.

Dairy intake has been thought to influence the pathogenesis of acne vulgaris due to its containment of androgens, steroids and other nonsteroidal growth factors that affect the pilosebaceous unit. In theme two, the influence of dairy products on the pathogenesis of acne revealed varying results.

Adebamowo et al. determined there was a weak association between milk intake and acne in boys, when compared to that of girls, but nevertheless provides backing of their hypothesis. Milk intake is thought to affect comedogenicity through the insulin-like growth factor (IGF)-1 pathway, more specifically the ability of IGF-1 to increase levels of circulating androgens within the body. It is well known that girls at this age are at a greater degree of maturation than boys. The insulin-like growth factor (IGF)-1 levels in girls tend to peak around age 15, whereas the peak of IGF-1 levels in boys are closer to age 18. The authors state that the specific cohort of boys examined in this study had not yet entered their IGF-1 mediated growth spurt, so they are not influenced by their endogenous hormones as much as girls are influenced by their endogenous hormones at this age. They concluded that their findings were considered an adequate representation of the influence of their exogenous dairy hormones.

The data in the study conducted by LaRosa et al. supports the previously acknowledged notion that there is an association between the presentation of acne vulgaris and consumption of skim milk products. No associations between acne vulgaris and the consumption of full-fat dairy products, macronutrient composition, glycemic index, or glycemic load were found. LaRosa et al. stated, "Although there is statistical significance in P values for total dairy consumption and total low-fat/fat-free dairy consumption, the P values of these variables are reduced by the consumption of total low-fat/skim milk in the 2 groups, as low-fat/skim milk consumption is a component of both total dairy and total low-fat/fat-free dairy groups" (2016, p. 320). When low-fat/ skim milk was removed from those groups, statistical differences were lost.

Ulvestad et al. conducted a longitudinal, population-based study that demonstrated an association between high dairy intake consumed in early adolescence and the presentation of acne vulgaris occurring later in adolescence. A large intake of dairy consumption by girls,

regardless the amount of fat content, was associated with acne presentation later in adolescence. In boys, high intake of only full-fat dairy products seemed to be associated with the presence of acne later in adolescence. However, there were no significant findings between the consumption of skimmed or semi-skimmed dairy products and the presentation of acne vulgaris; the presence of acne vulgaris in relation to consumption of only skimmed milk products has been supported through several recent studies. The results of this study add to the arguments that support a link between milk consumption and acne vulgaris presentation. Ulvestad et al. stated that "It has been suggested that the acnegenic effect of dairy is unlikely to be caused by its fat content, but rather by hormones and other bioactive molecules contained in the milk" (2017, p. 533).

Overall, the question of whether or not dairy-rich foods have an effect on the manifestation of acne vulgaris should be addressed. There seems to be conflicting results among the analyzed literature presented in the studies. Overall, there seems to be a positive relationship between consumption of a dairy-rich diet and acne vulgaris, only when the dairy-rich diet is broken down and insulin sensitivity is specifically studied.

All in all, more current studies are warranted to thoroughly examine the link of insulin resistance among the high glycemic load and dairy-rich foods that make up Western diet. Ideally, data using the same parameters to measure acne manifestation and assessed by a dermatologist, as well as a controlled, easily measured diet consumed by all participants would be used to better understand if this relationship is, indeed, significant. With a controlled diet, macronutrient breakdown, mTORC1, and serum insulin levels, could be specifically studied and compared to the participants' acne manifestation designations.

In theme three, the pathophysiology of hyperinsulinemia and insulin resistance in relation to acne vulgaris was thoroughly examined, with IGF-1 IGFBP-3, and mTORC1 acting as the key players in the pathogenesis of acne vulgaris. These increases in insulin and IGF-1 stimulate the synthesis of androgens, which for years, have been believed to be a key component in acne pathogenesis. In addition, insulin and IGF-1 inhibit hepatic synthesis of sex hormone binding globulin (SHBG), which therefore increases the bioavailability of circulating androgens to all tissues. In sum, sebum production is stimulated from multiple facets, increased circulating androgens, as well as increased concentrations of insulin and IGF-1.

High-glycemic-load carbohydrates and dairy products now comprise nearly 40% of the daily energy in the typical Western diet in the United States, which is a secular increase in the glycemic load that has been occurring in the last few decades. With the increase in consumption of high glycemic-load and dairy rich diets, the concentrations of insulin and IGF-1, as well as free-circulating androgens, has increased, leading to hyperinsulinemia. Taken together, these data suggest that the endocrine cascade induced by hyperinsulinemia enhances sebum synthesis; with sebum production being essential to the development of acne vulgaris, this increase is paramount.

CLINICAL APPLICABILITY

Acne vulgaris now affects around 85% of adolescents in Westernized nations (Melnik, 2018). With most cases of acne occurring during adolescent years where individuals are already typically experiencing emotional vitality, the presence of acne can lead to greater sensitivity to the adverse effects on their physical appearance. Not only can the presence of acne cause physical discomfort and scarring to an individual, but it can also cause life-long psychological and emotional scarring, increasing one's risk of depression and in some instances, suicidal ideation. Approximately 7% of patients with acne exhibit depression or suicidal ideation (Mancini, 2008). The emotional impact of acne is often extremely difficult for patients to endure. In addition to emotional complications, this adolescent population tends to expect immediate improvement in their dermatological condition; thus, they are often impatient with and poorly adherent to acne treatment. Patient education is of utmost importance in order to fully disclose the treatment time frame and hopefully prevent the emotional consequences that can be associated with adolescent acne presentation.

With acne vulgaris accounting for 35.0% of family medicine office visits in adolescent males and 66.9% of family medicine office visits in adolescent females, trying to determine a likely cause that is relatively modifiable, such as diet, is extremely applicable to primary care clinic providers (Verhoeven et al., 2008). In addition, greater maladies than acne manifestation have been found to be associated with consuming a high-glycemic-load, dairy-rich Western diet. The hyperinsulinemia that is linked with Western diet, can cause a number of diseases, such as

hypertension, type II diabetes, dyslipidemia, coronary artery disease, obesity, and abnormal glucose tolerance, which makeup a majority of maladies that primary care providers follow.

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