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The Impact of Diet on Acne

(title)

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A B S T R A C T

Background: Despite a high populational prevalence of acne, emerging studies and self–perceived societal belief on a relationship between western diet and acne, the topic remains controversial. To date, no dietary recommendations have been involved in current guidelines on the management of acne.

Objective: The aim of this research work is to analyze the impact of diet on acne.

Methods: A narrative review was conducted using recent evidence of the PubMed database, focusing on human studies from the last ten years (2012 – 2022).

Results: Insulinotropic western diet enhances insulin-like growth factor-1 mediated activation of mammalian target of rapamycin complex, thereby increasing sebum production and keratinization involved in the pathogenesis of acne. A significant association between acne and consumption of food high in glycemic load, dairy products, whey protein and chocolate as well as an abnormal lipid profile was observed. A relationship between acne and BMI as well as adiponectin levels remains controversial. Consumption of a Mediterranean diet that is low in glycemic load and high in polyunsaturated fatty acids and maintenance of sufficient micronutrient levels are protective factors against the onset of acne. First research results on probiotics promise positive effects on acne, but more in vivo human studies should be performed in the future.

Conclusion: Diet has a significant impact on acne and therefore, dietary recommendations should be added to the current guidelines. However, more research with high-quality evidence has to be conducted in the future.

Keywords: “acne” AND “diet”, “nutrition”, “food”, “IGF-1”, “mTORC”, “glycemic index / load”, “dairy”, “chocolate”, “Mediterranean”, “fish”, “whey”, “vitamins”, “probiotics”, “BMI”

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I. INTRODUCTION

Globally, the sum of prevalent cases of acne has increased to 231,2 million in 2019 compared to 156,7 million prevalent cases in 1990. (1) The Global Burden of Skin Disease study in 2010 stated that acne is among the ten most prevalent diseases in 2010, ranking the 8th place. (2)

3 billion dollars of cost are created by acne per year regarding lost productivity and treatment in the U.S. (3) In comparison to other dermatological diseases, i.e. atopic dermatitis and urticaria, the public interest is highest in acne, found out by a study analyzing data from Google Trends between 2004 and 2019. (4)

Acne has a psychological impact on humans by negatively affecting relationships, lowering self – esteem, increasing fear of embarrassment and hence reducing overall quality of life according to questionnaire – based cross – sectional studies. (5,6)

It is considered a 'westernized disease' as the prevalence is significantly higher in developed compared to non – developed countries. (7) Serving as popular example, the inhabitants of the island Kitava in Papua New Guinea, living a traditional life apart from western civilization, were observed to have no cases of acne at all. (8) The indigenous Dogon people from Mali have an acne prevalence of 28.3 % among the adolescents, aged between 11.5 to 18.8 years, with 90.8 % of cases being mild, whereas as a prevalence of 50 – 95 % with 21 to 47 % of them having moderate to severe acne was noted in adolescents from developed countries i.e UK, Belgium, New Zealand and Singapore. (9)

In a study among 1277 Lithuanian pupils, 64,5 % of participants mentioned diet as one of the main exacerbating factors related to acne. (10) Many observational studies like this to explore the self – perception of people about a possible association of diet and acne have been performed around the world. There, participants often associate exacerbation of acne with the increased consumption of milk, cheese, chocolate, sweets and foods rich in saturated fats and limited intake of fish, fruits and vegetables. (11–17)

However, the association between diet and acne remains controversial and up until today, no dietary – based treatment recommendations are found in the most recent guidelines about the management of acne. (18,19)

The aim of this research work is to analyze and review current evidence on the impact of diet on acne in order to decide whether it should take a role in its management and to which extent. After giving a brief overview on current knowledge of the disease and it's management,

nutritional components, patterns and related metabolic parameters will be individually discussed for a possible association with acne.

II. METHODS

A PubMed search was conducted by inserting the keywords “diet”, “food” and “nutrition”, each separately in combination with the term “acne”. In order to obtain only the most recent data, a timeframe only including articles from the last ten years (2012 – 2022), was set within the PubMed database. Sorted by best match, the search “food” and “acne” yielded 402 matches, the search “diet” and “acne” 249 matches and the search “nutrition” and “acne” 137 matches, potentially giving 788 articles to choose from. As a matter of fact, the actual number was lower as there was a considerably high number of cross – matches between the searches of the mentioned keywords.

Nonetheless, inclusion and exclusion criteria, apart from the timeframe, were set to create a relevant literature review on the research topic. Regarding language, only articles published in English were considered. Studies were included if performed on humans and mode of administration was per os. Articles not focusing directly on acne, but on other medical conditions featuring acne as a symptom as for example polycystic ovary syndrome were excluded. Foods, micronutrients (e.g. vitamins), dietary supplements (e.g. whey protein), certain diets and metabolic parameters had to be put at least in an association to acne by an article in order to get involved in this research work. Articles specializing on diet only as a supporting role to adherence or effectiveness of pharmacological agents of acne therapy were excluded as they undermine the aim of this review to analyze the direct impact of diet on acne. Some additional papers found by reviewing the reference list of articles meeting the inclusion criteria have been included. In order to not start this literature review with a preconceived opinion, reviews of other authors on the impact of diet on acne were neglected on the first search attempt. In later stages of the work process, narrative reviews, exclusively focusing on the pathogenetic relationship between dietary factors and acne, as well as systematic reviews were included.

In addition to the main search criteria, another search on the PubMed database with the same timeframe has been conducted using only the keyword “acne”, filtered exclusively for reviews and guidelines. The intention was to involve general knowledge about acne as a disease into

this research work and to connect collected evidence to principals of recent clinical practice, represented by guidelines. The most recent NICE guideline "Acne vulgaris: management" and "Guidelines of care for the management of acne vulgaris" from the American Academy of Dermatology were involved.

III. RESULTS

3.1 Definition, diagnosis, classification, epidemiology and treatment principles of acne

The American Academy of Dermatology defines acne vulgaris as "a chronic inflammatory dermatosis notable for open or closed comedones (blackheads and whiteheads) and inflammatory lesions, including papules, pustules, or nodules (also known as cysts)". (18)
Diagnosis of acne does not require any specialized tests and is performed clinically by visual inspection of lesions and subsequent grading. (20)

Figure 1. "Non – inflammatory acne lesions consisting of open and closed comedones." (20)

Figure 2. "Severe inflammatory acne lesions with comedones, several papules and pustules, multiple nodules, and scarring." (20)

Beside the consistent classification of acne lesions into inflammatory (see Figure 1.) and non – inflammatory type, often appearing together in acne patients (see Figure 2.), severity can be graded by numerous scores and scales. However, by reviewing articles on this research topic, the "Global Acne Grading System" was found to be used the most as an outcome measure of acne severity. It includes six areas of the face and trunk where acne lesions most commonly

appear, namely forehead, cheeks, nose, chin, chest as well as upper back and assigns a factor to them, based on “surface area, distribution and density of pilosebaceous units”. (21) Lesions in each of the regions are given a score related to their type (comedo, papule, pustule, nodule). The product of the factor of an area and score of lesion type yields a local score and the sum of all the local scores results in a global score. Scores between 1 to 18 are considered mild in severity, 19 -30 are moderate, 31-38 are severe and >38 are considered very severe.

The onset of acne usually corresponds to the onset of puberty and carries on into the 20s to 30s, but may be seen already in prepubertal children of non – inflammatory type as sebum production, important for the colonization of *Cutibacterium acnes*, is still low. (3) The peak incidence in boys is observed in the age of 16 to 19 and in between 14 to 17 years of age in girls. (22) However, acne can also begin in adulthood which is more prevalent in women than men. (23)

Pharmacologically, benzoyl peroxide, retinoids and antibiotics (especially erythromycin and clindamycin) are shown to be effective in the treatment of acne. (18) They are prescribed either as monotherapy or in combinations, applied topically in milder forms and orally in severe forms of acne. Additionally, estrogen – containing combined oral contraceptives are an effective treatment for females with inflammatory acne. (18) Apart from mentioned treatment options, guidelines ask practitioners to consider intralesional corticosteroids and systemic retinoids as adjunctive in acute flares and physical therapy modalities (e.g. photodynamic therapy, pulsed dye lasers, peels) if pharmacological treatment fails to succeed. (18,19) Beside the consistent risk of resistances towards frequently used antibiotics, reasons for unsuccessful pharmacological therapy are mostly attributed to low compliance e.g. due to early discontinuation of medication by patients on first visible improvement of lesions or due to difficulties in adherence to complicated combinational therapy schemes. (24)

Recommendation 1.3.1 of the current NICE guideline on the management of acne vulgaris states to “advise people that there is not enough evidence to support specific diets for treating acne”. (19) The committee bases its decision by reviewing only the evidence from four randomized controlled trials about the impact of a diet low in glycemic load on acne vulgaris of which only two of them are within the research criteria of this work due to date of publication. Under this circumstances, the committee is more concerned about the onset of eating disorder in the mostly young acne population and states that “the recommendation will not have an substantial impact on the current practice”. (19)

3.2 Etiopathogenesis of acne

Traditionally, four major interrelated contributors in the etiopathogenesis of acne are often described and targeted by current therapy (see yellow boxes in Figure 3): follicular hyperkeratinization, androgen - induced overproduction of sebum, hypercolonization and biofilm formation of *Cutibacterium acnes* as well as resulting inflammatory and immunological reactions. (20,25,26)

In the recent decades, scientific research collected evidence on the influence of previously unknown hormonal and cellular pathways on the mentioned contributors of acne development. (27)

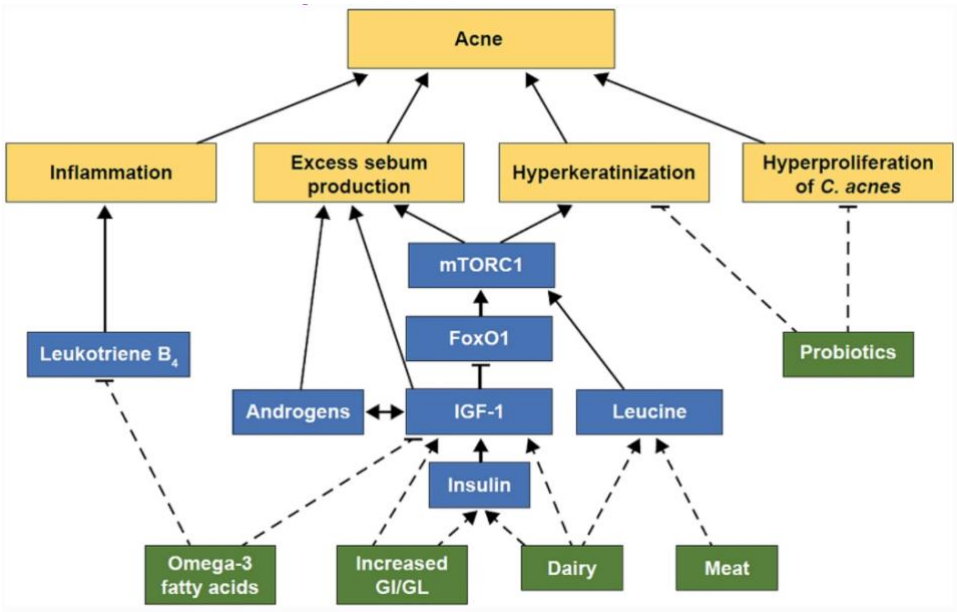

Figure 3. "Dietary impact on mammalian target of rapamycin complex 1 (mTORC1) signaling." (28) Abbreviations: *FoxO1* = forkhead box class O transcription factor 1, *GI* = glycemic index, *GL* = glycemic load, *IGF – 1* = insulin – like growth factor – 1.

In a case – control study of fourty acne patients and twenty age- and gender – matched healthy controls, significantly elevated serum levels of insulin – like growth factor – 1 (IGF-1), expression of mammalian target of rapamycin complex (mTORC) and cytoplasmic form of forkhead box class transcription factor O1 (FoxO1) were measured in acne patients compared to the other group. (29) In vitro treatment of cultured sebocytes with IGF – 1 was shown to increase the production of sebum and expressed levels of inflammatory mediators (e.g. interleukin – 6 and tumor necrosis factor alpha). (30) Mainly, mTORC1 is known to regulate lipogenesis as well as proliferation and growth of cells. (31) Hence, overexpression of mTORC1 in acne is associated with excessive lipid synthesis by sebocytes and over

proliferation of keratinocytes. Western diet, consisting mainly of insulinotropic food items, activate mTORC1 indirectly via increased hepatic release of IGF – 1 which in turn mediates the suppression of nucleic FoxO1, which is responsible for downregulation for mTORC1. (32) Suppression of FoxO1 involves a kinase – mediated phosphorylation leading to its export from nucleus to cytoplasm. (31) Mammalian target of rapamycin complex 1 can also be activated directly by branched – chain amino acids (e.g. leucine), which are found abundantly in dairy, egg and meat proteins of western diet. (33) Insulin – like growth factor – 1 levels generally, coinciding with androgen levels, peak during puberty and may superimpose with diet – induced IGF – 1 signaling. (32)

Dietary components (see green boxes in Figure 3.) are under research for their possible influence on the mentioned cellular and hormonal pathways of acne and will be reviewed individually within this research work.

3.3 Impact of glycemic index and glycemic load on acne

Before reviewing the evidence on the relationship between glycemic index or glycemic load and acne, the meaning of both terms should be explained. The glycemic index uses postprandial changes of the blood glucose level after ingestion of carbohydrate – containing substances to rank food items accordingly and glycemic load is "the product of glycemic index and the total available carbohydrate content in a given amount of food". (34) Carbohydrate – containing foods with a high glycemic index (e.g. white bread, potatoes, sweets and confectionary) are characterized by quick digestion and metabolization whereas those foods with a low glycemic index (e.g. vegetables, fish, legumes) are digested and metabolized slower. (34,35) Numerous observational studies, based on self – questionnaires with subsequent clinical evaluation, have found a connection between acne and consumption of food high in glycemic index and load. (12,36,37)

A cross – sectional study from New York with 64 participants, 32 patients with moderate or severe acne and 32 without acne, was performed to analyze the association between acne, glycemic load, glycemic index and blood levels of biological factors that are all thought be involved in the pathogenesis of acne. (38) Statistically significant ($p < 0.05$) elevation of insulin levels, IGF – 1 concentration, insulin resistance and lower sex hormone binding globulin concentration was observed in the group with moderate to severe acne in comparison to the participants without acne. No statistically significant differences in insulin growth factor binding protein – 3 or glucose concentration have been found between both groups. Sex hormone binding globulin and insulin growth factor binding protein are known to be

downregulated by increased insulin levels, but would normally inhibit bioavailability of androgens and circulating IGF – 1. (39) By this theory, concentration of both should be decreased in hyperinsulinemia, which was proven at least for the sex hormone binding globulin in this study. Furthermore, a statistically significant elevated consumption of high glycemic index food, presented as " greater total carbohydrate (P=0.003), available carbohydrate (total carbohydrate minus dietary fiber) (P<0.001) and percent energy from carbohydrate (P<0.001)" as well as glycemic load was revealed in the acne group. (38) The results tie in well with the previously described insulinotropic – mediated pathogenesis of acne by successfully associating food high in glycemic load/index to high IGF – 1 levels that in turn enhance the activation of mTORC1. (29,30)

An interventional approach to study the influence of food different in glycemic loads was made in Korea by randomly allocating 32 participants with mild to moderate acne to follow either a diet low in glycemic load (n=17) or high in glycemic load (n=15) over a 10 – week period with subsequent assessment of changes in lesion count as a primary outcome. (40)

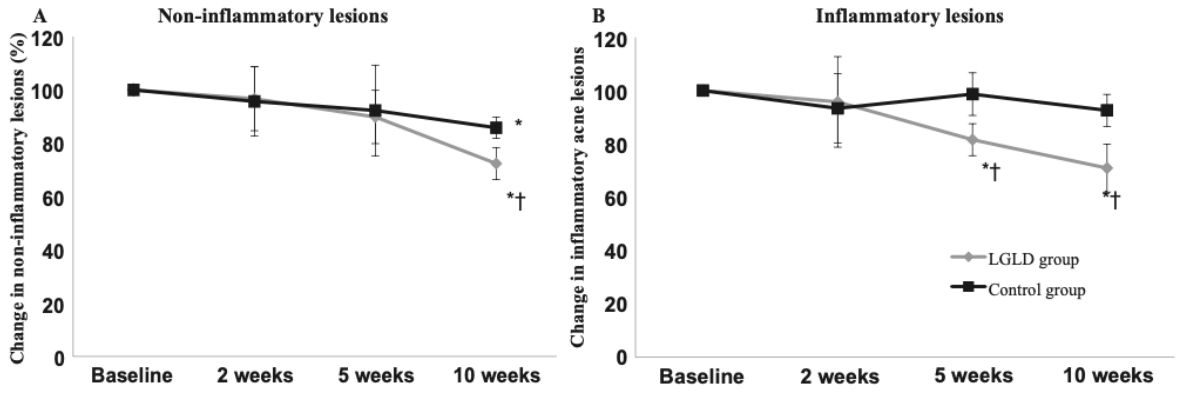

Figure 4. "Mean percentage change in (A) the non – inflammatory lesion counts and (B) the inflammatory acne lesion counts at each visit. *= p<0.05 vs. baseline, †= p <0.05 between the 2 groups". (40)

A statistically significant reduction (p<0.05) in inflammatory lesions in the group with low glycemic load compared to the group with high glycemic load diet and compared to baseline values was already observed after 5 weeks (see Figure 4B.). Looking at non – inflammatory lesions, it took 10 weeks until statistically significant changes were seen between the two groups in comparison to baseline values (see Figure 4A.). Additionally, statistically significant decrease in the size of mean area of sebaceous glands was noted after 10 weeks, compared to baseline. Another randomized controlled trial, similar to this, was performed in 2018, but only

following the diet for a two – week period. (41) The sixty – six participants, that were either told to eat diet low in glycemic load or follow a normal eating plan were assessed for changes in IGF – 1 level as an outcome measure. As in previous studies, statistically significant reduction (p <0.05) in IGF – 1 concentration in the group with low glycemic diet was noted but should be observed carefully here as the p value was only marginally significant (P=0.049). This might be explained by the short duration of two weeks in comparison to the previous study of ten weeks where visual changes appeared significantly earliest from the fifth week.

3.4 Impact of dairy on acne

Dairy products are thought to be involved in the pathogenesis of acne due to their milk proteins, rich in insulinotropic branched – chain amino acids (valine, leucine, isoleucine), activating mTORC1 either indirectly through enhanced insulin – like growth factor – 1 signaling in postprandial hyperinsulinemia or directly via an L-type amino acid transporter. (33)

In Pennsylvania, a case – control study with 225 participants, in the age between 14 to 19 years, was performed to investigate a potential association between acne and dairy consumption in adolescents. (42) The control group was composed of 105 participants without acne and the other group of 120 people with moderate acne (according to the Global Acne Assessment Scale). There was a significant statistical increase in number of servings of dairy per day (in mean SD) of low fat/skim milk consumption between acne and control group (p value of 0.01) whereas there was no significant difference of full – fat or reduced – fat milk consumption between acne and control group (p value 0.75 and 0.44 respectively). Looking at the total dairy, firstly there seems to be a statistically significant difference between the groups, which is lost when removing low – fat/skim milk from total dairy consumed. Contradicting to these findings, inflammatory acne was correlated with the daily consumption of whole fat milk, but not low fat milk by crude analysis of an cross – sectional study of 2,201 18 year - old Brazilian male participants enlisted in the army. (43) On the one hand, it could be hypothesized that the aspect of daily consumption is of higher importance than the fat content of the milk, on the other hand the study has severe limitations as there is no specification for the quantity of daily consumption and the statistical significant difference gets lost when considering inflammatory and non – inflammatory acne as a sum or even when looking at non – inflammatory acne exclusively or preforming multivariate analysis.

It remains controversial within observational studies to which extent the fat content of milk plays a role in pathogenesis of acne, but a general relationship between daily consumption of milk and acne was shown. (16,37,44,45) No interventional studies to test the impact of different

types of milk on acne were found within the research criteria of this work and research towards this direction should be conducted in future.

Expanding the view on other dairy products than milk, a case – control study conducted between October 2017 and May 2018 indicates an association between increased cheese consumption and acne by revealing a statistically significant difference (p value < 0.05) of cheese consumption between a group of 53 acne vulgaris patients and their demographically – matched healthy control group, consisting of 53 participants as well. (46) Coinciding with this, a correlation of consumption of cheese and acne was found in many other observational studies. (35,47)

3.5 Impact of chocolate on acne

Chocolate is one of the most mentioned factors that is thought to potentially aggravate acne in self – perceptual questionnaire – based observational studies. (11,13,14,16) Looking at interventional studies, a clinical trial from Thailand aimed to study a possible relationship between acne exacerbations and dark chocolate consumption in 25 male participants, aged between 18 and 30, having acne – prone skin grade 1 – 4 by evaluation using the Leeds revised acne grading system. (48) All participants were required to eliminate all cocoa – containing items from their diet for four weeks before the start of the trial. Participants were advised to eat 25 g of dark chocolate once a day for a period of four weeks. In order to inhibit false conclusions associated with dairy and acne, a chocolate with 99% cocoa content was used for this trial. Compared to baseline values, statistically significant changes (p<0.01) in Leeds score on visual inspection (see Figure 5.) were seen after 14 days, proving an association between acne and dark chocolate consumption. As the chocolate in this study contained no milk, an explanation of chocolate induced onset of acne by cross - interfering increased IGF – 1 signaling by dairy, was excluded.

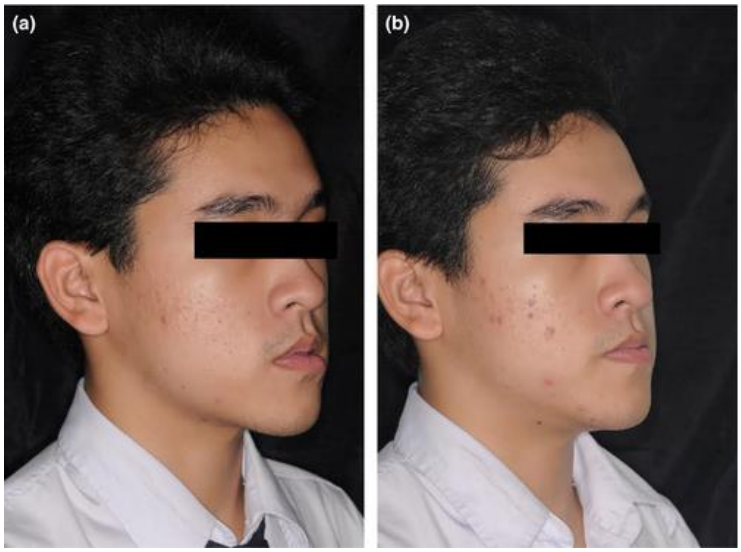

Figure 5. "(a) Baseline, subject 13. (b) Week 2, subject 13." (48)

In order to exclude a high glycemic index as an explanation of the impact of chocolate on acne, a study was conducted comparing chocolate with another sweet, jelly beans, having an equally high glycemic index. In this randomized crossover study, 54 students were randomly chosen to consume either 43 g of "Hershey's" milk chocolate bar or 15 "Jelly Belly" jellybeans and acne lesions were counted and compared to pre – study pictures after 48 hours. (49) After a four – week washout phase, the same steps were taken again. A statistically significant (p<0.0001) difference in acne lesions can be seen comparing chocolate consumers (+4,8 lesions) to the jelly bean consumers (-0.7 lesions) leading to the hypothesis that certain specific components of chocolate may be the explanation for its impact on acne.

The mechanism by which chocolate exacerbates acne formation remains unclear. Most likely, the fatty acids in cocoa butter, namely stearic and oleic acid, play a role in the pathogenesis of acne as animal studies have observed an oleic acid - induced comedones formation by alteration of follicular epithelial keratinization. (48) Involvement of flavonoids from cocoa in the pathogenesis of acne is unlikely as they are known to have anti-inflammatory properties and hence theoretically should be protective against acne. (50)

A study of double – blinded and placebo – controlled type was conducted by randomizing fourteen males with history of acne to consume capsules for seven days, consisting of either hydrolyzed gelatin powder (controls), unsweetened pure cocoa (100%) or both together as a combination. A statistical significant increase in number of total lesions (involving comedones, pustules, papules and nodules) was achieved both on the 4^{th} and 7^{th} day (p= 0.006 and p=0.043,

respectively). (51) This ties in well with the hypothesis that components of cocoa might be involved in the pathogenesis of acne but more studies towards specific components must be conducted in the future.

3.6 Impact of whey protein supplementation on acne

Protein supplementation, especially using whey protein, is a popular tool in body building promising accelerated muscle growth and enhanced training performance to consumers. A cross - sectional study of 180 physical exercise practitioners, performed in Brazil, answering questions about supplementation and related self - perceived side effects not only showed that there is a high prevalence of intake of nutritional supplement among participants (58.3 %), but also that the most common self-perceived adverse effect is acne (21.9 %). (52)

Isolating proteins from whey, a liquid byproduct of milk leftover during cheese production, yields a supplement containing "beta lactoglobulin, alpha lactalalbumin, bovine serum albumin and immunoglobulin". (53) Although there appears to be a relationship between dairy products and acne, and whey protein supplements can be classified as a dairy (by-)product in broadest sense, no recent high level evidence was found within the research criteria of this work on the impact of protein supplementation on acne, apart from level 4 evidence case studies. (54) It is especially surprising regarding the fact that a common whey supplement concentration used in body building contains the same amount of whey protein as in 6 – 12 liters of milk. (53) Alpha lactalalbumin of whey protein has a higher tryptophan content than any other dietary protein source, increasing pituitary synthesis of serotonin which results in growth hormone secretion that in turn enhances IGF – 1 synthesis in liver and ultimately participates in pathogenesis of acne via increased mTORC1 signaling. (32) Generally, whey protein is rich in branch – chained amino acids, especially leucine, which were already proposed to cause acne in a previous section. (33,55)

A small case study, performed by the Department of Dermatology of the St. Luke's – Roosevelt Hospital Center in New York, reported a link between the onset of acne after the initiation of whey supplementation using different brands in five adolescent male teenagers aged between 14 and 18 years. (56) All of the participants denied the usage of other supplements, like creatinine or steroids. The exclusive pharmacological therapy with topical benzoyl peroxide, retinoids and oral antibiotics given in various dosages failed to achieve clinical improvement whereas the combination of pharmacological treatment and discontinuation of supplementation intake led to full remission in four out of five participants. Overall these findings are in

accordance with findings reported by another case study from 2017 involving six male patients aged between 16 and 18 years, all showing acne lesions on the trunk after starting oral supplementation with whey protein, which improved by the administration of oral antibiotics and topical benzoyl peroxide gel together with discontinuation of whey protein. (53) Interestingly, two of the six participants refused to discontinue protein supplementation firstly, resulting in less remission than the others which raises thoughts that the impact of discontinuation of whey supplementation is bigger than the pharmacological treatment. In both case studies, patients were described as overall healthy, but in this recent one from 2017, laboratory values of all patients were determined including AST, ALT, total bilirubin and antibodies against hepatitis A, B and C as well as BMI to provide a more detailed picture of participants' health.

Both smaller case studies tie in well with the results of the biggest case series study on this topic up until today, including 30 participants in Brazil with a mean age of 23, revealing a correlation between acne severity and whey protein supplementation by clinical evaluation of photography before and after a 60 day period of supplementation. (57)

3.7 Impact of Mediterranean diet on acne

The beneficial effects of a diet low in glycemic index on acne were discussed in a previous section. The dietary style reflecting these properties the most is the Mediterranean diet by being rich in whole grains, seeds, nuts, unsaturated fats (e.g. olive oil an fish), fruits, vegetables, legumes as well as low in animal – based products (e.g like dairy or meat) and processed foods (e.g. sugary beverages or confectionary). In metabolic disorders and associated cardiovascular diseases and as an protection against several cancer types, it is already recommended as the diet of choice. (37)

A cross – sectional study from Naples with 102 participants in the age between 18 to 42, including 51 acne patients and 51 healthy controls was analyzing the association between acne and adherence to Mediterranean diet using a questionnaire involving 14 – food items and the frequency of their consumption (see Table 1). (58)

Table 1. "Response frequency of dietary components included in the PREDIMED questionnaire in patients with acne and control Group" (58)

Questions of PREDIMED questionnaire	Patients with acne		Control group			
	n	%	n	%	χ	*p*-value*
Use of extra virgin olive oil as main culinary lipid	48	94.1	44	86.3	0.99	0.318
Extra virgin olive oil > 4 tablespoons	42	82.4	42	82.4	0.07	0.795
Vegetables ≥ 2 servings/day	25	49.0	37	72.5	4.98	**0.026**
Fruits ≥ 3 servings/day	25	49.0	39	76.5	7.09	**0.008**
Red/processed meats < 1/day	37	72.5	27	52.9	3.39	0.065
Butter, cream, margarine < 1/day	39	76.5	45	88.2	1.69	0.194
Soda drinks < 1/day	29	56.9	40	78.4	4.48	**0.034**
Wine glasses ≥ 7/week	17	33.3	23	45.1	1.03	0.311
Legumes ≥ 3/week	33	64.7	43	84.3	4.18	**0.041**
Fish/seafood ≥ 3/week	23	45.1	45	88.2	19.46	**< 0.001**
Commercial sweets and confectionery ≤ 2/week	33	64.7	44	86.3	5.30	**0.021**
Tree nuts ≥ 3/week	22	43.1	38	74.5	9.11	**0.003**
Poultry more than red meats	36	70.6	45	88.2	3.84	0.051
Use of sofrito sauce ≥ 2/week	29	56.9	32	62.7	0.16	0.686

Patients with acne consumed less vegetables, fruits, legumes, fish, and nuts; and more soda drinks, commercial sweets, and confectionery, as compared with the control group. Results are expressed as numbers and percentage. Differences in the frequency response of dietary components included in the PREDIMED questionnaire were analysed by Chi-square (χ^2) test

PREDIMED PREvención con DIetaMEDiterránea

*A *p* value in bold type denotes a significant difference ($p < 0.05$)

As shown in Table 1, a statistically significant difference ($p < 0.05$) in vegetable, fruit, nuts, fish, legume, confectionary and soda drink consumption between acne and control group can be drawn associating the beneficial effects of Mediterranean dietary components on acne.

These results tie in well with a previous case – control study with 93 cases and 200 controls published in 2012, wherein a high score of adherence to Mediterranean diet revealed protective effects towards acne. (37)

Fiber consumption was significantly lower in acne group compared to controls in an Iranian study. (59) This leads to the hypothesis that a diet rich in fibers, such as the Mediterranean diet, might be protective against acne. Unfortunately, no more recent research focusing only on fibers was found.

Many observational studies have shown an association between acne and a diet low in weekly consumption of fruits, vegetables and fish. (12,60) However, no interventional studies on the impact of Mediterranean diet on acne were found within the research criteria of this work. Although most of the components of the Mediterranean diet, individually and collectively, appear to be beneficial in prevention of acne, a specific component emerges to be associated with an aggravation of acne vulgaris. To analyze the effect of sunflower seed consumption on acne, 50 female acne patients, aged 15 – 30, were randomly split into two groups, an intervention and a control group in a randomized controlled trial performed in Iran. (61) The intervention group was advised to eat 25g of sunflower seeds daily for seven days and the

control group was permitted to eat any sunflower seeds during the trial. After 7 and 14 days, outcomes were measured by changes in Acne Severity index (ASI) compared to baseline evaluation at the beginning of the trial. Statistically significant elevation of ASI ($p < 0.001$) was seen in the intervention group comparing baseline values to the values after two weeks and also comparing intervention group to control group.

With fish, plants and seeds being a major part of the Mediterranean diet, it is characterized by an abundance of essential polyunsaturated fatty acids, namely omega – 3 and omega – 6 fatty acids. Omega – 3 – fatty acids act anti-inflammatory by competitively inhibiting the conversion of arachidonic acid into prostaglandin E2, leukotrienes B4 and B5, thromboxane A2 and A3 and prostacyclin GI3, all being involved in the pathogenesis of acne by inducing inflammation. (62) Furthermore, they are involved in the suppression of cytokines, namely interleukin 1b and tumor necrosis factor alpha and participate in T – cell modulation. (62) In a randomized double – blinded controlled trial, 45 participants in the age between 18 and 33, were divided into three groups either being given dietary omega 3 – fatty acid, gamma – linolenic acid or not given a dietary supplement at all (control group) in order to explore the efficacy of polyunsaturated fats on acne vulgaris severity and acne counts. (63) Baseline acne severity and counts were analyzed and then compared to assessments on week 2, 5 and 10 after start of dietary intervention. A statistically significant decrease ($p<0.05$) in acne count and severity after 10 weeks of dietary supplementation with omega – 3 fatty acids and gamma – linolenic acid compared to control group was noted. However, no significant differences between the two treatment groups were seen, making them appear homogenous in terms of beneficial effects. The mechanism by which gamma – linolenic acid, an omega 6 – fatty acid, is thought to act against the development of acne is of anti-inflammatory nature similar to omega – 3 fatty acids. It's conversion into dihomo-γ-linolenic acid yields a substrate that participates in the production of anti-inflammatory prostaglandin E1 and 15-hydroxydihomo-γlinolenic acid, resulting in suppression of cytokines (e.g. TNF, IL- 6) and reduction of arachidonic acid mediated leukotriene production by inhibition of 5-lipoxygenase. (63) In a case – control study in Italy with 205 moderate to severe acne patients and 358 controls with no or mild acne, a protective effect of fish consumption was observed. (44)

In a small study with 13 healthy male participants with mild to severe acne, 8 participants showed improvement in acne grades on a 12 week diet with fish oil supplementation as an addition to their regular diet in comparison to baseline values. (62) Nonetheless, it has to be mentioned that 4 participants worsened in acne grades and one participant did not change at all making the results not statistically significant ($p=0.338$). Some observants might even

hypothesize that the impact of fish supplementation on acne is rather ineffective, but conclusions from this study have to be drawn with caution regarding the small sample size.

3.8 Impact of micronutrients on acne

The benefits of vitamins and essential trace elements (e.g. zinc, copper) for general health are well accepted in society. In a study published in 2013, 94 patients with acne, subdivided according to Global Acne Grading System into a group with mild to moderate disease and another one with severe to very severe acne, were compared in terms of vitamin A, E and zinc levels in blood to 56 healthy controls with same age and sex that have never encountered acne. (64) A statistically significant reduction ($p<0.001$) in vitamin A, E and zinc levels in acne groups compared to healthy controls was observed. Furthermore, when looking at the results of the two acne groups, the group with severe to very severe acne showed a significant reduction in Vitamin E and zinc levels in comparison to the group with mild to moderate acne. However, no statistically significant difference in vitamin A levels between the two acne groups could be noted. From this study, it may be concluded that there is an association between acne vulgaris and low levels of vitamins and essential trace elements. The exact mechanism by which vitamins and zinc inhibit the onset of acne is unclear, but it is proposed that the antioxidant properties of vitamin A and E result in reduction of inflammatory reactive oxygen species and zinc inhibits production of inflammatory cytokine TNF, chemotaxis and acts bacteriostatic against *C. acnes.* (65)

Similar to this, vitamin D has many anti-inflammatory properties and is thought to play a role in acne by modulating innate and adaptive immunity and in cultured sebocytes, treatment with vitamin D was already shown to reduce the expression of inflammatory biomarkers (IL – 6 and IL – 8). (66,67) In a case – control study using 10 years of records of a clinic for family medicine, serum levels of vitamin D and BMI were screened for 453 acne patients and 250 age- and sex – matched controls. (68) A statistically significant difference in vitamin D deficiency in patients (n= 192 or 42.4 % of patients) compared to control group (n= 61 or 24.4% of controls) was detected. No significant difference between increased BMI levels among participants of both groups were visible in this study, concluding that here the vitamin D deficiency was independently associated with acne vulgaris.

Contradictory to this study, a case – control study from 2021 with 55 acne patients and 30 gender - and age – matched controls showed a significant association between increased BMI and low vitamin D levels in participants with very severe acne ($p = 0.0214$). (69) It was generally noted in this study that with a rising grade of acne severity, BMI increased and

inversely vitamin D levels decreased. The mechanism believed to explain this association is that vitamin D is fat soluble and therefore the bioavailability of dietary and cutaneous input into body is decreased as it gets stored in body fat compartments.(68) However, confluently with the results of the other study, vitamin D was inversely associated with acne vulgaris.

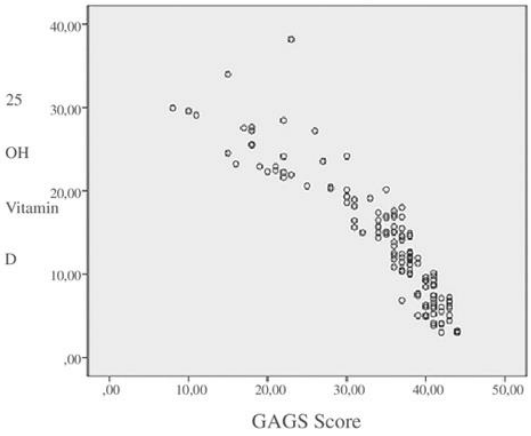

Figure 6. "Correlation of GAGS Scores and 25 – OH vitamin D levels" (70)

Published in 2020, a case – control study with 134 acne patients, aged between 18 – 65 years, and 129 healthy controls with matching age and sex was conducted aimed to analyze the association of acne and serum vitamin D levels as well as the relation of vitamin D levels to acne severity measured by Global Acne Grading Scale. (70) A statistically significant difference between acne and control group could be seen in the prevalence of vitamin D deficiency and the general serum vitamin D level. Furthermore, a significant negative correlation between vitamin D levels and GAGS score can be observed within the acne group (see Figure 7.)

A study that not only tried analyze a possible correlation of vitamin D and acne, but also the effect of vitamin D supplementation was published in 2016. (71) Firstly, in case – control study manner, 25 – hydroxyvitamin D serum levels of 80 acne patients were compared to 80 healthy controls showing a statistically significant difference (p=0.019) in vitamin D deficiency (n=39 and n= 18, respectively). Secondly, in a randomized controlled trial study design, the 39 patients with acne and vitamin D deficiency were divided into two groups. Over 2 months, one group received oral cholecalciferol supplementation (1000 IU/day) and the other group was given an identical – appearing placebo tablet. Patients were assessed before, after and at 2,4 and 8 weeks of treatment and no participant got lost to follow up. Compared to placebo groups, supplementation resulted in statistically significant rise in Vitamin D levels and decrease of

inflammatory acne lesions (reduction by 34.6%) for intervention group. Nonetheless, inspecting non-inflammatory lesions and overall lesion count, there are no statistically significant differences between intervention and placebo groups.

In difference to all the before mentioned studies, a cross-sectional study with 714 randomly selected school children, aged between 11 – 16 years, in Kuwait, revealed no significant difference in 25 – OH – Vitamin D levels between clinically diagnosed acne patients and those without clinically diagnosed acne. (66) However, in univariable analysis, there was a significant difference in vitamin D levels (p=0.002) among those participants who self – reported acne in difference to those who did not. The main advantage of this study in comparison to previously described studies is that Kuwait has an abundance of sun light, reducing the risk of interference by cutaneous related vitamin D deficiency, but the main disadvantage is that all the participants presented only with mild to moderate acne vulgaris.

Nonetheless, a question arising from all the mentioned studies of vitamin D and its observed association to acne is whether it would be useful or not to involve vitamin D levels into the routine work up in the diagnosis of acne vulgaris and further studies towards this direction should be conducted in the future.

3.9 Impact of metabolic parameters on acne

Apart from reviewing the impact of selective dietary factors on acne, it is important to evaluate the relationship between human metabolic parameters and acne as they are well known in clinical medicine to reflect the healthiness of patients and their dietary pattern.

In a case – control study of 64 women with post – adolescent acne and 20 healthy age – and gender - matched controls plasma levels of total cholesterol (TC), high – and low – density lipoprotein cholesterol (HDL - C and LDL - C) as well as triglycerides got compared. (72) Statistically significant ($p < 0.05$) increased values in LDL-C, TC and TG were noted in the acne group in comparison to controls. However, no statistically significant difference in HDL – C values were observed between the two groups. Opposing to this, a statistically significant reduction in HDL – C levels have been found in a study from Iran with 40 female acne vulgaris patients and 40 age – and gender – matched controls. (59) An imbalanced lipid profile is believed to change sebum lipid composition, promoting sebaceous gland activity and consequently increasing inflammation involved in pathogenesis of acne. (73)

This ties in well with a cross – sectional study of 143 adolescents, with a mean age 14.6 years who were analyzed for the connection between BMI and prevalence as well as severity of acne. (74) There was no significant difference between the prevalence of acne and different BMI

values of teenagers, but a significant increase (P=0.03) of inflammatory acne lesions in overweight and obese teenagers compared with slim, underweight or normal weight teenagers. A statistically significant relationship between acne severity and higher BMI values was observed (p<0.001). Lower BMI was protective against moderate to severe acne in male adolescents and young adults in the Italian case - control study mentioned in a previous section of this research work. (44) In a cross – sectional study from Norway with collected data on acne and on BMI of adolescents (from 3655 and 3584, respectively) a relationship between obesity and acne in 18 to 19 years old girls, but not in boys, was observed. (75)

A bigger cross-sectional study of 600,404 soldiers in Israel with a mean age of 18.9 years in males and 18.7 in females aimed to study the relationship between acne and BMI in young population. (76) In contrast to other studies presented here, an inverse relationship between acne and BMI was observed as "overweight, obese, and severely obese participants had 20%, 35% and 50% decreased odds of acne compared with normal – weight participants". (76) The authors of this study attempted to explain it by adipose tissue induced increased activity of aromatase leading to decreased androgen level due to increased turnover to estrogen and ultimately reduced sebum production.

Western diet, especially involving meat, dairy and food with high glycemic load are associated with acne via increased mTORC1 signaling according to recent studies. (33) Therefore it appears logical that an increased BMI that is often caused by western diet could be related to acne. However, the relationship between BMI and prevalence of acne remains unclear and can't be more clarified within the research criteria of this work due to the lack of high-level evidence studies focusing on it. An association between another pathogenetic factor attributing to acne and higher BMI was established. In a case – control study of 60 acne patients and 40 healthy control subjects using immunohistochemical techniques, higher BMI values were statistically significant related to strong IGF – 1 intensity. (77)

High BMI values are known to be associated with insulin resistance and insulin resistance is thought to be involved in the pathogenesis of acne. (33) The previously discussed cross – sectional study from New York found a correlation between insulin resistance and acne in 64 patients. (38) This correlates with findings of a larger study in which fasting insulin levels were statistically significant elevated in a group of 243 patients with severe acne compared to their 156 healthy controls. (78) A protein, adiponectin, known to sensitize insulin is believed to be reduced in insulin resistance. (59) Therefore, studies have been conducted to analyze a possible association between adiponectin levels and acne, but most of them could not find a statistically significant relationship between them. (59,79) However, one cross – sectional study, published

in 2016, observed a statistically significant reduction in adiponectin levels in a group of 50 acne patients compared to their 36 healthy controls (P=0.015). (36) Furthermore, a marginally significant inverse relationship was oserved between adiponectin levels and consumption of food low in glycemic load (P=0.049, r = -0.212). As the mean BMI of both groups in this study was 21 and the average age 19 years, chronic metabolic diseases as etiology for the depression of adiponectin levels can be excluded, emphasizing the importance of interplay between diet, biochemical factors, and the pathogenesis of acne.

3.10 Impact of probiotics on acne

Potential mechanisms by which probiotics could help therapeutically against acne are the inhibition of *C.ances* growth, reduction of local and systemic inflammation and influence on absorption of nutrients. (80) It remains theoretical, as most of the research is performed in vitro or in vivo in animals and not many dietary human studies, in which probiotics are not only co-administered to a medication, have been found within in the scope of this research criteria.

A randomized trial allocated forty five, otherwise healthy, female acne patients in the age of 18 to 35 years, into three groups receiving either a probiotic supplementation, an antibiotic or both together over 12 weeks and assessed changes in total lesion count. (81) Of interest for this review are only the changes within the group supplemented by the probiotic supplement consisting of a mixture of *Lactobacillus acidophilus, Lactobacillus del – brueckii* and *Bifidobacterium bifidum.* A statistically significant reduction in total lesion count after probiotic supplementation was observed already after 4 weeks compared to baseline values and after 8 and 12 weeks, each compared with the lesion count of their respective previous visit. Probiotics, found in fermented foods such as e.g. yoghurt or kefir, have been researched for their impact on lipid profile in patients with metabolic diseases and have been observed to significantly improve total cholesterol status in those patients. (82,83) Regarding the fact that acne was associated to an abnormal lipid profile in a previous section, this could offer possibilities to indirectly improve acne by improving the lipid profile.

Using prebiotic supplementation with galacto – oligosaccharides (GOS) and oligosaccharides (FOS) over a period of 3 months, changes in metabolic parameters of twelve female acne patients was observed in a pilot trial. (84) A statistically significant reduction ($p < 0.05$) in fasting blood glucose, total cholesterol and triglycerides levels was observed after completion of the study period. Plasma levels of insulin and c – peptide were not significantly reduced in comparison to baseline values looking at all the 12 participants. When comparing changes of subjects with insulin values >6 μUI/mL, representing 50 % of participants, before starting

supplementation, significant reduction of insulin levels were observed (P=0.03) after the 3 months of prebiotic administration.

In a double – blinded trial, 20 acne patients were randomly assigned to a group receiving a liquid probiotic supplementation containing *Lactobacillus rhamnosus* SP1 or to receive a liquid placebo for a duration of 12 weeks in addition to their normal unchanged diet. (85) Within the intervention group, a significant reduction in skin expression of IGF – 1 (P<0.001) and a significant increase in expression of FoxO1gene (P<0.001) was noted compared to baseline values. These results suggest an association between the previously discussed mTORC1 signaling pathway and probiotics in the context of pathogenesis of acne. However, more research has to be conducted towards this direction in the future.

IV. DISCUSSION

The main opposition to overcome in this research work is the current lack of studies with high quality level of evidence and studies of interventional type. A systemic review categorized primary studies about most researched food items in relation to acne into level of evidences and found no evidence level 1 primary studies, corresponding to "double – blinded randomized studies with a high number of cases" in the timeframe from 2004 to 2014. (86) Most of the involved studies are of level 3 evidence, representing individual case – control studies and very few case – report studies of level 4 evidence were included. Nonetheless, due to an increase of performed randomized controlled trials in the last decade with smaller subject size, level 2 evidence was also captured into this narrative review. (54)

The mismatch between the low quality and the high quantity of performed studies, proving elevated interest on this topic, might be explained by the difficulties in performing dietary studies. Dietary studies are mainly challenged by bias created through human senses of gustation and olfaction, as most of the food components are identifiable by structure and flavor, making double – blinded studies very challenging. An idea to overcome this obstacle is by deconstructing a researched food item into its main components on a chemical or molecular level, thereby eliminating taste, shape and color of the original product. (86) However, three recent double-blinded randomized controlled trial about chocolate consumption, polyunsaturated fatty acids and probiotics were involved in this research work. (51,63,81) Herein, the main component of chocolate, namely cocoa, was used to analyze the impact on

acne and probiotics as well as extracted fatty acids are free of identifiable texture and flavor. Apart from having acne, study participants often differ significantly in terms of dietary behavior and composition as well as metabolic factors making it more complex to draw a conclusion in studies focusing on particular food items due to the abundance of interfering variables to take into consideration.

The additional availability of a dietary source e.g. sun – mediated source of vitamin D in certain countries, different variants of food items e.g. milk with different fat contents (skimmed, fat reduced, whole milk) and subjective errors in fulfillment of questionnaires are some examples of often encountered interferences within studies involved in this research work. The conduction of appropriate dietary studies is associated with high expenditures financially and it has to be questioned whether economical conflicts of interest inhibit appropriate funding as study results may provide an alternative treatment approach that could deprive the pharmacological industry of high profits.

Nonetheless, conclusions on the question whether there is an impact of diet on acne and to which extent it should participate in its management could be drawn from the high quantity of studies involved in this research. The long – believed and self – perceived relationship of acne and western diet was clearly confirmed by the studies in our research work.

Within this research work, the following dietary factors were associated with acne in one way or another: glycemic index and load, dairy, chocolate, whey protein supplementation, Mediterranean diet, micronutrients, metabolic parameters and probiotics. Exact mechanisms to understand the correlation with acne often remain unclear. However, a pathogenetic connection between acne and insulinotropic mTORC1 and IGF – 1 pathway were often shown by articles used within this work as many dietary factors analyzed here induce them. Therefore, research should focus more on those interrelated dietary factors.

The decision not to recommend any dietary treatment for acne by the current guidelines cannot be accepted by the contradicting results of this research. From an utilitarian ethical point of view, the benefits, namely improvement of acne and psychologically related problems and a reduction of financial burden outweigh the non – existent harms of a dietary recommendation for patients. Certain concluding statements and practical recommendations can be achieved by information from current evidence on this topic. Nevertheless, towards finding a precise beneficial dietary regimen for acne patients, more interventional investigations with bigger sample sizes providing high quality of evidence are needed in the future.

V. CONCLUSIONS

1. Diet has a significant impact on acne and therefore, dietary recommendations should be added to the current guidelines. However, more research with high-quality evidence has to be conducted in the future.
2. Food with a high glycemic index and load as well as dairy products were shown to be involved in the pathogenesis of acne via enhanced IGF – 1 pathway mediated activation of mTORC1.
3. Consumption of chocolate and whey protein was shown to cause acne, but the exact mechanism must be researched more extensively in the future.
4. A Mediterranean diet, characterized by a low glycemic load and high in fruits, vegetables, legumes, and fish with an abundance of polyunsaturated fatty acids were observed to be protective against acne.
5. Although positive effects of probiotics could be revealed in limited studies, more in vivo research is necessary in this relatively new field of nutritional science.
6. Sufficient blood level of micronutrients, such as Vitamin A, E, D and zinc, are inversely related to acne. Investigations should be carried out to analyze the potential predictive value of the diagnosis of vitamin D deficiency for acne onset.
7. Association between acne and an abnormal lipid profile high in cholesterol and triglycerides was established. Still, the role of other metabolic factors, such as BMI and adiponectin levels, remains controversial.

VII. PRACTICAL RECOMMENDATIONS

1. Dietary recommendations should be reevaluated and added to the current acne treatment guidelines.
2. A diet low in glycemic index, involving components of the Mediterranean diet (especially fish) with additional supplementation of deficient micronutrients (e.g. vitamin D or zinc) and avoidance of chocolate and protein supplement consumption can be recommended.

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