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INVESTIGATIVE REPORT

Clinical and Histological Effect of a Low Glycaemic Load Diet in Treatment of Acne Vulgaris in Korean Patients: A Randomized, Controlled Trial

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Recent studies have suggested that dietary factors, specifically glycaemic load, may be involved in the pathogenesis of acne. The aim of this study was to determine the clinical and histological effects on acne lesions of a low glycaemic load diet. A total of 32 patients with mild to moderate acne were randomly assigned to either a low glycaemic load diet or a control group diet, and completed a 10-week, parallel dietary intervention trial. Results indicate successful lowering of the glycaemic load. Subjects within the low glycaemic group demonstrated significant clinical improvement in the number of both non-inflammatory and inflammatory acne lesions. Histopathological examination of skin samples revealed several characteristics, including reduced size of sebaceous glands, decreased inflammation, and reduced expression of sterol regulatory element-binding protein-1, and interleukin-8 in the low glycaemic load group. A reduction in glycaemic load of the diet for 10 weeks resulted in improvements in acne. ***Key words: acne; epidemiology; IGF-1; diet; glycaemic load.***

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An association between diet and acne has long been postulated, and there has been an increase in research in this area in recent years (1–4). Specifically, there has been a re-evaluation of nutritional influences related to endocrine factors involved in promoting the development of acne (5–7). Current research interests have focused on the concept of glycaemic load. Glycaemic load is interpreted as the measure of the increased blood glucose and insulin-raising potential of a meal, linking acne and hyperinsulinaemia (8). Hyperinsulinaemia has been implicated in acne pathophysiology through mediation of increased androgen bioavailability and free concentrations of insulin-like growth factors-1 (IGF-1), which aggravate acne by stimulating androgen synthesis, androgen receptor signal transduction, and sebocyte lipogenesis (6, 9, 10). In fact, a high prevalence of acne in Westernized countries, where individuals consume a high glycaemic load, is observed.

Therefore, it is clinically intriguing as to whether the low glycaemic load diet (LGLD) might have a beneficial effect on acne. Reynolds et al. (11) did not find statistically significant changes in acne severity by modification of the glycaemic index and glycaemic load over a relatively short period of 8 weeks. Another study by Kaymak et al. (12) reported that no significant differences were observed between patients with acne and control subjects in serum glucose, insulin, overall glycaemic index, or dietary glycaemic load. However, Smith et al. (3) demonstrated a link between reduction in glycaemic load and severity of acne in a 12-week randomized, controlled trial.

The present study was initiated to clarify these contradictions and to further include histological examination of acne lesions before and after dietary intervention. We expected that histopathological changes may provide valuable insight into the molecular mechanisms involving a reduction in acne lesions as a direct result of dietary control.

MATERIALS AND METHODS

Subjects and study design

This study was designed as a parallel dietary intervention study with investigator-blinded dermatological assessments. A total of 32 participants (age range 20–27 years; 24 males, 8 females) with mild to moderate acne were randomly assigned to either the LGLD group ($n = 17$) or the control group ($n = 15$) at the acne clinic of Seoul National University Hospital between August and February 2011 (Table I). A blocked random allocation sequence was created by computer-generated random numbers, and allocation to specific groups was performed by a research nurse. A washout period of 6 months was required for subjects who had previously taken oral retinoids or received physical treatments, and 2 months for subjects who had taken oral antibiotics or applied topical agents. Facial acne was scored at each visit (weeks 0, 2, 5 and 10). At each visit, body weight of all subjects was measured in light clothes, and body mass index (BMI) was calculated as the weight (kg)/height squared (m^2). At the first and final visit, 2-mm punch biopsies were taken from facial acne lesions.

The primary end-points of the study were changes in the number of inflammatory lesions (papules, pustules and nodules), the number of non-inflammatory lesions (open comedones and closed comedones) and histopathological changes in the acne lesions.

Table I. *Clinical characteristics of the low glycaemic load diet (LGLD) group and the control group at baseline*

Variable	LGLD group ($n=17$)	Control group ($n=15$)	p
Males/females, *n*	13/4	11/4	0.88
Age, years, mean ± SD	23.5 ± 3.2	23.7 ± 2.6	0.34
Body weight, kg, mean (SD)	62.3 ± 8.5	65.4 ± 10.1	0.43
BMI, kg/m^2, mean ± SD	23.4 ± 4.2	24.7 ± 2.2	0.52
Inflammatory lesion counts, mean ± SD	21.3 ± 9.6	24.7 ± 6.8	0.34
Non-inflammatory lesion counts, mean ± SD	8.3 ± 7.1	8.1 ± 5.6	0.45

BMI: body mass index.

Secondary end-points included changes in patient's subjective assessments. Informed consent was obtained from each participant, and the study was approved by the Institutional Review Board (IRB) of Seoul National University Hospital (H-1007-083-323).

Dietary intervention

The LGLD was achieved mainly by modifying the type and amount of carbohydrates consumed. The LGLD group was instructed to substitute high-glycaemic index (GI) foods with foods with lower GI foods (e.g. barley, wholegrain breads, fruits, beans, vegetables and fish).

In order to maintain standard levels of energy intake, the percentage of energy lost by reduced intake of carbohydrates was partially replaced with energy from protein. The recommended LGLD consisted of 25% energy from protein, 45% from low-GI carbohydrates, and 30% energy from fats. In contrast, the control group was instructed to eat carbohydrate-rich foods daily. All participants were educated repeatedly as to food record-keeping protocol throughout the study. A qualified nutritionist was available for consultation with each participant. Her role included a review of the food diary and helpful instruction to participants in the LGLD group about how to maintain the LGLD. Nutritional information based on the submitted food diaries of all participants were calculated, and participants received individualized dietary plans. Recommended eating habits for the LGLD group were also finalized and presented to participants during each visit. The control group was not informed about GI, but was urged to maintain their regular diets. Nutrient intake was calculated from a 7-day timeframe of weighed and measured food records during each visit (2, 5 and 10 weeks) by using the Computer Aided Nutritional Analysis program version 3.0 software (The Korean Nutrition Society, Seoul, Korea). Based on this tool, the total calorie intake per day, the mean GL, GI and total amount of carbohydrates, protein and lipid were calculated. Dietary compliance was monitored periodically (2/week) via telephone interviews and e-mails from physicians participating in the study. A nutritionist regularly answered questions about LGLD via e-mail from all participants.

Calculation of dietary glycaemic index and glycaemic load

The dietary glycaemic load was calculated using the following equations: dietary GI = ∑(GI for each food item × proportion of total carbohydrate contributed by item), and the dietary glycaemic load = ∑(GI for each food item × its carbohydrate content in grams ÷ 100). The GI values related to glucose as a reference food were taken from reference data (13) and related websites (www.glycaemicindex.com, www.gitest.co.kr). The GI values of unlisted Korean foods in the database were estimated by an experienced nutritionist.

Dermatology assessment

During each visit, clinical assessments of the number of inflammatory and non-inflammatory acne lesions and the overall severity of acne were performed blind by 2 independent dermatologists using the Leeds revised acne grading system, described by O' Brien et al. (14). To ensure that all acne lesions were counted, located and graded by size and severity, standardized digital photographs were taken prior to initiation of the dietary intervention and at each follow-up visit using identical camera settings (Nikon D70, Nikon Corp., Tokyo, Japan). An independent dermatologist performed acne grading based on photographs to ensure objective clinical evaluations of the acne severity grade. Patient's subjective self-assessments of acne severity were also recorded. The disease-free state was designated as 0, and acne state at the initial visit was set as 10. If patients felt that their acne had been aggravated in relation to the first visit, they could choose scores of greater than 10 for grading to allow the recording of any acne deterioration during the period of dietary intervention.

Immunohistochemical procedures

Immunohistochemical (IHC) analysis of skin samples was performed using the streptavidin-biotin amplification method. Tissue samples were processed for IHC staining using antibodies to interleukin-8 (IL-8) (R&D systems, GA, USA), sterol regulatory element-binding protein-1 (SREBP-1) (Santa Cruz Biotechnology, Santa Cruz, CA, USA) and transforming growth factor beta 1 (TGF-β1) (Santa Cruz Biotechnology). In samples stained with haematoxylin and eosin (H&E), the severity of inflammation was ranked from 0 (no inflammation) to 4 (very severe inflammation). In immunohistochemical staining for SREBP-1, TGF-β1 and IL-8, the intensity of staining was ranked from 0 (unstained) to 4 (very intensely stained). Skin biopsies and histopathological evaluations were performed independently by 2 dermatologists.

Image analysis of sebaceous gland size

Following H&E staining of sections from each of the biopsies, image analysis was performed to calculate sebaceous gland size in all available tissue sections. Images were captured using a Spot digital camera (Leica Camera AG, Solms, Germany), and measurements were obtained with TINA (Raytest Isotopenmebgerate, Straubenhardt, Germany) software after calibration with a micrometer slide under the 10× objective. All areas of sebaceous glands were circled using a freehand measuring tool, and the mean area of a distinct sebaceous gland for each section was calculated from the baseline and 10-week biopsies.

Statistical analysis

Comparison between the 2 dietary groups was performed using the likelihood ratio test and the Mann-Whitney *U* test for categorical and continuous values, respectively. Repeated measures analysis of variance (ANOVA) was used to explore the effects of dietary intervention, the time course of the study, and the potential influence of these 2 factors. Pooling data from both groups, bivariate linear regression analysis was also conducted to explore relationships between the LGLD and decrease in acne. All statistical analyses were performed with the use of SPSS 17.0 for Windows (SPSS Inc., Chicago, IL, USA), and significance was accepted for p-values < 0.05.

RESULTS

Dietary intake

Table II shows the nutritional composition of the mean diet of both the LGLD and the control groups

Table II. *Detailed information of the dietary intakes in the low-glycaemic-load diet (LGLD) group and control group at baseline and intervention periods (mean value at week 2, 5, and 10)*

Variable	LGLD group ($n=17$) Mean ± SD	Control group ($n=15$) Mean ± SD	p-value[a]		
			Group	Time	Group × time
Energy, kcal/day					
Baseline[b]	2024 ± 264.6	2182.6 ± 584.6			
Intervention period[c]	1900.3 ± 333.2	2133.9 ± 477.9	0.25	0.36	0.50
Dietary glycaemic load					
Baseline	177.2 ± 41.5	190.5 ± 33.1			
Intervention period	129.5 ± 22.2	207.2 ± 23.2	0.001	0.041	0.23
Dietary glycaemic index					
Baseline	65.9 ± 4.5	63.9 ± 5.8			
Intervention period	50.1 ± 6.3	69.5 ± 2.4	<0.001	0.001	0.19
Carbohydrate, g					
Baseline	275.9 ± 47.4	262.5 ± 79.0			
Intervention period	233.7 ± 40.0	283.2 ± 63.9	0.029	0.15	0.31
Protein, g					
Baseline	78.2 ± 17.4	88.6 ± 22.6			
Intervention period	88.1 ± 16.8	83.8 ± 24.6	0.44	0.76	0.42
Lipid, g					
Baseline	69.5 ± 7.2	76.1 ± 7.7			
Intervention period	61.9 ± 6.7	74.3 ± 6.9	0.006	0.098	0.38

[a]Repeated-measures analysis of variance (ANOVA) was performed to incorporate data from all time-points during intervention periods. We evaluated the differences between the LGLD and the control groups (main effect of group), and the change over time (main effect of time).
[b]An independent-sample t-test showed no significant differences between the LGLD and the control groups for all the listed dietary variables at baseline.
[c]Means of data collected at 2, 5 and 10 weeks.

at the baseline and final 10-week visit. No significant differences between the group or time-frame were observed in the total energy intakes of both groups. In addition, there were no significant changes in the calculated BMI for both groups throughout the research period (23.4 ± 4.2→22.7 ± 5.3 in the LGLD group and 24.6 ± 2.2→24.1 ± 2.9 in the control group). On the contrary, a significant reduction in glycaemic load was observed during dietary intervention in the LGLD group. This change was attributed mainly to the reduction in carbohydrate and lipid intake and the consumption of low GI foods ($p<0.05$).

Acne severity and lesion counts

The mean baseline acne scores for both LGLD and control groups were 2.18 and 2.08, respectively. After the 10-week dietary intervention, only the LGLD group demonstrated a significant decrease in acne grades, to 1.60 ($p=0.02$). The difference in severity between the 2 groups was also significant at the final visits ($p=0.02$) (Fig. 1). In detail, the mean non-inflammatory lesion counts for the LGLD group and the control group were significantly decreased, by 27.6% and 14.2%, respectively ($p=0.02$, $p=0.04$), at the final visit compared with the baseline. The difference between the 2 groups was evident only after the full 10 weeks of dietary intervention ($p=0.02$) (Fig. 2A). Inflammatory acne lesions were significantly decreased in the LGLD group at the earlier time-point of 5 weeks ($p=0.03$) (Fig. 2B). At the final visit, the mean number of lesions had decreased to 70.9% of baseline, while there was no significant reduction in the lesions in the control group.

Patient subjective assessments

After 5 weeks of treatment, the patients' subjective self-assessment scores started to decrease significantly for both groups (7.2 for the LGLD group and 7.5 for the control group) ($p=0.03$). At the final visit, the patients' self-assessment scores had decreased to 6.7 and 6.8, respectively ($p=0.01$) (Fig. S1; available from: http://www.medicaljournals.se/acta/content/?doi=10.2340/00015555-1346).

Correlation between changes in glycaemic load and improvement in severity of acne

Linear regression analysis showed that there was a significant correlation between the changes in total number of acne lesions and a reduction in the glycaemic load

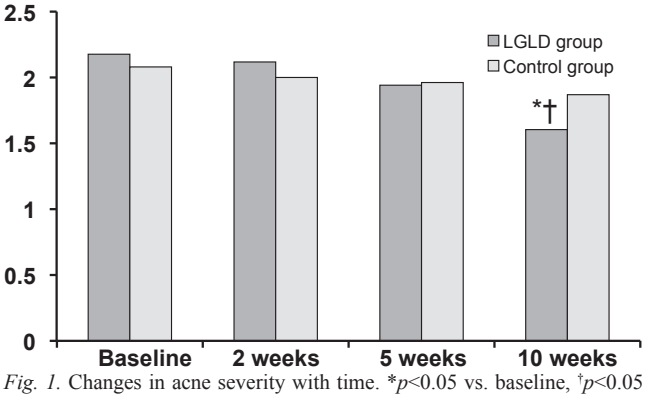

Fig. 1. Changes in acne severity with time. *$p<0.05$ vs. baseline, †$p<0.05$ between the 2 groups.

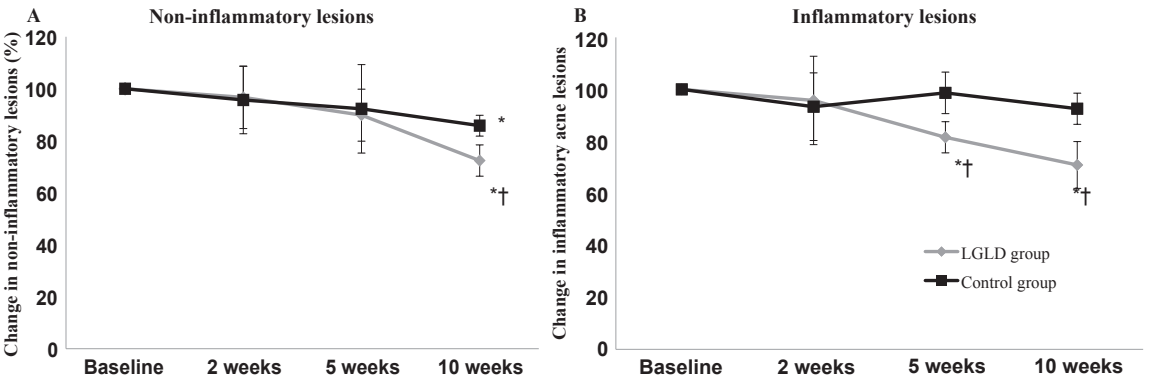

Fig. 2. Mean percentage change in (A) the non-inflammatory lesion counts and (B) the inflammatory acne lesion counts at each visit. *$p < 0.05$ vs. baseline, †$p < 0.05$ between the 2 groups.

($y = 0.1337$, $x - 7.1437$, $R^2 = 0.35$, $p < 0.01$), suggesting that lowering the glycaemic load mitigated the overall number of acne lesions (Fig. 3).

Changes in the overall size of sebaceous glands

A significant decrease in the overall size of the sebaceous glands was observed in the LGLD group compared with baseline measurements. The mean area of sebaceous glands in the baseline samples was 0.32 ± 0.03 mm^2 (mean ± standard error of the mean (SEM)), compared with 0.24 ± 0.03 mm^2 in the 10-week samples, which is a statistically significant reduction ($p = 0.03$).

Immunohistochemical findings

Mean scores for H&E, SREBP-1 and IL-8 staining demonstrated reductions after 10-week dietary intervention (H&E: 2.7→1.6, $p = 0.023$, SREBP-1: 2.6→1.3, $p = 0.03$, IL-8: 2.9→1.7, $p = 0.03$). However, there was no significant change in mean intensity of TGF-β1 at the final visit (3.5→3.6, $p = 0.83$) (Fig. S2; available from: http://www.medicaljournals.se/acta/content/?doi=10.2340/00015555-1346). In the control group, no significant changes in intensities for H&E staining and immunohistochemical staining were observed ($p > 0.05$).

DISCUSSION

Epidemiological studies have suggested that components of the Western diet are associated with the development of acne (1, 15). Previous research has also revealed that a high glycaemic load diet can induce significant hyperinsulinaemia, causing a hormonal cascade leading to androgen-induced sebum production and keratinocyte growth (5, 16, 17). In fact, endocrine disorders with increased insulin and IGF-1 serum levels, such as premature adrenarche, polycystic ovary syndrome, and acromegaly, are clinically associated with a high prevalence of acne (18–20). In addition, individuals with congenital deficiency of IGF-1 or Laron syndrome were almost free of acne (21).

In our study, the severity of acne in the LGLD group demonstrated a significant improvement after 10 weeks of dietary intervention. This observation might be important in order to understand the kinetics of acne response to dietary modifications, including the glycaemic load. In contrast to the 8-week study performed by Reynolds et al. (11), Smith et al. found a significant reduction in the level of acne lesions after a reduction in the glycaemic load over a period of 12 weeks (3). Therefore, we determined that a period of 10 weeks on the LGLD most likely did not reach the possible clinical end-point of a dietary intervention in

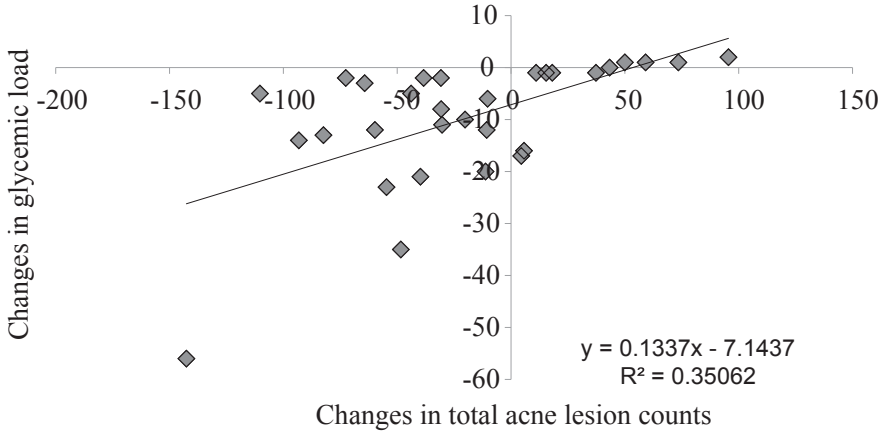

Fig. 3. Relationship between changes in dietary glycaemic load and improvement in acne. Bivariate analysis was performed with a 2-tailed Pearson's correlation.

acne. This result is of importance for further studies with longer study periods designed to assess the clinical and metabolic end-point of dietary intervention in acne. In both the LGLD group and the control group, no statistically significant changes in the BMI were observed, which is probably due to the short study period of 10 weeks. However, long-term dietary interventions (>3 months) with the LGLD generally reduced the overall BMI. It is noteworthy that the BMI has been identified as a risk factor for the development of acne (22, 23). Taken together, our data demonstrate a linear correlation between improvement in acne and reduction in glycaemic load.

However, our study did not consider other dietary components, including milk and dairy products leading to increased insulin/IGF-1 signalling (24), which have been identified as nutrient-derived acne-aggravating risk factors, as shown in our previous study (25). During puberty, there is a physiological onset of increased levels of growth hormone secretion, leading to an increase in IGF-1 serum levels, which is further enhanced by the consumption of milk (26). In this context, the epidemic incidence of adolescent acne in Western milk-consuming societies can be also explained by the increased insulin- and IGF-1-stimulation of sebaceous glands mediated by milk consumption. Therefore, we hypothesized that additional studies should not only consider the impact of the glycaemic load, but also that of milk and dairy products.

Following the 10-week LGLD, we found that the mean size of the sebaceous glands was significantly reduced, and the expression of SREBP-1 protein, master regulator of lipid synthesis, was also decreased. IGF-1 normally activates PI3K/Akt and MAPK/ERK-signal transduction pathways and induces the SREBP-1 expression, resulting in increased sebaceous lipogenesis (27–29). Since the LGLD is expected to decrease the biological activity of IGF-1, the decrease in non-inflammatory acne lesions during our dietary intervention might be partially elucidated by the proposed mechanisms. We also found that the results of H&E staining and IL-8 immunostaining of acne lesions demonstrated decreased inflammation in the LGLD group. Increased IL-8 expression in skin has been reported to be significantly associated with follicular hyperkeratosis, and acne inflammation (30). Since IGF-1 has also been identified as inducing acne inflammation through the Phospholipase C-γ pathway (29), we suggest that a LGLD might also mitigate inflammation through the modulation of related pathways. Therefore, our findings correlated well with previous dietary trials and *in vitro* research.

Interestingly, through our subjective testing, patients in the control group believed that acne lesions improved after the 5-week trial. This may indicate a placebo effect, or slight improvements in non-inflammatory acne lesions might also affect patients' satisfaction. Several methodological aspects of our study deserve mention. First, a self-reporting food diary might have prevented the accurate calculation of the nutritional composition of the food consumed during the study. Under-reporting the quantity of food eaten is a well-known source of error when evaluating adolescent diets (31). Secondly, other dietary factors, including saturated fat, fibre content, and zinc and iodine intake, might confound the relationship between diet and acne improvement.

Our results showed a beneficial effect of a LGLD in both non-inflammatory and inflammatory acne lesions, both clinically and histopathologically, in this 10-week dietary intervention study. In conclusion, these results show that a reduction in glycaemic load can result in a reduction in the level of acne lesions.

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The authors declare no conflicts of interest.

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