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The Effects of a Low Glycemic Load Diet on Acne Vulgaris in Adolescents and Young Adults

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The Effects of a Low Glycemic Load Diet on Acne Vulgaris in Adolescents and Young Adults

Abstract

Background:

Acne vulgaris is a common disease amongst adolescents in Western societies. It is an interesting problem because, while it is very common among this particular population, it is very rare in non-Westernized societies. This observation has lead to recent exploration of what factors in Western society may, at least in part, be responsible for this. Recently there have been several epidemiological studies linking certain foods to acne. Of the foods showing a positive correlation, high glycemic load foods have been the most extensively studied. There have been a number of studies examining the possible mechanism of this. To date, there have been no systematic reviews done reviewing the available RCTs on the effect of low glycemic load (LGL) diets on acne in adolescents and young adults.

Methods:

An exhaustive search of the available medical literature was conducted using Medline-OVID, CINAHL, and Web of Science using the MeSH terms: acne vulgaris, dietary carbohydrates, and glycemic index. Relevant studies were assessed for quality using GRADE.

Results:

Three studies met the inclusion criteria and were included in this systematic review. One randomized controlled trial found statistically significant improvement in objective measures of acne as well as BMI and insulin resistance with a 12 week trial of a LGL diet. Another randomized controlled trial of 8 weeks in duration failed to find a statistically significant difference in weight, insulin resistance, and objective measures of acne improvement. The final randomized controlled trial, which lasted 10 weeks, found statistically significant improvement in objective measures of acne but not until 10 weeks (significant improvement seen in inflammatory lesions alone at 5 weeks). This study also found a positive correlation between the level of glycemic load reduction and improved acne severity. In addition this final study found no significant change in BMI.

Conclusion:

LGL diets, especially those that replace high glycemic carbohydrates with foods high in fiber and protein, may improve acne vulgaris in adolescent and young adult males. This improvement is likely to be seen in females however the studies examined were in themselves underpowered to make this conclusion. There appears to be a dose response both to time and amount of glycemic load reduction with the greatest improvement in acne occurring in patients who followed a diet which induced at least a 13-point reduction in glycemic load from the control diet and those that completed therapy for at least 10 weeks. It can also be concluded that the greatest effect of this therapy is seen in the reduction of inflammatory lesions as compared to non-inflammatory and total lesion counts.

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Keywords
Acne vulgaris, dietary carbohydrates, glycemic index, glycemic load

Subject Categories
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The Effects of a Low Glycemic Load Diet on Acne Vulgaris in Adolescents and Young Adults

Andrew White

A Clinical Graduate Project Submitted to the Faculty of the
School of Physician Assistant Studies
Pacific University
Hillsboro, OR
For the Masters of Science Degree, August 8, 2015

Faculty Advisor: Mark Pedemonte, MD
Clinical Graduate Project Coordinator: Annjanette Sommers, PA-C, MS
Biography

Andrew is originally from Ohio. He attended The Ohio State University majoring in Exercise Science and ultimately graduated from the University of Western States, in Portland, OR with a Bachelor of Science in Human Biology. During this time he worked as a Certified Personal Trainer. Upon completion of his undergraduate degree, he moved back to Ohio where he worked for a year as an STNA at a nursing home. He is interested in pursuing a career in dermatology or primary care.
Abstract

Background:
Acne vulgaris is a common disease amongst adolescents in Western societies. It is an interesting problem because, while it is very common among this particular population, it is very rare in non-Westernized societies. This observation has lead to recent exploration of what factors in Western society may, at least in part, be responsible for this. Recently there have been several epidemiological studies linking certain foods to acne. Of the foods showing a positive correlation, high glycemic load foods have been the most extensively studied. There have been a number of studies examining the possible mechanism of this. To date, there have been no systematic reviews done reviewing the available RCTs on the effect of low glycemic load (LGL) diets on acne in adolescents and young adults.

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An exhaustive search of the available medical literature was conducted using Medline-OVID, CINAHL, and Web of Science using the MeSH terms: acne vulgaris, dietary carbohydrates, and glycemic index. Relevant studies were assessed for quality using GRADE.

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Conclusion:
LGL diets, especially those that replace high glycemic carbohydrates with foods high in fiber and protein, may improve acne vulgaris in adolescent and young adult males. This improvement is likely to be seen in females however the studies examined were in themselves underpowered to make this conclusion. There appears to be a dose response both to time and amount of glycemic load reduction with the greatest improvement in acne occurring in patients who followed a diet which induced at least a 13-point reduction in glycemic load from the control diet and those that completed therapy for at least 10 weeks. It can also be concluded that the greatest effect of this therapy is seen in the reduction of inflammatory lesions as compared to non-inflammatory and total lesion counts.

Keywords: Acne vulgaris, dietary carbohydrates, glycemic index, glycemic load
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To my wife and son, your love and support are what inspire me to achieve my best.

To my parents for teaching me to dream and to work hard for those dreams. My education has required both.

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List of Abbreviations

BMI........................................................................................................................Body Mass Index
GI..............................................................................................................................Glycemic Index
GL..............................................................................................................................Glycemic Load
GRADE........................Grading of Recommendations, Assessment, Development and Evaluations
HOMA-IR…………………………….....................…Homeostasis Model Assessment of Insulin Resistance
IGF-1....................................................................................................Insulin Like Growth Factor-1
IR..........................................................................................................................Insulin Resistance
LGL.....................................................................................................................Low Glycemic Load
LGLD.................................................................................................................Low Glycemic Load Diet
RCT......................................................................................................Randomized Controlled Trial
The Effects of a Low Glycemic Load Diet on Acne Vulgaris in Adolescents and Young Adults

BACKGROUND

Acne vulgaris is a common disease affecting 79-95% of adolescents in Western populations.¹ Often mistaken as a simple cosmetic disease, acne can be associated with significant psychological and social stress in its sufferers including increased depression and anxiety, lower self-esteem, and even higher rates of unemployment.²-⁵ Interestingly, acne vulgaris is normally absent in non-Westernized populations, but when these populations adopt Western lifestyles it begins to appear.¹,⁶,⁷ Several epidemiological studies have sought to explore this and have shown a correlation between several dietary factors and acne vulgaris including glycemic index and load, fat composition of foods, and dairy.⁸-¹⁰ Of these, the only ones that have been addressed by randomized controlled trials (RCTs) are glycemic index and load.

Glycemic index (GI) and glycemic load (GL) are both measures of the ability of a carbohydrate containing food to elevate blood glucose. GI is calculated based on the quantity of a given food that constitutes 1 g of carbohydrates. Glycemic load (GL) is calculated based on one serving size of a food. The higher the GI or GL, the greater the increase in blood glucose and subsequently the greater the rise in insulin after eating said food.¹¹

When insulin levels rise following ingestion of carbohydrates, there is an increased secretion of insulin like growth factor-1 (IGF-1), which in turn causes increased androgen
production by the adrenal glands and increased androgen receptor signal transduction. These combine to complicate acne by causing increased keratinocyte proliferation.\textsuperscript{12-14}

Low glycemic load (LGL) diets are known to reduce hyperinsulinemia and insulin resistance, as measured by Homeostatic Model Assessment Insulin Resistance (HOMA-IR).\textsuperscript{15} Thus it is reasonable to hypothesize that LGL diets may also improve acne. Furthermore, it has been shown that treating hyperinsulinemia with metformin in women with PCOS improves acne in those patients.\textsuperscript{16} There have been a number of studies conducted to examine the potential link between diet and acne but to date there has not been a systematic review of the RCTs that investigated the effects of a LGL diet on acne. A number of studies have examined the potential link between diet and acne but to date there has not been a systematic review of the RCTs investigating the effects of a LGL diet on acne.

METHODS

An exhaustive search of the medical literature was conducted by the two authors independently using Medline-OVID, CINAHL, and Web of Science using the MeSH terms: acne vulgaris, dietary carbohydrates, and glycemic index. The results were then narrowed to include only English language articles, articles published within the past 10 years, human studies, and RCTs. Relevant studies were evaluated using GRADE.\textsuperscript{17}

RESULTS
The initial search of the databases revealed a total of 75 studies between the three sources. Application of limits narrowed the results to 11 studies. When screened for eligibility 7 studies remained. Screening for duplicates resulted in 3 studies.\(^{18-20}\) See Table I.

**Smith et al**

This randomized controlled trial\(^{18}\) investigated the effect of a 12-week long low glycemic load diet (LGLD) on acne in adolescent and young adult males 15-25 years old. It was the first RCT to investigate the effects of a LGLD on acne vulgaris. Patients were recruited through university posted fliers and newspaper advertisements. Exclusion criteria included currently taking any acne medications or medications known to affect glucose metabolism. Furthermore, patients were excluded if they had used oral retinoids within the past 6 months or oral antibiotics, topical antibiotics, or topical retinoids within the past 2 months.\(^{18}\)

54 subjects were randomly assigned to either LGLD group (n=27) or the control group (n=27). Baseline analysis showed no significant differences in demographics or diets between groups. Subjects were blinded to the study's true intent. Subjects were told that the study was examining the difference between protein and carbohydrate levels in their diets. The patients all used a standardized cleanser and were allowed no other topical therapy. Subjects were given individualized dietary guidance according to their allocation but generally subjects in the LGLD group were instructed to replace high GI foods with low GI foods, including those higher in protein, whereas the control group was instructed to eat carbohydrate-containing foods with no reference to GI or GL. Subjects in both groups were provided with some staple foods. The actual makeups of subjects’ diets were calculated each month from 3 day weighed and
measured food records. Compliance to the assigned diet was assessed via regular telephone interviews and 24-h urine samples to evaluate urea excretion relative to urinary creatinine. Acne lesions were assessed at baseline and every 4 weeks thereafter for 12 weeks using a validated grading system by one dermatologist who was blinded to the group allocation. The investigators also evaluated BMI at each of these visits and drew blood at baseline and 12 weeks for evaluation of insulin resistance.\textsuperscript{18}

The authors stated that they were able to achieve significantly different diets between the two groups in regards to GI (p<0.001), GL (p<0.001), and percentage of carbohydrate intake (p=0.001). Specifically, they were able to accomplish an average difference of 13.2 points in GI and 72.8 points in GL. However, the diets also differed significantly in regard to percentage of protein (p<0.001), percentage of saturated fat (p<0.001), and amount of fiber consumed (p<0.001), with the LGLD group consuming a higher percentage of protein and fiber and a lower percentage of saturated fat. The study revealed statistically significant decreases in total acne lesion counts (Control (-12.0±3.5), LGLD (-23.5±3.9), p=0.03), inflammatory acne lesion counts (Control (-7.4±2.5), LGLD (-17.0±3.1), p=0.02), HOMA-IR (Control (0.47±0.31), LGLD (-0.22±0.12), p=0.026), and BMI (Control (0.01±0.11), LGLD (-0.92±0.25), p=0.001) all favoring the LGLD group. Furthermore, they noted a positive correlation between the amount of reduction in GL and amount of reduction in acne lesions (r=0.49, see Figure I). However, when the change in BMI was corrected for, statistical significance was lost for the changes in total acne lesion count (p=0.07) and HOMA-IR (p=0.10), but not for the change seen in inflammatory lesion count (p=0.04). Drop out was minimal (7 from control group and 4 from LGLD group) and
intention to treat showed that this did not create a statistically significant difference. Images of typical patients in LGLD group are seen in Figure II.\textsuperscript{18}

There were several limitations noted by the study authors. The first was that acne lesions did improve in the control group and that this might be an effect from the cleanser or due to the natural fluctuation of acne. Secondly, they note that they could not isolate GI and GL from fiber, protein, saturated fat, or percentage of carbohydrates. Finally, the study\textsuperscript{18} relied on self-reported diets, noting that, underreporting of food eaten is a known error in assessing adolescent diets.\textsuperscript{21} See Table I.

\textbf{Reynolds et al}

This randomized controlled trial\textsuperscript{19} sought to clarify the effects of GI and GL on acne vulgaris by isolating them from fiber, protein, and percentage of carbohydrates. The investigators enrolled 58 adolescent males (average age of 16.5 years), with facial acne. Inclusion criteria included acne severity of Grade 1-3 and stable weight for the past 3 months. Exclusion criteria included previous use of isotretinoin, antibiotics in the past month, excessive alcohol intake, illicit drug use, smoking, physical or mental illness, food allergy or intolerance, vegetarianism, previous surgery on the gastrointestinal system, black skin (due to difficulty in visualizing lesions), and having school finals during the study.\textsuperscript{19}

The patients were not truly randomized, and instead, every other subject enrolled was assigned to each group (Control: n=29, LGLD: n=29). As a result, baseline comparison shows significant difference in DHEA-S levels (Control (4.5 ± 0.4), LGLD (5.9 ± 0.6), p=0.04). Baseline
diets were not evaluated. Subjects were not blinded to group allocation, and they were informed of the study's true intent. The subjects' weight, acne severity, and HOMA-IR were evaluated at baseline and 8 weeks. Acne severity was ranked by blinded dermatologists (scores were averaged when different). The dermatologists ranked the acne based on a novel 4-point scale that had not been externally validated and did not have an objective component such as lesion count. School cafeterias assured that both low and high GI foods were available to all students and diet was controlled through weekly one-to-one counseling sessions. Dietary intake was assessed by self-reported food diaries, which were completed on weekends. There was significant drop out of 26% but this was fairly evenly distributed between the groups (6 in LGLD, 9 in control) and there was no statistically significant difference in age or BMI between those who were lost to follow up and those who were not.¹⁹

At 8 weeks, this study saw a significant difference in GI (p=0.0002), GL (p=0.01), and saturated fat (p=0.01) between the two groups' diets with all being lower in the LGLD group. Specifically they saw a 10 point difference in GI and a 55 point difference in GL between groups. There was no significant difference between fiber (p=0.50), protein (p=0.06), or percentage of carbohydrates (p=0.25). The study found no significant difference between the two groups in acne severity (Control (-0.35±0.15), LGLD (-0.65±0.14), p=0.15), HOMA-IR (Control (0.1±0.1), LGLD (0.2±0.1), p=0.60), or weight (Control (1.1±0.6), LGLD (-0.3±0.4), p=0.053). However, the authors noted that there was a trend toward a significant difference in favor of the LGLD group (see Figure III).¹⁹
The authors noted several limitations. The first limitation of note is the significant drop out of 26%. Secondly they note that their acne grading system was not validated and that it was relatively insensitive to smaller changes that may be important to patients. They also mention the lack of randomization and the resultant difference in DHEA-S between the two groups, of particular concern due to the conversion of DHEA to DHT, which plays an important role in acne pathogenesis.\(^\text{16}\) Furthermore, they note that because the diet was not assessed at baseline, it is impossible to know whether the LGLD was actually an intervention for the test group. In addition, they note that their LGL diet may not have induced a large enough change to affect the postprandial insulin response. They note that in a previous study\(^\text{22}\), a difference of 13 or great in GI was needed to affect change in glycated proteins in adults. They also note that they relied upon self-reported diets as well. Finally, the study authors note that at the time of publication, 12 weeks was the most common and appropriate period for acne treatment trials, but that they had to limit theirs to 8 weeks due to school terms.\(^\text{19}\) See Table I.

**Kwon et al**

This randomized controlled trial\(^\text{20}\) of 10 weeks in duration sought to clarify the discrepancy between the Smith et al\(^\text{18}\) and Reynolds et al\(^\text{19}\) studies. The study enrolled 32 participants with mild to moderate acne 20-27 years old (24 males and 8 females). Subjects were excluded if they had used oral retinoids or physical treatments within the past 6 months or oral antibiotics or topical agents within the past 2 months.\(^\text{20}\)

The subjects were randomized to either the LGLD group (n=17) or control group (n=15). When compared at baseline there were no significant differences in demographics or diets
between groups. The study makes no mention of blinding of the subjects or of standardization of hygiene. Facial acne was evaluated using a validated grading system by two independent and blinded dermatologists. Subjects were all provided individual dietary guidance but in general the LGLD subjects were encouraged to replace high GI foods with low GI foods including those with more protein, while the control group was encouraged to maintain their regular diets. Dietary adherence was evaluated by twice weekly phone interviews and emails. Dietary intake was measured by 7-day weighed and measured food records at 2 weeks, 5 weeks, and 10 weeks.20

At 10 weeks, the diets were significantly different between the two groups in regards to GI (p=0.001), GL (p<0.001), amount of carbohydrates (p=0.029), and amount of lipids (p=0.006) with all being lower in the LGLD group. Specifically, they recorded an average difference of 19.4 points in GI and 77.7 points in GL between the two groups. There was no significant difference in amount of protein (p=0.44) or total energy intake (p=0.25) between groups. The study did effectively control for BMI with no significant differences between groups (Control (23.4±4.2 → 22.7±5.3), LGL (24.6±2.2 → 24.1±2.9)).20

This study found significant improvement in acne in the LGLD group at 5 weeks (in inflammatory lesions only (p=0.03)) and at 10 weeks (in inflammatory and non-inflammatory lesions (Control (-27.6), LGL (-14.2), p=0.02)). Furthermore they noted that linear regression analysis showed a significant positive correlation between reduction of GL and reduction of acne lesions (R=0.35, see Figure III).20
The first limitation noted by authors is that the study used self-reported diets. In addition, they mention that they were unable to effectively control for lipids and neither saturated fat nor fiber intake were evaluated. See Table I.

DISCUSSION

This review provides enough evidence to support a general recommendation of a low glycemic load diet to otherwise healthy adolescent and young adult males suffering from facial acne. Although, this review only provides low to moderate quality evidence for a positive treatment effect, this recommendation can be made to otherwise healthy patients in this age group, as there are likely no serious risks from this diet. To the contrary, it is likely that patients will reap other health benefits from said diet including, improved insulin sensitivity, improved cardiovascular profile, a lower risk of developing DM, great satiety, and decreased risk of diverticular disease.

Smith et al\textsuperscript{18} set the precedent that a LGLD could improve objective measures of acne. However they were unable to isolate this effect from changes in BMI (inflammatory lesions alone were not affected by this correction). Reynolds et al\textsuperscript{19} placed tighter dietary controls on subjects and saw no significant difference in the change in weight or acne severity. However this study also induced the smallest change in GI (\textasciitilde10 points) and had the shortest duration (8 weeks). Kwon et al\textsuperscript{20} helped to clarify the other studies\textsuperscript{18,19} by controlling for BMI changes while inducing a larger change in GI and having a longer duration than Reynolds et al\textsuperscript{19}. Similar to Smith et al\textsuperscript{18}, this study did find significant changes in objective measures of acne.
When considering the lack of significance seen by Reynolds et al\textsuperscript{19}, it is important to consider several other things. The first is that Reynolds et al\textsuperscript{19} saw a trend toward significant improvement favoring the LGLD group at 8 weeks, and Kwon et al\textsuperscript{20} did not see significant improvement until 10 weeks. It should also be noted that Reynolds et al\textsuperscript{19} used a subjective measure of acne severity which the authors noted was likely insensitive. Furthermore, when Smith et al\textsuperscript{18} published their results in another study\textsuperscript{29}, they showed a positive correlation between reduction in HOMA-IR and improvement in acne (See Figure IV). However, the LGL diet used in Reynolds et al\textsuperscript{19} failed to create a change in insulin resistance (as measured by HOMA-IR).

It should also be noted that the effect seen on inflammatory lesions appears to be greater than the effect on non-inflammatory or total lesions as supported by both Smith et al\textsuperscript{18} and Kwon et al\textsuperscript{20} (this was not evaluated by Reynolds et al\textsuperscript{19}).

Limitations of Study

In addition to those mentioned by the authors, there are several collective limitations of the studies and thus of this review. The first is that females were underrepresented in one study\textsuperscript{20} and were excluded from the other two\textsuperscript{18,19}. This limits the ability of this study to extend the recommendation of LGLD to female acne patients. Furthermore, the results are limited in extension to acne other than facial acne and to patients with chronic illness due to the inclusion and exclusion criteria of the studies evaluated.
The next major limitation is the inability to completely control all dietary variables. Only one study (Reynolds et al\textsuperscript{19}) was able to control for fiber and none of them were able to control for saturated fat. The significant difference in fiber is of little concern given its known association with LGL diets.\textsuperscript{11,30} However, the potential innate relationship between LGL diets and decreased saturated fat is not intuitive and needs to be further examined. In addition, none of the studies controlled for dairy products, a dietary variable that has also been implicated in the pathogenesis of acne in epidemiological studies. Also, it is also not possible to estimate the magnitude of effect that a LGLD will have in patients receiving contaminant acne therapy (topical or oral), as this was an exclusion criterion for all three studies.

Lastly, while all three studies were downgraded for using self-reported diets (See Table I), but it should be noted that this error might have actually underestimated the treatment effect as groups may have reported diets more similar to those prescribed than to what they actually ate.

In addition to these collective limits, neither Reynolds et al\textsuperscript{19} nor Kwon et al\textsuperscript{20}, reported any effort to blind subjects and neither had standardization of hygiene, such as a supplied facial cleanser.

\textit{Recommendations for further study}

Although it remains unclear what specific roles protein and fiber play in the treatment of acne, it is unnecessary to further control for or investigate them because these are two dietary variables that are commonly used to convert a standard Western diet into a low
glycemic load diet.\textsuperscript{11,30} The role that lipid profile (saturated v. unsaturated, etc.) and dairy play in the pathogenesis of acne warrant further investigation given the support of epidemiological studies and the biochemical basis of their potential role in acne.\textsuperscript{8,9,31} Smith et al\textsuperscript{18} standardized facial hygiene in subjects, and this should be continued in future studies due to its potential role in acne treatment. Additionally, a larger study that includes more females will allow for better generalization of the results to the entire adolescent and young adult populations suffering from acne.

CONCLUSION

Acne vulgaris is a common and often devastating disease within adolescent and young adult populations. There are many factors that influence acne and treatment should be multifactorial. Together these studies indicate a positive effect of LGL diets on acne lesions in otherwise healthy adolescent and young adult males. The effect appears to increase with both time and decreased GI of diet. The recommended LGLD therapy should be at least 10 weeks in duration (with 12 being the ideal goal) with at least a 13-point reduction in GI from the baseline diet. The recommendation to begin a LGLD can be made to otherwise healthy patients in this demographic, as there are minimal if any risks from this diet. In fact, there are likely other health benefits.

This recommendation can probably be made to both males and females though support for application to female patients is limited and needs further evaluation. Furthermore, other dietary variables warrant investigation including fats and dairy. Nonetheless there is sufficient evidence at this time for healthcare providers involved in the care of adolescents and young
adults suffering from acne to feel comfortable in making a general recommendation to
decrease the GL and GI of their patients' diets with little concern for possible side effects.
References


12. DD, RR. Growth hormone and insulin-like growth factors have different effects on sebaceous cell growth and differentiation. *Endocrinology.* 1999 Sep;140(9):4089-94.


Table I. Characteristics ofReviewed Studies, GRADE$^{17}$ Profile

<table>
<thead>
<tr>
<th>Quality Assessment</th>
<th>Downgrade Criteria</th>
<th>Quality</th>
</tr>
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<tbody>
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<td>Not Serious</td>
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<td>Very Serious$^{a,b,c,d}$</td>
<td>Serious$^a$</td>
</tr>
<tr>
<td>Kwon et al$^{26}$</td>
<td>Very Serious$^{a,b,c,d}$</td>
<td>Not Serious</td>
</tr>
</tbody>
</table>

$^a$ Use of self-reported diet data
$^b$ Lack of blinding
$^c$ Lack of randomization; failure to assess baseline diet content
$^d$ Lack of standardization of hygiene
$^e$ Use of invalidated outcome assessment tool and lack of prognostic variables between groups (treatment group had higher DHEA-S levels)
$^f$ Large loss to follow-up
Figure 1: Relationship Between Total Acne and Dietary Glycemic Load (Smith et al\textsuperscript{18})
Figure II: Photographs of Improvement of Acne Lesions on LGL Diet (Smith et al\textsuperscript{18})
Figure III: Changes in Facial Acne Severity in LGLD Group and Control Group Show Trend Favoring LGLD Group but a Lack of Significance (Reynolds et al19).

"Change in facial acne severity from week 0 to week 8. Facial acne severity decreased more on the low glycemic index (GI) diet, but the difference between diets did not reach significance (acne score change: low GI mean ± SEM, n = 23, -0.65 ± 0.14 vs. high GI mean ± SEM, n = 20, -0.35 ± 0.15, p = 0.15)."

Figure IV: Relationship Between Acne Improvement and Dietary Glycemic Load (Kwon et al20)
Figure V: Relationship Between Acne Improvement and HOMA-IR Reduction (Smith et al\textsuperscript{29})

\hspace{1cm}
a)  

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure_v}
\caption{Relationship between change in total lesion count and change in \textit{log(HOMA-IR)}. The correlation coefficient is \( r = 0.38 \) and the significance level is \( P = 0.01 \).}
\end{figure}