What's Diet Got to Do With It? Basic and Clinical Science Behind Diet and Acne

Melissa Dodds, MD; Apple Bodemer, MD; Bridget E. Shields, MD

PRACTICE **POINTS**

- Patients are frequently interested in the role that diet plays in acne, and dermatologists should be aware of the current evidence to answer these questions effectively.
- One of the primary pathways in acne pathogenesis, mTORC1 (mammalian target of rapamycin complex 1), is partially regulated by nutrient availability, insulin, and insulinlike growth factor 1.
- Dietary recommendations for acne based on available evidence may include a low glycemic index diet and avoidance of certain dairy products.
- Insulin resistance may underlie the pathogenesis of acne in a subset of patients, and assessing insulin resistance in acne patients should be considered.

Acne has been considered a disease of Western society, which consumes a diet that includes high glycemic index dairy and fatty foods. Although large, blinded, randomized controlled trials surrounding the impact of diet on acne are challenging to conduct, there is early evidence from small clinical trials and larger observational studies as well as other basic scientific research on the contributions of diet in the pathogenesis of acne. This article will focus on the existing evidence behind one of the proposed pathways of acne pathogenesis—mammalian target of rapamycin complex 1 (mTORC1), which is a major promoter of cellular growth and proliferation and is primarily regulated through nutrient availability, insulin, and insulinlike growth factor 1 (IGF-1).

Cutis. 2022;110:13-16.

The current understanding of the pathogenesis of acne includes altered keratinization, follicular obstruction, overproduction of sebum, and microbial colonization (*Cutibacterium acnes*) of the pilosebaceous unit resulting in perifollicular inflammation.[1] A deeper dive into the hormonal and molecular drivers of acne have implicated insulin, insulinlike growth factor 1 (IGF-1), corticotropin-releasing hormone, the phosphoinositide 3-kinase/Akt pathway, mitogen-activated protein kinase pathway, and the nuclear factor κB pathway.[2-4] A Western diet comprised of high glycemic index foods, carbohydrates, and dairy enhances the production of insulin and IGF-1. A downstream effect of excess insulin and IGF-1 is overactivity of the mammalian target of rapamycin complex 1 (mTORC1), a major promoter of cellular growth and proliferation that primarily is regulated through nutrient availability.[5] This article will review our understanding of the impact of the Western diet on acne pathogenesis and highlight the existing evidence behind the contributions of the mTORC1 pathway in this process. Although quality randomized controlled trials analyzing these effects are limited, dermatologists should understand the existing evidence supporting the potential impacts of diet on acne.

The Western Diet

Glycemic Index—To assess the impact of a high glycemic index diet on acne, Kwon et al[6] evaluated 32 patients with mild to moderate acne and placed them on a low or high glycemic index diet for 10 weeks. The low glycemic index diet group was found to have a 70% reduction in the mean number of inflammatory acne lesions from

From the Department of Dermatology, University of Wisconsin, Madison.
The authors report no conflict of interest.
Correspondence: Bridget E. Shields, MD, Department of Dermatology, University of Wisconsin, 1 S Park St, Madison, WI 53715 (bshields@dermatology.wisc.edu).
doi:10.12788/cutis.0565

baseline ($P<.05$), while the high glycemic index diet group had no significant reduction. Noninflammatory lesion counts remained statistically unchanged.[6] Smith et al[7] studied 43 male patients with acne on either a low glycemic index diet or a self-directed high glycemic diet that was carbohydrate dense. The low glycemic index group showed greater improvement in lesion count as well as improved insulin sensitivity at 12 weeks. Specifically, the mean lesion count (SEM) decreased by 23.5 (3.9) in the low glycemic index group and by only 12.0 (3.5) in the control group ($P=.03$).[7] Observational studies also have supported this hypothesis. After adjustment, an analysis of 24,452 participants in the NutriNet-Santé cohort found significant associations between current acne and the consumption of sugary beverages (adjusted OR, 1.18; 95% CI, 1.01-1.38) and the consumption of fatty and sugary products (adjusted OR, 1.54; 95% CI, 1.09-2.16).[8] A Cochrane review that included only 2 studies (Kwon et al[6] and Smith et al[7]) did not find evidence to suggest a low glycemic index diet for noninflammatory lesion count reduction but did note possible benefit for a reduction in inflammatory and total lesion counts; however, Kwon et al[6] had incomplete data.[9]

Dairy—A large retrospective study including 47,355 nurses noted the frequency of milk intake was significantly associated with increased prevalence of acne in adolescence (prevalence ratio, 1.22; 95% CI, 1.03-1.44; $P=.002$).[10] A 2019 meta-analysis further suggested a significant relationship between acne and milk in highest vs lowest intake groups (OR, 1.48; 95% CI, 1.31-1.66) with no significant heterogeneity between the studies ($I^2=23.6\%$, $P=.24$ for heterogeneity), as well as a positive relationship between the highest vs lowest intake of low-fat milk (OR, 1.25; 95% CI, 1.10-1.43) and skim milk (OR, 1.82; 95% CI, 1.34-2.47). In this meta-analysis, yogurt and cheese consumption were not significantly associated with acne (OR, 0.90; 95% CI, 0.73-1.11).[11] One non–evidence-based explanation for this may be that fermented dairy products have different biological actions. Pasteurized milk allows microRNAs that directly activate mTORC1 to persist, whereas the bacteria present in the fermentation process may augment this.[12] A separate meta-analysis from 2018 did find that yogurt consumption was positively associated with acne (OR, 1.36; 95% CI, 1.05-1.77; $P=.022$), highlighting the need for larger, more rigorous studies on this topic.[13]

Insulin and IGF-1—As reviewed above, acne has been considered a disease of Western society, with the Western diet at the center of this association.[14] A typical Western diet consists of high glycemic index foods, carbohydrates, and dairy, all of which enhance the production of insulin and IGF-1. Insulin levels increase secondary to high blood glucose and to a lesser degree by protein intake.[15] Insulinlike growth factor 1 production is most influenced by age and peaks during puberty; however, high protein diets also increase liver IGF-1 production and release.[16] When present in excess, insulin can function as a growth factor. Insulin exerts its anabolic effects through the IGF-1 pathway; however, insulin and IGF-1 are produced in response to different signals.[17] Endocrine production of IGF-1 represents 70% of blood levels, peaks at puberty, and rapidly declines in the third decade of life.[18] Insulin is produced by the pancreas, and levels correspond to lifestyle and genetically induced insulin resistance.[19]

Adolescents have elevated levels of IGF-1 as a major driver of puberty-associated growth.[20] Despite the natural decrease in IGF-1 following puberty, acne persists in many patients and can even develop for the first time in adulthood in a subset of patients. A study of 40 acne patients and 20 controls found that patients with acne who consumed a high glycemic–load diet was significantly higher than the number of controls consuming a similar diet ($P=.008$). Additionally, significantly higher levels of mean (SD) serum IGF-1 on quantitative sandwich enzyme-linked immunosorbent assay in acne patients vs controls (543.2 [174.7] ng/mL vs 316.9 [95.7] ng/mL; $P<.001$) was identified, and these levels correlated significantly with high glycemic–load diet consumption.[21] In another study, Kartal et al[22] found that basal and fasting insulin levels and homeostasis model assessment scores evaluating for insulin resistance were significantly higher in 36 women compared with 24 age/sex-matched controls ($P<.05$). This finding remained significant even after excluding women with hyperandrogenemia ($P<.05$).[22]

Highlighting the importance of IGF-1 in the pathogenesis of acne, patients with genetic disorders characterized by IGF-1 deficiency, such as Laron syndrome, do not develop acne despite having a functional androgen receptor. Treatment with IGF-1 in these patients induces acne, further supporting the role of IGF-1 in the pathogenesis of this condition.[23]

The mTORC1 Pathway

Comprised of mTOR in addition to other proteins, mTORC1 is a nutrient-sensitive regulator of cellular growth, proliferation, lipid synthesis, and protein translation.[5] Increased activity of mTORC1 has been described in diabetes, neurodegenerative disease, and cancer,[14,24] while decreased activity may promote longevity.[25] Regulation of mTORC1 occurs through several mechanisms. Growth factors such as insulin and IGF-1 promote mTORC1 activation through the PI3K/Akt pathway. Several amino acids—specifically branched chain amino acids such as alanine, arginine, asparagine, glutamine, histidine, leucine, methionine, serine, threonine, and valine—also can activate mTORC1 independently.[26] Excess glucose leads to decreased adenosine monophosphate–activated protein kinase and increased activity of mTORC1, which occurs separately from insulin or IGF-1.[27] Starvation blocks mTORC1 via increased adenosine monophosphate–activated protein kinase and starvation-induced hypoxia.[26,28] To activate mTORC1, both the IGF-1 or insulin signal and amino acid excess must be present.[29] Although not studied in acne, altering the dietary protein

content in obese mice has been shown to perturb the mTORC1 pathway, leading to pathologic changes in the mTORC1-autophagy signaling axis, increased amino acid release into the blood, and an acute elevation in mTORC1 signaling.[30]

Another major regulator of mTORC1 is Forkhead box protein O1 (FOXO1), which is a transcription factor that regulates mTORC1 through sestrin 3.[31,32] Sestrin 3 is a stress-induced protein that helps regulate blood glucose and promote insulin sensitivity.[33] When FOXO1 is translocated to the cell nucleus, it upregulates the expression of sestrin 3, resulting in mTORC1 inhibition.[31,32] Insulin, IGF-1, and nutrient excess lead to FOXO1 translocation to the cell cytoplasm where it can no longer mitigate mTORC1 activity, while the fasted state leads to translocation to the nucleus.[34] A single study evaluated the association between FOXO1, mTORC1, a high glycemic–load diet, and acne development. Immunohistochemical detection of mTORC1 assessed by digital image analysis revealed significantly greater expression in inflamed pilosebaceous units found in acne patients ($P<.001$). Immunohistochemical cytoplasmic expression of FOXO1 and mTOR (used as a proxy for mTORC1) was significantly higher in patients on a high glycemic–load diet ($P=.021$ and $P=.009$, respectively) as well as in patients with more severe forms of acne ($P=.005$ and $P=.015$, respectively) and elevated IGF-1 levels ($P=.004$ and $P=.003$, respectively).[21]

mTORC1 contributes to the proliferation of keratinocytes and excess sebum production, both independently and through androgen-mediated processes.[35-40] Insulinlike growth factor 1 binding the IGF-1 receptor leads to proliferation of keratinocytes lining the sebaceous gland and hair follicle in vivo.[35] In mice with epidermis-specific deletion of mTOR, keratinocyte proliferation was decreased and hair follicles were diminished both in number and development. Genetic loss of mTOR in the epidermis led to attenuated signaling pathways of mTORC1 and mTORC2.[36]

Androgen function is augmented by mTORC1, FOXO1, and IGF-1 through several mechanisms, which may partially explain the hormonal relationship to acne. Androgens increase IGF-1 within the hair follicle.[37] In prostate cancer cells, IGF-1 then facilitates movement of FOXO1 to the cytoplasm, preventing it from blocking mTORC1. This effective inactivation of FOXO1 thus further augments the impact of androgens by both allowing unchecked mTORC1 pathway activity and increasing translocation of the androgen receptor (AR) to the nucleus where it exerts its effects.[38] Interestingly, genetic polymorphisms of the AR have been shown to cause variable affinity of FOXO1 for the AR; specifically, shorter CAG (cytosine, adenine, guanine) repeat length may lead to decreased FOXO1 binding and is associated with an increased risk for acne.[41-43] In addition to its effects on the hair follicle, IGF-1 stimulates production of testosterone and dehydroepiandrosterone as well as activates 5α-reductase, leading to higher dihydrotestosterone levels, which activate the AR with higher affinity than testosterone.[44] In some tissues, androgens help regulate the mTORC1 pathway through positive feedback loops.[45,46] At this time, we do not know if this occurs in the pathogenesis of acne.

Isotretinoin is the treatment of choice for refractory acne. It has been hypothesized that isotretinoin induces sebocyte apoptosis via the upregulation of FOXO transcription factors and p53.[47] Elevated levels of nuclear FOXO1 have been found in the sebaceous glands of patients following initiation of treatment with isotretinoin and are hypothesized to play a major role in the drug's effectiveness. Specifically, biopsies from 14 acne patients before and after 6 weeks of isotretinoin therapy were analyzed with immunohistochemical staining and found to have a significantly improved nuclear to cytoplasmic ratio of nonphosphorylated FOXO1 ($P<.001$).[47]

Practical Recommendations

Given the available evidence, it is important for dermatologists to address dietary recommendations in acne patients. Although large randomized controlled trials on diet and acne severity are challenging to conduct in this population, the existing literature suggests that patients should avoid high glycemic index simple sugars and processed grains, and patients should focus on eating more complex carbohydrates in the form of legumes, vegetables, fruits, and tubers.[6-8] With regard to dairy, milk (especially skim) has been associated with increased risks for acne.[11,13] Fermented dairy products may have less impact on acne severity and include cheese, yogurt (unsweetened to keep glycemic index low), and sour cream.[12] Additionally, dermatologists can consider evaluating acne patients for insulin resistance with a hemoglobin A_{1c} or oral glucose tolerance test; however, these are not perfect markers of insulin sensitivity. This should be considered in patients with clinical features suggesting metabolic derangement such as acanthosis nigricans; elevated nonfasting triglycerides; or symptoms of polycystic ovarian syndrome, which include irregular menstruation, hirsutism, and early-onset androgenetic alopecia (also an independent sign of insulin resistance in men).[48-51]

REFERENCES

1. Zaenglein AL. Acne vulgaris. In: Bolognia JL, Schaffer JV, Cerroni L, eds. *Dermatology*. Elsevier; 2017:588-603.
2. Ganceviciene R, Graziene V, Fimmel S, et al. Involvement of the corticotropin-releasing hormone system in the pathogenesis of acne vulgaris. *Br J Dermatol*. 2009;160:345-352.
3. Kang S, Cho S, Chung JH, et al. Inflammation and extracellular matrix degradation mediated by activated transcription factors nuclear factor-kappaB and activator protein-1 in inflammatory acne lesions in vivo. *Am J Pathol*. 2005;166:1691-1699.
4. Cong TX, Hao D, Wen X, et al. From pathogenesis of acne vulgaris to anti-acne agents. *Arch Dermatol Res*. 2019;311:337-349.
5. Pópulo H, Lopes JM, Soares P. The mTOR signalling pathway in human cancer. *Int J Mol Sci*. 2012;13:1886-1918.
6. Kwon HH, Yoon JY, Hong JS, et al. Clinical and histological effect of a low glycaemic load diet in treatment of acne vulgaris in Korean patients: a randomized, controlled trial. *Acta Derm Venereol*. 2012;92:241-246.

7. Smith RN, Mann NJ, Braue A, et al. A low-glycemic-load diet improves symptoms in acne vulgaris patients: a randomized controlled trial. *Am J Clin Nutr*. 2007;86:107-115.
8. Penso L, Touvier M, Deschasaux M, et al. Association between adult acne and dietary behaviors: findings from the NutriNet-Santé prospective cohort study. *JAMA Dermatol*. 2020;156:854-862.
9. Cao H, Yang G, Wang Y, et al. Complementary therapies for acne vulgaris. *Cochrane Database Syst Rev*. 2015;1:CD009436.
10. Adebamowo CA, Spiegelman D, Danby FW, et al. High school dietary dairy intake and teenage acne. *J Am Acad Dermatol*. 2005;52:207-214.
11. Aghasi M, Golzarand M, Shab-Bidar S, et al. Dairy intake and acne development: a meta-analysis of observational studies. *Clin Nutr*. 2019;38:1067-1075.
12. Melnik BC, Schmitz G. Pasteurized non-fermented cow's milk but not fermented milk is a promoter of mTORC1-driven aging and increased mortality. *Ageing Res Rev*. 2021;67:101270.
13. Juhl CR, Bergholdt HKM, Miller IM, et al. Dairy intake and acne vulgaris: a systematic review and meta-analysis of 78,529 children, adolescents, and young adults. *Nutrients*. 2018;10:1049. doi:10.3390/nu10081049
14. Melnik BC. Linking diet to acne metabolomics, inflammation, and comedogenesis: an update. *Clin Cosmet Investig Dermatol*. 2015;8:371-388.
15. Smart CEM, King BR, Lopez PE. Insulin dosing for fat and protein: is it time? *Diabetes Care*. 2020;43:13-15.
16. Wan X, Wang S, Xu J, et al. Dietary protein-induced hepatic IGF-1 secretion mediated by PPARγ activation. *PLoS One*. 2017;12:E0173174.
17. Bedinger DH, Adams SH. Metabolic, anabolic, and mitogenic insulin responses: a tissue-specific perspective for insulin receptor activators. *Mol Cell Endocrinol*. 2015;415:143-156.
18. Gubbi S, Quipildor GF, Barzilai N, et al. 40 YEARS of IGF1: IGF1: the Jekyll and Hyde of the aging brain. *J Mol Endocrinol*. 2018;61:T171-T185.
19. Kolb H, Kempf K, Röhling M, et al. Insulin: too much of a good thing is bad. *BMC Med*. 2020;18:224.
20. Wood CL, Lane LC, Cheetham T. Puberty: normal physiology (brief overview). *Best Pract Res Clin Endocrinol Metab*. 2019;33:101265.
21. Agamia NF, Abdallah DM, Sorour O, et al. Skin expression of mammalian target of rapamycin and forkhead box transcription factor O1, and serum insulin-like growth factor-1 in patients with acne vulgaris and their relationship with diet. *Br J Dermatol*. 2016;174:1299-1307.
22. Kartal D, Yildiz H, Ertas R, et al. Association between isolated female acne and insulin resistance: a prospective study. *G Ital Dermatol Venereol*. 2016;151:353-357.
23. Ben-Amitai D, Laron Z. Effect of insulin-like growth factor-1 deficiency or administration on the occurrence of acne. *J Eur Acad Dermatol Venereol*. 2011;25:950-954.
24. Kim LC, Cook RS, Chen J. mTORC1 and mTORC2 in cancer and the tumor microenvironment. *Oncogene*. 2017;36:2191-2201.
25. Weichhart T. mTOR as regulator of lifespan, aging, and cellular senescence: a mini-review. *Gerontology*. 2018;64:127-134.
26. Melick CH, Jewell JL. Regulation of mTORC1 by upstream stimuli. *Genes*. 2020;11:989. doi:10.3390/genes11090989
27. Li M, Zhang CS, Feng JW, et al. Aldolase is a sensor for both low and high glucose, linking to AMPK and mTORC1. *Cell Res*. 2021;31:478-481.
28. Yan T, Zhang J, Tang D, et al. Hypoxia regulates mTORC1-mediated keratinocyte motility and migration via the AMPK pathway. *PLoS One*. 2017;12:E0169155.
29. Dennis MD, Baum JI, Kimball SR, et al. Mechanisms involved in the coordinate regulation of mTORC1 by insulin and amino acids. *J Biol Chem*. 2011;286:8287-8296.
30. Choi BSY, Daniel N, Houde VP, et al. Feeding diversified protein sources exacerbates hepatic insulin resistance via increased gut microbial branched-chain fatty acids and mTORC1 signaling in obese mice. *Nat Commun*. 2021;12:3377.
31. Chen CC, Jeon SM, Bhaskar PT, et al. FoxOs inhibit mTORC1 and activate Akt by inducing the expression of Sestrin3 and Rictor. *Dev Cell*. 2010;18:592-604.
32. Chen Y, Huang T, Yu Z, et al. The functions and roles of sestrins in regulating human diseases. *Cell Mol Biol Lett*. 2022;27:2.
33. Tao R, Xiong X, Liangpunsakul S, et al. Sestrin 3 protein enhances hepatic insulin sensitivity by direct activation of the mTORC2-Akt signaling. *Diabetes*. 2015;64:1211-1223.
34. Gross DN, Wan M, Birnbaum MJ. The role of FOXO in the regulation of metabolism. *Curr Diab Rep*. 2009;9:208-214.
35. Gilhar A, Ish-Shalom S, Pillar T, et al. Effect of anti–insulin-like growth factor 1 on epidermal proliferation of human skin transplanted onto nude mice treated with growth hormone. *Endocrinology*. 1994;134:229-232.
36. Ding X, Bloch W, Iden S, et al. mTORC1 and mTORC2 regulate skin morphogenesis and epidermal barrier formation. *Nat Commun*. 2016;7:13226.
37. Inui S, Itami S. Androgen actions on the human hair follicle: perspectives. *Exp Dermatol*. 2013;22:168-171.
38. Fan W, Yanase T, Morinaga H, et al. Insulin-like growth factor 1/insulin signaling activates androgen signaling through direct interactions of Foxo1 with androgen receptor. *J Biol Chem*. 2007;282:7329-7338.
39. Alestas T, Ganceviciene R, Fimmel S, et al. Enzymes involved in the biosynthesis of leukotriene B4 and prostaglandin E2 are active in sebaceous glands. *J Mol Med*. 2006;84:75-87.
40. Smith TM, Gilliland K, Clawson GA, et al. IGF-1 induces SREBP-1 expression and lipogenesis in SEB-1 sebocytes via activation of the phosphoinositide 3-kinase/Akt pathway. *J Invest Dermatol*. 2008;128:1286-1293.
41. Furtado GV, Yang J, Wu D, et al. FOXO1 controls protein synthesis and transcript abundance of mutant polyglutamine proteins, preventing protein aggregation. *Hum Mol Genet*. 2021;30:996-1005.
42. Melnik BC. Isotretinoin and FoxO1: a scientific hypothesis. *Dermatoendocrinol*. 2011;3:141-165.
43. Heng AHS, Say YH, Sio YY, et al. Gene variants associated with acne vulgaris presentation and severity: a systematic review and meta-analysis. *BMC Med Genomics*. 2021;14:103.
44. Li J, Al-Azzawi F. Mechanism of androgen receptor action. *Maturitas*. 2009;63:142-148.
45. Zhao Y, Tindall DJ, Huang H. Modulation of androgen receptor by FOXA1 and FOXO1 factors in prostate cancer. *Int J Biol Sci*. 2014;10:614-619.
46. Hamdi MM, Mutungi G. Dihydrotestosterone stimulates amino acid uptake and the expression of LAT2 in mouse skeletal muscle fibres through an ERK1/2-dependent mechanism. *J Physiol*. 2011;589(pt 14):3623-3640.
47. Agamia NF, Hussein OM, Abdelmaksoud RE, et al. Effect of oral isotretinoin on the nucleocytoplasmic distribution of FoxO1 and FoxO3 proteins in sebaceous glands of patients with acne vulgaris. *Exp Dermatol*. 2018;27:1344-1351.
48. Kolovou GD, Watts GF, Mikhailidis DP, et al. Postprandial hypertriglyceridaemia revisited in the era of non-fasting lipid profile testing: a 2019 expert panel statement, main text. *Curr Vasc Pharmacol*. 2019;17:498-514.
49. Svoboda SA, Shields BE. Cutaneous manifestations of nutritional excess: pathophysiologic effects of hyperglycemia and hyperinsulinemia on the skin. *Cutis*. 2021;107:74-78.
50. González-González JG, Mancillas-Adame LG, Fernández-Reyes M, et al. Androgenetic alopecia and insulin resistance in young men. *Clin Endocrinol* . 2009;71:494-499.
51. Livadas S, Anagnostis P, Bosdou JK, et al. Polycystic ovary syndrome and type 2 diabetes mellitus: a state-of-the-art review. *World J Diabetes*. 2022;13:5-26.