

Because we are only beginning to understand this disease process, I cannot argue that this is not a possibility. However, I am concerned that the authors did not report any other possible explanations for this finding. First, 88% of patients with NSF had a serum creatinine greater than 5 mg/dL as compared with only 21% of control subjects. The fact that these patients had significantly worse renal function as compared with most of the control subjects puts them at higher risk for requiring recombinant epoetin therapy for management of anemia. Because NSF is only seen in patients with severe renal insufficiency, the epoetin requirement in this group may simply be a manifestation of decreased renal function. Second, patients with NSF had longer cold ischemia times and a greater incidence of delayed graft function as compared with control subjects. Both of these factors are associated with the development of acute rejection.<sup>4</sup> This finding might explain the increased incidence of posttransplantation kidney biopsy among patients with NSF. The inflammation associated with both acute and chronic rejection can have marrow-suppressive effects that may increase the need for recombinant epoetin therapy. Indeed, transplant nephrectomy can ameliorate serum markers of inflammation and result in reduced epoetin requirements among patients with failed renal transplants who have returned to dialysis.<sup>5</sup> It would be interesting to know whether any of the patients with NSF had evidence of rejection on their renal biopsy specimens.

Recently, Marckmann et al<sup>6</sup> also looked at the association between epoetin and NSF. First, not all patients with NSF were treated with epoetin. This finding suggests that epoetin is not necessary for the development of NSF. In addition, although patients with severe NSF received significantly higher doses of epoetin than those with less severe disease, they also received significantly higher cumulative doses of gadolinium. Because epoetin resistance is associated with inflammation, could high-dose epoetin requirements simply reflect disease states or conditions that require gadolinium-enhanced imaging, particularly at high doses? Further studies are required to address this issue.

In conclusion, NSF is a complex disease process that is strongly associated with the administration of gadolinium-based contrast media to patients with severe kidney disease. At this stage of our understanding of this disease, it is not possible to completely exclude that epoetin therapy may also play a role. However, it is important to note that epoetin requirements, particularly at high doses, may simply be a manifestation of a disease process that leads to an increased risk of gadolinium exposure or a

heightened susceptibility to develop NSF after exposure.

*Georges Saab, MD*

*Department of Internal Medicine, Division of Nephrology, University of Missouri-Columbia School of Medicine*

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*Reprint requests: Georges Saab, MD, Department of Internal Medicine, Division of Nephrology, University of Missouri-Columbia School of Medicine, One Hospital Dr, MA436 Health Sciences Center, Columbia, MO 65212*

*E-mail: [saabg@health.missouri.edu](mailto:saabg@health.missouri.edu)*

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#### Comment on acne and glycemic index

*To the Editor:* We commend Kaymak et al<sup>1</sup> for tackling a subject largely ignored by the research community for 30 years; however, we have a few concerns about their study. These include: the validity of the “voluntary self-completed questionnaires”; the timing of the phlebotomy; the decision to assign no glycemic load (GL) values for meat, poultry, fish, vegetables, cheese, or eggs; the failure to address the statistically significant differences in insulin-like growth factor (IGF-1) and IGF binding protein (IGFBP-3) between the two groups; and the choice of the control.

The authors wisely chose the Consensus Conference on Acne Classification system to document the physical findings in their participants. Unfortunately, they chose an unvalidated tool for assessing the diet and they did not append the questionnaire they created. Knowing that even validated food frequency questionnaires suffer from inaccuracy,<sup>2</sup> we should be able to review this document. The unspecified "voluntary" nature of the questionnaire is another area of concern. The manner in which data are collected has a powerful influence on outcome.

As the authors state, the glycemic index (GI) is a "relative comparison of the potential of various foods or combinations of foods to increase blood glucose, based on equal amount of carbohydrate in the food." GI adjusts to account for the usual serving size. Insulin levels chase blood glucose to bring levels back down after eating. High GI/GL foods tend to increase blood glucose levels and subsequent insulin levels "high and fast." Low GI/GL foods increase insulin "lower and slower." Regardless of GI/GL, the process is complete within a few hours of eating. Measurements of serum levels are taken every 15 to 30 minutes to reveal the pattern.<sup>3</sup> A high GI/GL diet results in higher area under the curve insulin levels over the course of a day. The fasting levels used in this study tell us nothing about insulin level excursions and total insulin exposure throughout the day.

Excluding meat, poultry, fish, vegetables, cheese, and eggs from the dietary assessment could be misleading. Many vegetables are rich in carbohydrates and the cooking technique can alter the GI dramatically. Processed meats have been shown in a number of studies to adversely affect glycemic control.<sup>4</sup> Conversely, dietary fish, rich in omega-3 fatty acids, lowers fasting glucose levels and improves glycemic control.<sup>5</sup> A 12-week trial of the Paleolithic diet, with its emphasis on lean meat, fish, fruits, vegetables, root vegetables, eggs, and nuts, resulted in significant improvement in these parameters.<sup>6</sup> Focusing almost entirely on carbohydrates, Kaymak et al<sup>1</sup> do not account for the effects of these other elements.

Of particular interest is the dissociation seen between the GI/GL and the insulin response to milk products. In most carbohydrate-containing foods, the blood insulin response is predictable and is closely linked to the food's GI/GL. For both skim and whole milk, the actual areas under the curve for insulin were significantly greater than predicted.<sup>7</sup> Given that the hormone response to diet appears to depend more on the insulinemic response than the glycemic response, we may need

to evaluate milk products differently. Dairy ingestion directly correlates with acne.<sup>8</sup> Whether this is a result of the insulin effect mediated through IGF-1 and/or bovine reproductive steroidal hormone influence is not yet clear.

The text of the "Results" section states: "The levels of IGF-1 were significantly lower and IGFBP-3 were significantly higher in control subjects compared with the patients with acne." The reader is referred to Table II, which shows the opposite. We assume that the labels for the columns in the table are transposed, but a casual reader will interpret the data incorrectly. We believe these statistically significant findings deserve discussion.

Elevation of IGF-1 in patients with acne is well documented.<sup>9</sup> IGFBP-3 binds IGF-1 thereby blocking its action. That IGF-1 is higher and IGFBP-3 is lower in patients with acne in this study should not surprise us. Although we do not fully understand the roles these molecules play in acne, we do have a few hints. Free IGF-1 directly stimulates basal keratinocyte proliferation, thereby contributing to the follicular hyperkeratosis that is considered the initial step in acne lesion formation, whereas IGFBP-3 inhibits it.<sup>10</sup> In addition, IGFBP-3 and tretinoin bind the same retinoid X nuclear receptor (alpha).<sup>11</sup>

Diet clearly affects IGF-1 and IGFBP-3. Insulin increases IGF-1 levels. IGFBP-3, on the other hand, decreases after ingestion of high GI foods and increases after eating low GI foods.<sup>12</sup> Lower levels of IGF-1 and higher levels of IGFBP-3 are associated with greater intake of omega-3 fatty acids, tomatoes, vegetables, and dietary fiber. In contrast, higher levels of IGF-1 are associated with dietary saturated fat, vegetable oils, milk, and dairy products.<sup>13,14</sup> Ingestion of a tomato extract decreases plasma IGF-1 levels by 25% in patients with colon cancer.<sup>15</sup> Could it be that retinoids, the darlings of the acne armamentarium, act by restoring the retinoid X receptor signal that decreases with a diet-induced decline in IGFBP-3?<sup>11</sup>

In this study, the dietary GI of patients with long-term acne was significantly higher than that of the healthy control subjects. These data force us to disagree with the authors' conclusion that "results of this study do not reveal a relationship between high glycemic index diets and acne." On the contrary, the correlation between high GI diet and acne of greater than 2 years' duration appears to be very real and deserves further rigorous study.

The authors differentiate between teen acne and acne in "those showing insulin resistance, which is seen mainly in overweight adults." In fact, insulin resistance is the common thread connecting these two groups. In 2001, Goran and Gower<sup>16</sup> found that

the pubertal transition from Tanner stage I to Tanner stage III was associated with a 32% reduction in insulin sensitivity and increases in fasting glucose and insulin. This insulin resistance resolves as teens progress through Tanner stage V, normalizing about the time that acne tends to remit. We suspect that insulin (and the diet that stimulates it) may turn out to be one of the more profound influences in acne.

Setting the above considerations aside, we wish to stress that the authors studied not one population but two, parallel populations that have one glaring difference: the constitutional ability to develop acne. Although the authors admit that “genetic susceptibility” may be a factor, the very existence of two well-matched populations on the same diet, one with and one without acne, strongly suggests that the two are essentially different. To truly test diet’s effect, the investigators must take a population with acne and selectively control GL, as in the work of Smith et al.<sup>17</sup>

We are delighted to see nutrition research in major dermatology journals and look forward to more of the same. We expect that the same high review standards to which we have become accustomed will be applied to work in this field.

Valori Treloar, MD, CNS,<sup>a</sup> Alan C. Logan, ND, FRSH,<sup>b</sup> F. William Danby, MD, FRCPC,<sup>c</sup> Loren Cordain, PhD,<sup>d</sup> and Neil J. Mann, PhD<sup>e</sup>

*Integrative Dermatology PC, Newton, Massachusetts<sup>a</sup>; CAM Research Consulting, Yonkers, New York<sup>b</sup>; Department of Medicine (Dermatology), Dartmouth Medical School, Hanover, New Hampshire<sup>c</sup>; Department of Health and Exercise Science, Colorado State University, Fort Collins<sup>d</sup>; and School of Applied Sciences, RMIT University, Melbourne, Australia<sup>e</sup>*

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*Reprint requests: Valori Treloar, MD, CNS, Integrative Dermatology PC, 1172 Beacon St, Suite 402, Newton, MA 02461*

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## Vitamin D: The sun as an essential source

*To the Editor:* Is the commentary “A responsible approach to maintaining adequate serum vitamin D levels” responsible?

In their admirable concern for sun safety in their commentary with the above-stated title in the *Journal*, Lim et al<sup>1</sup> express their recommendations that intentional ultraviolet radiation (both solar and artificial) should be avoided, and that reliance should be placed on oral intake of vitamin D from food and