Effects of Anti-Tumor Necrosis Factor Therapy on Body Composition and Insulin Sensitivity in Patients With Psoriasis

Epidemiologic studies have shown an association between psoriasis and cardiovascular diseases. An interesting but unproven hypothesis ascribes this association to the psoriatic march, the process by which inflammatory mediators released in the course of the psoriatic autoimmune reaction cause insulin resistance, which ultimately leads to atherosclerosis.¹

Tumor necrosis factor (TNF) is a proinflammatory cytokine that impairs response to insulin in adipocytes and muscle cells via inhibition of tyrosine kinase activity of the insulin receptor, activation of peroxisome proliferator-activated receptor-δ, and changes in secretion of adipokines.² For the present study, we investigated the effect of anti-TNF treatment on insulin resistance and body composition in patients with psoriasis.

Methods. Eligible participants were anti-TNF–naïve male patients with psoriasis recalcitrant to other systemic treatments and UV-B therapy. They also had a PASI (Psoriasis Area and Severity Index) or a DLQI (Dermatology Life Quality Index) of 10 or higher. The selection of the TNF agent was left to the treating dermatologist. Patients were asked to maintain their usual physical activity and to stay on their usual diet during the 12-week study period. Approval was granted by the scientific ethical committee (approval No. H-D-2009-040).

Insulin sensitivity was determined by a 2-hour hyperinsulinemic euglycemic clamp. Body composition was estimated by dual-energy x-ray absorptiometry. Peak oxygen uptake was assessed during a progressive exercise test. Patients completed the International Physical Activity Questionnaire. A sample size of 18 was required to detect an increase of 15% or more in insulin sensitivity (1-sided α = .05 and power=0.91). An interim analysis after 9 completed patients was performed to indicate a trend for a difference. A P < .20 was needed to justify study continuation. A more detailed description of methods is available in the eAppendix (http://www.archdermatol.com).

Results. The interim analysis did not indicate a trend; therefore, the study was terminated. Baseline patient characteristics are summarized in Table 1. Truncal fat percentage was negatively correlated with insulin sensitivity (r = −0.78, P = .01) and positively correlated plasma leptin (r = 0.88, P = .002). After 12 weeks of therapy (infliximab=5, adalimumab=4), there were no significant changes in insulin sensitivity or levels of fasting glucose, hemoglobin A₁c, or C-peptide. Body fat increased by 6.5%, and truncal fat increased by 11.4%. Leptin concentrations significantly decreased after anti-TNF treatment (Table 2).

Comment. It is known that anti-TNF therapy increases body weight in patients with psoriasis. In line with our results, Renzo et al³ observed a gain in the body fat of 8.6% in patients with psoriasis after 24 weeks of anti-TNF therapy. It is known that TNF stimulates lipolysis...
Dermatology Life Quality Index; GR, Grenz rays; IFX, infliximab; MTX, methotrexate; PASI, Psoriasis Area and Severity Index; Tar, topical coal or pine tar; TNF, tumor necrosis factor; TS/CAL, topical steroids and calcipotriol in combination or as single therapies.

divide by 6.945.

decimal, divide by 0.055; insulin to micro–International Units per milliliter,

Resistance index; IPAQ, International Physical Activity Questionnaire; IQR, interquartile range; M, glucose uptake per kg lean body mass; MET, metabolic equivalent task; PASI, Psoriasis Area and Severity Index; TNF, tumor necrosis factor; VO\textsubscript{2} peak, peak oxygen uptake.

Conventional unit conversion factors: To convert glucose to milligrams per deciliter, divide by 0.0555; insulin to micro–International Units per milliliter, divide by 6.945.

Table 1. Disease Severity, Physical Activity, Peak Oxygen Uptake, Insulin Sensitivity, Leptin Concentration, and Body Composition at Baseline and After Anti-TNF Treatment

Table 2. Disease Severity, Physical Activity, Peak Oxygen Uptake, Insulin Sensitivity, Leptin Concentration, and Body Composition at Baseline and After Anti-TNF Treatment

in human adipocytes; thus, anti-TNF may reduce lipolysis and thereby accumulation of fat in adipocytes.

We confirmed an inverse correlation between truncal fat percentage and insulin sensitivity, but anti-TNF therapy had no significant influence on insulin sensitivity. Martinez-Abundis et al\textsuperscript{5} reported no effect on insulin sensitivity measured using a hyperinsulinemic clamp during 2 weeks of etanercept treatment, but Marra et al\textsuperscript{6} reported a decrease in insulin resistance assessed by homeostatic model assessment after 24 weeks of etanercept treatment. The clamp primarily measures insulin-mediated glucose disposal by skeletal muscles. To investigate insulin sensitivity in adipose tissue, other methods should have been used.

Epidemiologic evidence indicates a lower risk of developing diabetes mellitus for patients with psoriasis who are treated with a TNF inhibitor compared with several other drugs.\textsuperscript{7} Leptin is a fat-tissue hormone. Reduction in plasma leptin is associated with suppression of metabolic rate and stimulation of appetite in lean subjects.\textsuperscript{8} Plasma leptin level is increased in patients with psoriasis.\textsuperscript{9} Tumor necrosis factor is capable of inducing leptin production, and infusion of infliximab decreases leptin levels in rodents.\textsuperscript{8} Thus, the observed decrease in plasma leptin level is in line with experimental data. On the other hand, the increase in fat should have resulted in an increase in leptin levels, and clinical studies on other autoimmune diseases have found unchanged or even increased leptin levels after anti-TNF treatment.\textsuperscript{10} An interesting note is that plasma leptin level indicates that anti-TNF treatment reduces the risk of cardiovascular disease.
Weaknesses of the present study include the limited number of patients, the fact that only men were included, the uncontrolled study design, and the use of 2 different anti-TNF antibodies. Using the gold-standard methods, we found that the increase in body weight in patients with psoriasis treated with anti-TNF is due to an increase in the amount of truncal fat, but we were unable to demonstrate any significant effect of anti-TNF therapy on insulin sensitivity. Future studies should investigate the mechanism behind the increase in body fat.

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COMMENTS AND OPINIONS

Pitfalls of Evidence-Based Medicine Revisited

I enjoyed greatly the article in the Archives by Gilchrest and Martin about some of the pitfalls of evidence-based medicine. The article was insightful and nuanced, so much so that I cannot but believe that their first sentence was written with a degree of irony. The authors state that “No one can argue about the merit of evidence-based medicine.”1(p528) Well, of course, the medical literature is full of cogently argued expressions of doubts about the epistemology of evidence-based medicine (for a recent review, see Goldenberg et al and all articles in that same volume of Perspectives in Biology and Medicine devoted to this subject).

Most physicians have always claimed that they practice medicine on the basis of evidence, but what they have disagreed about is what types of knowledge constitute this evidence. Central to these concerns today is how we integrate evidence from randomized controlled trials (RCTs) with other sorts of knowledge.

First, we need to be cautious about our metaphors.2 Gold standard originally referred to the currency policy in which a given unit of (say) paper currency is exchangeable for a defined amount of gold. For this standard to