Tumor Necrosis Factor-α Antagonism Improves Vasodilation During Hyperinsulinemia in Metabolic Syndrome

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OBJECTIVE — Obesity is associated with chronic inflammation due to overproduction of proinflammatory cytokines, including tumor necrosis factor (TNF)-α. We assessed the effects of TNF-α neutralization by infliximab on vascular reactivity during hyperinsulinemia in obesity-related metabolic syndrome.

RESEARCH DESIGN AND METHODS — Vascular responses to intra-arterial infusion of acetylcholine (ACh) and sodium nitroprusside (SNP) were assessed in patients with metabolic syndrome, before and after administration of infliximab.

RESULTS — Patients had blunted vasodilator responses to ACh and SNP during hyperinsulinemia compared with control subjects; a potentiation of the responsiveness to both ACh and SNP, however, was observed in patients following infliximab. The antioxidant vitamin C improved the vasodilator response to ACh in patients with metabolic syndrome, but its effect was not further enhanced by concurrent administration of infliximab.

CONCLUSIONS — TNF-α neutralization ameliorates vascular reactivity in metabolic syndrome during hyperinsulinemia, likely in relation to decreased oxidative stress, thereby suggesting an involvement of inflammatory cytokines in vascular dysfunction of these patients.

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(12.9 ± 1.1 vs. 16.3 ± 0.6 ml · min⁻¹ · dl⁻¹, respectively; P < 0.001). In patients with metabolic syndrome participating in Study 1, infliximab improved the vasodilator response to both ACh (Fig. 1A) and SNP (Fig. 1B). In patients participating in Study 2, vascular response to ACh was significantly enhanced by administration of vitamin C compared with hyperinsulinemia alone (Fig. 1C); under those conditions, however, infusion of infliximab in conjunction with vitamin C did not modify vascular responsiveness to ACh versus vitamin C alone (Fig. 1D).

CONCLUSIONS — This study provides the novel finding that TNF-α neutralization improves NO-dependent vasodilation during hyperinsulinemia, thereby suggesting that TNF-α activation is involved in vascular dysfunction of metabolic syndrome.

Overexpression of TNF-α has previously been reported not only in obese adipose tissue (1) and in the skeletal muscle of insulin-resistant animals and humans (2), but also in vascular smooth muscle cells (VSMCs) (3). The decreased responsiveness to both endothelium-dependent and -independent stimuli seen during hyperinsulinemia in our patients, taken in conjunction with the favorable effect of infliximab on responses to both ACh and SNP, suggests that TNF-α activation in metabolic syndrome affects NO-dependent vasodilation through mechanisms other than endothelial dysfunction. This phenomenon might be determined by impaired insulin signaling within VSMCs, thus affecting the facilitatory action physiologically exerted by insulin on vasorelaxation. This hypothesis stems from studies showing that insulin may impact VSMCs relaxation.

Recent experimental evidence indicates that TNF-α overexpression increases oxidative stress (7) and that TNF-α–induced reactive oxygen species play a causal role in insulin resistance (8). We tested the possibility that increased oxidative stress could also be involved in human TNF-α vasculopathy by use of vitamin C. This antioxidant improved the vasodilator response to ACh during hyperinsulinemia in metabolic syndrome, whereas infliximab infusion on top of vitamin C did not exert additive effects. This suggests that increased oxidative stress is indeed involved in mediating the effects of TNF-α on vasodilation during hyperinsulinemia, a view supported by previous results showing that reactive oxygen species could affect vascular reactivity through changes in receptor function or activity of signaling pathways (9,10).

The beneficial action of infliximab demonstrated in our study suggests a novel mechanism by which TNF-α activation might be involved, via increased oxidative stress, in vascular dysfunction of patients with obesity-related metabolic syndrome; it remains to be elucidated whether interventions targeting cytokines may become an effective strategy for prevention in these patients.

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