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MARKED IMPAIRMENT OF ENDOTHELIAL FUNCTION WITHOUT INSULIN RESISTANCE IN HEALTHY MEN TREATED WITH THE HIV-1 PROTEASE INHIBITOR INDINAVIR

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BACKGROUND: The HIV-1 protease inhibitor indinavir (IDV) impairs endothelial function and basal nitric oxide (NO)-dependent tone in healthy men. Endothelial dysfunction is commonly observed in states of insulin resistance. We hypothesized that IDV-induced endothelial dysfunction occurs as a result of IDV-induced insulin resistance.

METHODS: We assessed insulin sensitivity, endothelial function and insulin-mediated vasodilation in 16 lean healthy male subjects before and after 4 weeks of IDV 800 mg twice daily. Insulin sensitivity was measured using the euglycaemic hyperinsulinaemic clamp for 240 mins. We assessed endothelial function by measuring changes in leg blood flow (LBF) in response to intra-arterial administration of graded doses of the endothelium-dependent vasodilator, methacholine chloride.

RESULTS: Our subjects were 37 ± 3 years old, with BMI of 25 ± 1 kg/m², body fat of 19.6 ± 1.9%, total cholesterol: 171 ± 8 mg/dl; LDL-cholesterol: 98 ± 7 mg/dl; HDL-cholesterol: 50 ± 4 mg/dl; triglycerides: 140 ± 39 mg/dl, and resting LBF of 0.207 ± 0.015 l/min. There was no significant change in any of these parameters after IDV. Plasma adiponectin levels increased after IDV (16.4 ± 2.2 µg/ml pre-IDV, 19.1 ± 2.3 µg/ml post-IDV, *P*<0.05). Normal, robust endothelium-dependent and insulin-mediated vasodilatory responses were present at baseline. After IDV, there was a marked blunting of endothelium-dependent vasodilation (258 ± 43% pre-IDV vs 60 ± 13% post, *P*<0.05) and insulin-mediated vasodilation (70 ± 10% pre-IDV vs 16 ± 6% post, *P*<0.05). In spite of these dramatic effects on vascular function, there was no significant change in the steady-

state whole body glucose-disposal rate with IDV (8.0 ± 0.6 mg/kg/min pre-IDV vs 7.5 ± 0.6 post, $P=NS$).

CONCLUSIONS: Four weeks of IDV markedly impairs endothelial function and insulin-mediated vasodilation, without significant impairment of whole-body glucose disposal. Thus, it appears unlikely that insulin resistance plays a major role in the induction of the endothelial dysfunction seen in this human model of IDV monotherapy.

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