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Vanadyl Sulfate Does Not Enhance Insulin Action in Patients With Type 1 Diabetes

Vanadium, a transition metal found in trace concentrations in humans, has insulin-like effects in vitro (1–3) and in vivo (4,5). In vitro, vanadium stimulates glucose uptake and oxidation, and glycogen synthesis in adipocytes, skeletal muscle, and hepatocytes (6). In diabetic rats, large doses of vanadium improve glucose tolerance without an increase in plasma insulin (5) and cause an increase in hepatic glycogen (5,7,8). Thus, interest in vanadium as a possible treatment for diabetes has been intense.

In humans, we have demonstrated that low doses of vanadyl sulfate (VS) given for 3 weeks increased insulin-mediated glucose uptake, glycogen synthesis, and suppression of endogenous glucose production (EGP) in type 2 diabetic patients (9) but not in obese nondiabetic subjects (10). These improvements in hepatic and peripheral insulin sensitivity were associated with reduced lipid oxidation rates and plasma free fatty acid (FFA) concentrations. On the other hand, a recent study in type 1 diabetic patients given sodium metavanadate demonstrated a decrease in insulin requirements with no change in glucose metabolism (11). However, the relationship between the clinical findings of reduced insulin requirements and vanadium action per se is unclear. For example, the intracellular—and hence active—form of vanadium associated with an insulin-like effect is the vanadyl (V^{4+}) oxidation state of the element, as used in our previous studies, not vanadate (V^{5+}) (12,13). Thus, a plausible mechanism for vanadium action in type 1 diabetes remains unclear.

Because the effects of VS in type 2 diabetes may be to augment insulin action on lipolysis and EGP and both parameters are very sensitive to insulin in vivo, we used a low-dose insulin infusion to determine whether there is enhancement of insulin action, as seen in patients with type 2 diabetes. VS (100 mg/day) was given for 3 weeks and compared with 3 weeks of placebo in five type 1 diabetic subjects (age 31 ± 2 years; BMI 24 ± 1.6 kg/m^2). Plasma vanadium concentrations were 83.0 ± 29.4 μg/l after VS. There were no changes in insulin dose, weight, or appetite during the study period. While HbA_{1c} declined slightly, from 8.1 ± 0.4 to 7.6 ± 0.3%, serum fructosamine levels were unchanged (2.5 ± 0.1 mmol/l after both placebo and VS). Euglycemic-hyperinsulinemic clamps combined with 3-[^{3}H]glucose and constant specific activity were performed after each 3-week period. Glucose disposal was unchanged (26.37 ± 3.16 vs. 23.59 ± 3.89 μmol · kg^{-1} · min^{-1}, placebo vs. VS, respectively, NS). Similarly, glucose infusion rates needed to maintain euglycemia were unchanged (24.53 ± 3.28 vs. 21.59 ± 3.28 μmol · kg^{-1} · min^{-1}, NS). With indirect calorimetry, there were no significant changes in the whole-body oxidation rates of glucose or lipid. Finally, insulin-induced suppression of EGP (by ~70–80%) and plasma FFA (by ~50–60%) were comparable after placebo and VS.

Thus, a dose of VS previously determined to be well tolerated in humans and effective in patients with insulin-resistant type 2 diabetes did not enhance the effects of physiologic hyperinsulinemia on glucose and fat metabolism in type 1 diabetes. These results suggest that vanadium improves insulin action selectively in subjects with insulin resistance. While currently available, vanadium compounds remain as experimental probes to examine the mechanism of altered insulin action (14); more studies will be needed to establish any role for their clinical usage.

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A Common Glu^{298}→Asp (894G→T) Mutation at Exon 7 of the Endothelial Nitric Oxide Synthase Gene and Vascular Complications in Type 2 Diabetes

Nitric oxide (NO) regulates endothelium-dependent vasodilatation and blood pressure, and reduced production has been implicated in hypertension, atherosclerosis, and diabetes (1–3). Endothelial constitutive nitric oxide synthase (ecNOS) mediates the oxidation of L-arginine to produce NO and determines basal vascular wall NO production (4). The gene encoding ecNOS is located on chromosome 7q35-36 and comprises 26 exons (5). To identify genetic markers relevant to NO-related vascular risk, we explored in 574 middle-aged Australian type 2 diabetic patients a possible role for a Glu^{298}→Asp mutation at exon 7 of the ecNOS gene; an association between the mutation and coronary risk was reported in the Cambridge Heart Anti-Oxidant Study (6). Patients recruited were those aged 62.4 ± 0.5 years (mean ± SEM), 329 men and 245 women, with and without documented macro- and microvascular complications. The genotype distribution was 7.5, 40.6, and 51.9% for TT, TG, and GG, respectively. It was in Hardy-Weinberg equilibrium (χ^2 = 0.088, $P > 0.05$) and not different between men and women (χ^2 = 0.713, P = 0.700). The ecNOS TT and TG genotypes were not associated with age, age at onset of documented diabetes, BMI, systolic and diastolic blood pressures (BPs), lipid profile, plasma creatinine and glycosylated hemoglobin (HbA_{1c}) levels, or urinary albumin index (UAI: albumin/creatinine ratio). Furthermore, as shown in Table 1, in χ^2 comparisons, the mutation was not associated with vascular events (χ^2 = 4.698, P = 0.095 for angina pectoris; χ^2 = 1.100, P = 0.577 for myocardial infarction; χ^2 = 0.181, P = 0.913 for stroke; χ^2 = 1.414, P = 0.493 for peripheral vascular disease; χ^2 = 2.372, P = 0.305 for microalbuminuria; χ^2 = 1.434, P = 0.488 for neuropathy; and χ^2 = 4.260, P = 0.119 for retinopathy). In a logistic regression analysis, in which vascular events were entered as dependent variables and age, sex, BMI, current smoking status, systolic and diastolic BPs, total cholesterol, triglycerides, HDL cholesterol, HbA_{1c}, and UAI were entered as independent variables, the ecNOS TT and TG genotypes were still not predictive of the occurrence of vascular events.

In conclusion, we identified a 27.8% allele frequency of the Glu^{298}→Asp mutation at exon 7 of the ecNOS gene in type 2 diabetic patients, but in these patients the mutation was not associated with macro- or microvascular complications or with any of the traditional atherogenic risk factors.

Table 1—*Vascular complications and the ecNOS genotypes in type 2 diabetes*

	TT	TG	GG	*P* value
Angina pectoris				
Yes	11 (25.6)	40 (17.2)	40 (13.4)	0.095
No	33	192	258	
Myocardial infarction				
Yes	6 (14.0)	35 (15.1)	54 (18.1)	0.577
No	37	197	244	
Stroke				
Yes	1 (2.6)	7 (3.6)	10 (3.9)	0.913
No	38	187	245	
Peripheral vascular disease				
Yes	5 (12.8)	41 (21.1)	51 (20.0)	0.493
No	34	153	204	
Microalbuminuria				
Yes	7 (20.6)	44 (28.8)	65 (30.5)	0.305
No	27	109	148	
Retinopathy				
Yes	5 (20.8)	23 (16.8)	43 (26.7)	0.119
No	19	114	118	
Neuropathy				
Yes	8 (21.1)	46 (26.0)	49 (21.1)	0.488
No	30	131	183	

Data are *n* or *n* (%). *P* values refer to comparisons of the frequencies of the occurrence of vascular complications among the three ecNOS genotypes by χ^2 analysis.

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