

## Metabolic effects of vanadyl sulfate in humans with non-insulin-dependent diabetes mellitus: in vivo and in vitro studies.

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### Source

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### Abstract

To investigate the efficacy and mechanism of action of vanadium salts as oral hypoglycemic agents, 16 type 2 diabetic patients were studied before and after 6 weeks of vanadyl sulfate (VOSO<sub>4</sub>) treatment at three doses. Glucose metabolism during a euglycemic insulin clamp did not increase at 75 mg/d, but improved in 3 of 5 subjects receiving 150 mg VOSO<sub>4</sub> and 4 of 8 subjects receiving 300 mg VOSO<sub>4</sub>. Basal hepatic glucose production (HGP) and suppression of HGP by insulin were unchanged at all doses. Fasting glucose and hemoglobin A1c (HbA1c) decreased significantly in the 150- and 300-mg VOSO<sub>4</sub> groups. At the highest dose, total cholesterol decreased, associated with a decrease in high-density lipoprotein (HDL). There was no change in systolic, diastolic, or mean arterial blood pressure on 24-hour ambulatory monitors at any dose. There was no apparent correlation between the clinical response and peak serum level of vanadium. The 150- and 300-mg vanadyl doses caused some gastrointestinal intolerance but did not increase tissue oxidative stress as assessed by thiobarbituric acid-reactive substances (TBARS). In muscle obtained during clamp studies prior to vanadium therapy, insulin stimulated the tyrosine phosphorylation of the insulin receptor, insulin receptor substrate-1 (IRS-1), and Shc proteins by 2- to 3-fold, while phosphatidylinositol 3-kinase (PI 3-kinase) activity associated with IRS-1 increased 4.7-fold during insulin stimulation (P = .02). Following vanadium, there was a consistent trend for increased basal levels of insulin receptor, Shc, and IRS-1 protein tyrosine phosphorylation and IRS-1-associated PI 3-kinase, but no further increase with insulin. There was no discernible correlation between tyrosine phosphorylation patterns and glucose disposal responses to vanadyl. While glycogen synthase fractional activity increased 1.5-fold following insulin infusion, there was no change in basal or insulin-stimulated activity after vanadyl. There was no increase in the protein phosphatase activity of muscle homogenates to exogenous substrate after vanadyl. Vanadyl sulfate appears safe at these doses for 6 weeks, but at the tolerated doses, it does not dramatically improve insulin sensitivity or glycemic control. Vanadyl modifies proteins in human skeletal muscle involved in early insulin signaling, including basal insulin receptor and substrate tyrosine phosphorylation and activation of PI 3-kinase, and is not additive or synergistic with insulin at these steps. Vanadyl sulfate does not modify the action of insulin to stimulate glycogen synthesis. Since glucose utilization is improved in some patients, vanadyl must also act at other steps of insulin action.

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