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Effect of Vanadium on Insulin Sensitivity in Patients with Impaired Glucose Tolerance

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Key Words
Impaired glucose tolerance · Insulin sensitivity · Triglycerides · Vanadium

Abstract
Background/Aim: Impaired glucose tolerance (IGT) is considered a risk factor for developing type 2 diabetes mellitus (T2DM) and is associated with insulin resistance. Vanadium seems to block protein tyrosine phosphatase with the consequent increment in insulin sensitivity (INS) in T2DM patients, but this effect has not been studied in IGT patients. The aim of this study was to evaluate the effect of vanadium on INS in IGT patients. ***Methods:*** A randomized, double-blind, placebo-controlled clinical trial was carried out in 14 overweight/obese patients with IGT. Intervention consisted of vanadyl sulfate (VS, 50 mg p.o. twice daily) or placebo for 4 weeks. Before and after the intervention, a metabolic profile was performed and INS was assessed using the euglycemic-hyperinsulinemic clamp technique. Mann-Whitney U and Wilcoxon rank tests were used for statistical analyses. ***Results:*** There were no significant differences in basal characteristics between groups. VS did not affect INS [2.7 ± 0.8 vs. 2.9 ± 0.9 mg/(kg/min), p = 0.735] but increased triglyceride levels (1.35 ± 0.61 vs. 1.70 ± 0.46 mmol/l, p = 0.018). ***Conclusions:*** VS administration in IGT patients increased triglyceride concentrations without changes in INS.

Introduction

A century ago, the element vanadium was used in diabetes mellitus (DM) [1]. This element could be considered as an essential dietary element [2] and as a nutritional factor to improve glucose-insulin metabolism [3–7]. Vanadium increases insulin sensitivity (INS) due to blocking of protein tyrosine phosphatase (PTP) [8].

Many inorganic and organic chemical forms of vanadium have been studied in association with INS in clinical trials [5]. Vanadyl sulfate (VS) is an inorganic vanadium compound studied for human use in subjects with insulin resistance (IR), e.g. type 2 DM (T2DM) patients [3, 4, 7, 9] who show increased INS and decreased blood cholesterol and triglyceride levels.

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Table 1. Lipid profile in both groups before and after intervention

	Placebo (n = 7)		Vanadium (n = 7)	
	basal	final	basal	final
Total cholesterol, mmol/l	4.6 ± 1.0	4.5 ± 0.7	4.6 ± 1.0	4.6 ± 1.0
Triglycerides, mmol/l	1.4 ± 0.6	1.5 ± 0.5	1.4 ± 0.6	1.7 ± 0.5*
HDL cholesterol, mmol/l	1.0 ± 0.2	1.0 ± 0.2	1.2 ± 0.3	1.2 ± 0.3
LDL cholesterol, mmol/l	2.9 ± 0.8	2.8 ± 0.7	2.8 ± 0.7	2.8 ± 0.7

* p = 0.018 vs. basal (Mann-Whitney U test).

Impaired glucose tolerance (IGT) is an endocrine disorder associated with IR and is considered to be a pre-diabetic state [10] linked to the metabolic syndrome. IGT precedes T2DM by many years [11].

Results of previous studies propose that vanadium could be used to treat DM. There is no evidence regarding the effect of vanadium in pre-diabetic patients. Therefore, the aim of this study was to evaluate the effect of vanadium on INS in IGT patients.

Patients and Methods

Participants

Patients diagnosed with IGT according to American Diabetes Association criteria [10] were selected. They were included independently of gender, with ages ranging from 40 to 50 years, body mass index (BMI) from 25 to 35 and a history of T2DM in the first branch. No subject was taking any medication with known effects on carbohydrate or insulin metabolism. The study was authorized by the local ethics committee of our institution and fulfilled all requirements for carrying out human investigations. Each subject provided written informed consent. Sample size was calculated with a clinical trial formula [12] with a confidence level of 95%, statistical power of 80%, standard deviation of M of 1.73 mg/(kg/min) and an expected difference of 2.59 mg/(kg/min) that resulted in 7 individuals per group.

Measures

Weight, height and resting blood pressure evaluations were registered on paper and electronically. The oral glucose tolerance test was carried out in order to diagnose IGT [10]. The euglycemic-hyperinsulinemic clamp (EHC) technique and metabolic profile (fasting glucose and lipids) were performed. Following EHC, subjects were randomly assigned to one of two groups: 100 mg/day VS (50 mg twice daily) or placebo at meal time. Clinical evaluation, metabolic profile and EHC technique were repeated 30 days after the pharmacological intervention.

The EHC technique [13] was used to assess INS and consisted of retrograde canalization of a dorsal hand vein heated in a thermal pad to 40–60°C to arterialize venous blood; this venous access was used to obtain blood samples. The second access was installed conventionally on an antecubital vein of the contralateral arm near the front elbow fold; this access was used for liquid infusion. Blood samples were collected at time zero and every 5 min to measure plasma glucose concentration. Calculations for infusion velocity were pre-established during the first 15 min of the test according to patients' weight, and insulin infusion velocity was then kept constant. Glucose infusion was calculated according to the glucose concentration of the previous 5- and 10-min samples. The purpose of the test was to maintain a blood glucose concentration of 5.0 ± 0.6 mmol/l. EHC calculated the glucose metabolized (M) in mg/(kg/min), and M was directly proportional to INS.

For the EHC technique, glucose concentration in plasma was measured by the glucose-oxidase method (Beckman Instruments, Brea, Calif., USA) with an intra- and interassay coefficient of variation <1%. Serum concentrations of total cholesterol, high-density lipoprotein cholesterol (HDL) and triglycerides were measured by enzymatic colorimetric methods (Ortho-Clinical Diagnostics, Rochester, N.Y., USA) with an intra- and interassay coefficient of variation <2%. Low-density lipoprotein cholesterol (LDL) levels were calculated using the Friedewald formula: total cholesterol – HDL – (triglycerides/5).

Data Analyses

Values were presented as means ± SD. Intention-to-treat analyses were conducted. Differences between groups were calculated by Mann-Whitney U test; intragroup differences were calculated by the Wilcoxon rank test. Statistical calculations were done using SPSS for Windows (version 10), and statistical significance was established when $p \leq 0.05$.

Results

Fourteen patients with IGT were included in this trial. Gender (4 women and 3 men in both groups, p = 1.000), age (48.9 ± 3.7 vs. 48.3 ± 4.0 years, p = 0.699), basal BMI (30.7 ± 3.0 vs. 28.8 ± 3.1, p = 0.338), systolic blood pressure (128 ± 14 vs. 127 ± 12 mm Hg, p = 0.790), diastolic blood pressure (84 ± 8 vs. 81 ± 7 mm Hg, p = 0.945) and serum glucose (5.7 ± 0.7 vs. 5.6 ± 0.4 mmol/l, p = 0.949) were similar between groups. There were no significant differences in the basal lipid profile between groups (table 1).

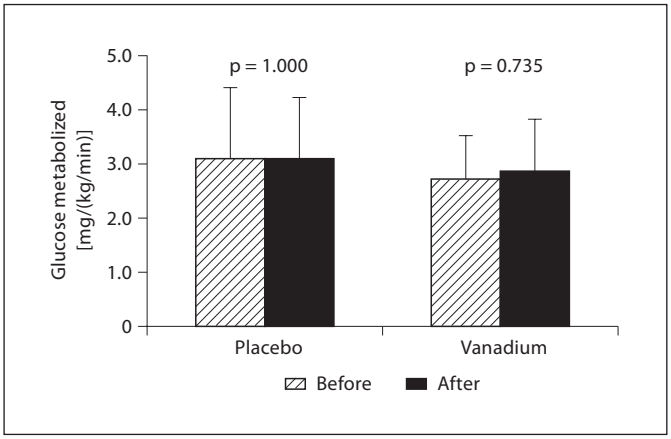

Fig. 1. Insulin sensitivity assessment [M, mg/(kg/min)] between placebo and vanadium groups.

The placebo group showed an increment in BMI (30.7 ± 3.0 vs. 30.9 ± 2.8, p = 0.043), whereas the vanadium group showed no change in BMI (28.8 ± 3.1 vs. 28.3 ± 3.0, p = 0.063). Blood pressure assessments and glucose concentrations showed no significant changes in both groups after intervention (data not shown).

Total cholesterol, HDL and LDL concentrations did not significantly differ in both groups after intervention; however, triglycerides increased after VS intervention (table 1).

INS (fig. 1) evaluated by M estimation obtained with EHC was similar between groups in the basal assessment and showed no change after placebo [3.1 ± 1.3 versus 3.1 ± 1.1 mg/(kg/min), p = 1.000] or VS treatment [2.7 ± 0.8 vs. 2.9 ± 0.9 mg/(kg/min), p = 0.735].

Regarding oral VS tolerability, one of our patients with a previous history of intestinal disorders complained of nausea, abdominal pain and diarrhea; these events were temporary and did not require VS treatment interruption.

Discussion

Vanadium increases INS in T2DM patients [3, 4, 7, 9]. This effect mediated by PTP enzyme blocking [8] has not been observed in obese subjects without diabetes [14], probably due to the absence of glucose concentration abnormalities. The lack of information about VS effects in an intermediate state of glucose abnormalities led us to hypothesize that PTP blocking may improve INS in the IGT pre-diabetic stage. Vanadium is considered an ultra trace element requiring an intake of 20 μg a day [15]. The therapeutic dose used in our study has shown to be effective and safe in previous studies [4, 14].

We did not observe INS improvement although the methodology was similar to previous studies; our patient cohort was larger than those in two previous studies on T2DM [9, 14] using the same VS dose, and the intervention period was equal or longer in our study. The PTP mechanism is probably not affected in IGT patients, and this may explain why INS has not changed in our sample.

In T2DM patients, administration of VS (100 mg/day) has been shown to reduce total cholesterol [7]; at higher doses, VS decreased LDL [14] and HDL concentrations [4]. In contrast, changes in total cholesterol or lipoproteins were not observed in other studies on T2DM patients [9, 16]. Our study did not find changes in total cholesterol, HDL and LDL, but triglycerides were significantly increased, which is in contrast to previous studies in VS-treated T2DM patients [4, 7, 9, 14, 16]; nonetheless, a nonsignificant increase in triglyceride levels has been observed in obese subjects without diabetes [14]. INS and changes in triglyceride levels render the obese group [14] similar to our IGT patients because both populations are nondiabetic subjects with inherent IR. These observations are in accordance with the knowledge that vanadium probably has a special effect on T2DM, which may be different for obese and IGT patients. The previously mentioned data possibly suggest that IR increases with increasing vanadium response. This affirmation must be proven in future studies assessing different IR levels and their response to vanadium.

The limitations of our study are related to the pharmacokinetics profile [15] in the subjects evaluated; we did not measure the concentration of the compound. Poor intestinal absorption of vanadium (<5%) has been reported, and although similar controlled conditions for the intervention in our study cohort were employed, we were not able to assess potential implications of the VS absorption rate on the metabolic effect.

The results of the present study suggest that this inorganic vanadium compound may not be suitable to treat IGT; moreover, it does not resolve the controversial findings regarding the action of vanadium in vitro or in vivo. Further studies on organic vanadium compounds may help to elucidate the effect of vanadium compounds on INS and the metabolic profile.

In conclusion, the 30-day administration of VS (100 mg/day) in patients with IGT did not modify INS and showed an increase in triglyceride levels.

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