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Review

Vanadium compounds for the treatment of human diabetes mellitus: A scientific curiosity? A review of thirty years of research

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ABSTRACT

In the second part of the 1980s, and in the 1990s, a number of investigators demonstrated —mainly in streptozotocin-induced (STZ) diabetic rats-that the vanadate and vanadyl forms of vanadium possessed a number of insulin-like effects in various cells. It was hypothesized that oral vanadium could be an alternative treatment to parenteral insulin in the therapy of diabetes mellitus. However, the long-term and/or chronic administration of vanadium compounds should also mean tissue vanadium accumulation and risks of toxicity. The purpose of this review was to revise the current-state-of-the-art on the use of vanadium in the treatment of human diabetes. It has been conducted more than three decades after the first report on the beneficial insulin-mimetic effects of oral vanadium administration in STZ-diabetic rats. Although the antidiabetic effects of vanadium in STZ-diabetic rodents are well supported, in the few studies on human patients with positive results, that are available in the literature, vanadium compounds were administered during very short periods. We conclude that vanadium administration for the treatment of human diabetes is misplaced.

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1. Introduction

Diabetes mellitus is a serious metabolic disease, which is mainly characterized by hyperglycemia, as well as disorders in the metabolism of carbohydrates, lipids and proteins. The tremendous importance of this disease can be reflected in the about 366 million diabetic patients expected in the world by 2030 (Li and Lian, 2016). There are two major forms of human diabetes. Type I diabetes, in which the pancreatic beta cells are not able to produce the required quantities of insulin -the main hormone that regulates the uptake of glucose-because of the destruction of beta cells by autoimmune responses. Type II diabetes (which means about 90% of the total population suffering diabetes mellitus), also known as non-insulin-dependent diabetes mellitus (NIDDM), in which the pancreatic beta cells may produce insulin, but the secretion is defective, resulting in hyperinsulinemia and insulin resistance (De Faria-Maraschin, 2012; Tuomi et al., 2014; Corcillo-Vionnet and Jornayvaz, 2015). The general treatment of NIDDM is mainly based on diet, exercise control, and drug therapy (Laws et al., 2012). Although an appropriate diet and exercise can help NIDDM patients, it cannot replace drug therapy. A variety of antidiabetic drugs with different

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mechanisms of action has been clinically used (Bolen et al., 2007). However, the oral drug therapy aimed at controlling hyperglycemia in NIDDM often fails, which means that a very important number of these patients require insulin administration to control the disease (Israili, 2011; Barnett et al., 2013). Although insulin results efficient in most cases, unfortunately, its continued administration means also a number of side effects and complications. For these reasons, the development of new drugs for the treatment of diabetes mellitus has been, and still it remains, extremely desirable.

Vanadium, atomic number 23, is a trace element widely distributed in nature, which occurs in polyvalences and whose individual compounds exhibit a number of biological effects (French and Jones, 1993; Nielsen, 1995; Gruzewska et al., 2014). Approximately a century ago, vanadium was used in the treatment of diabetes mellitus for the very first time (Thompson and Orvig, 2006a). In addition to vanadium's anti-diabetic (insulin enhancing) effect, vanadium compounds have also shown to possess pharmacological activity in the treatment of parasitic diseases, malign tumors, as well as bacterial and viral infections (Rehder, 2015). However, the highest scientific interest about the potential use of vanadium in diabetes treatment emerged from 1985, when Heyliger et al. (1985) reported that vanadium, given as sodium orthovanadate in the drinking water of streptozotocin-induced diabetic rats, reduced the blood glucose levels, as well as prevented the diabetes-associated depressed cardiac performance. In subsequent years, that finding attracted the interest of a number of investigators, who conducted a considerable number of studies on the potential value of vanadate in the alleviation of signs associated with diabetes (Meyerovitch et al., 1987; Brichard et al., 1988, 1993; Gil et al., 1988; Bendayan and Gingras, 1989; Blondel et al., 1989, 1990; Brichard, 1995). Moreover, other investigations showed that vanadium in the form of vanadyl (+IV) was also effective in diminishing the expression of diabetes in the rat (Pederson et al., 1989; Ramanadham et al., 1989). Because that therapy did not increase the level of endogenous insulin, it was hypothesized that vanadium presumably could directly act on insulin target tissues (Gil et al., 1988; Bendyan and Gingras, 1989; Blondel et al., 1989). Based on the notable number of positive reports on the potential use of vanadium in the treatment of experimentally (basically STZ-treated rats) induced diabetes, in the early 1990s there was interest in assessing if vanadium therapy might be also useful in the treatment of human diabetes. At that time, Brichard et al. (1991) revised the data concerning the cellular mechanisms by which vanadium salts could stimulate the metabolism of glucose, as well as the potential toxicity derived from the use of vanadium in diabetes treatment. Interestingly, the title of that review raised a key question on the insulin-like properties of vanadium. The question was if this was "a curiosity or a perspective for the treatment of diabetes".

Twenty-five years after of this question was raised, we are convinced that it was rather a scientific "curiosity". In a short review on the vanadium toxicity in diabetes treatment published in 2000 (Domingo, 2000), we already remarked that the tissue accumulation and the potential toxicity of vanadium were key issues, that had not been sufficiently taken into account in most studies conducted between 1985 and the 1990s. The main goal of the present review was to revise the current-state-of-the-art of the potential use of vanadium in the treatment of human diabetes. We have paid a very special attention to the few human studies available in the scientific literature. Although the interest on this topic has dramatically decreased since the relevance acquired in the last two decades of the previous century, surprisingly, the scientific literature still incorporates a notable number of annual publications on the topic vanadium and diabetes. Thus, using vanadium and diabetes as key words, Scopus (https://www.scopus.com/) shows 25 and 35 documents in 2015 and 2014, respectively, and 13 in 2016 (June 17), when the maximum number of documents was found in 2005 (49 documents).

2. Vanadium and human diabetes treatment: studies in the 1990s and early 2000s

This section revises in a chronological order all the available studies in Scopus and PubMed (http://www.ncbi.nlm.nih.gov/pubmed) published on this topic. The first study on the effects of vanadium in NIDDM patients was carried out by Cohen et al. (1995), at the Department of Medicine and Diabetes Research Center, Alberts Einstein College of Medicine, New York, who examined in six NIDDM subjects the metabolic effects of vanadyl sulfate. These patients received placebo for 2 weeks, then 100 mg/day of vanadyl sulfate for 3 weeks, and finally again placebo for 2 weeks. According to the authors, the treatment improved hepatic and peripheral insulin sensitivity, effects that were sustained for up 2 weeks after discontinuation of vanadyl administration. Plasma vanadium concentrations fell since a mean value of 73.3 to 9.5 μg/l. However, 5 patients experienced mild gastrointestinal symptoms (nausea in 3 patients, mild diarrhea in 4 patients, and abdominal cramps in 3 patients) during the first week of vanadyl treatment, but no evidence of gastrointestinal bleeding was noted. In another investigation corresponding at that time, Goldfine et al. (1995) administered oral sodium metavanadate (125 mg/day) during two weeks to 5 insulin-dependent diabetes mellitus (IDDM) and 5 NIDDM patients. A 1.7- to 3.9-fold increase in basal mitogen-activated protein and S6 kinase activities in mononuclear cells was observed in patients with IDDM and NIDDM that mimicked the effect of insulin stimulation in controls. As in the study of Cohen et al. (1995) the main side-effects were gastrointestinal intolerance, including vomiting in one patient, with 4 patients also showing mild diarrhea. In a second study conducted in the Albert Einstein College of Medicine, Halberstam et al. (1996) compared the effects of oral vanadyl sulfate (100 mg/day) in 7 moderately obese NIDDM patients, and 6 non-diabetic subjects, after 2 weeks of placebo, and 3 weeks of vanadyl sulfate treatment. Although vanadium administration did not alter insulin sensitivity in non-diabetic patients, it improved hepatic and skeletal muscle insulin sensitivity in NIDDM patients. The only reported side-effects were some minor gastrointestinal discomfort and stool discoloration. In turn, Boden et al. (1996) conducted a placebo-controlled study, in which 8 NIDDM patients were orally given 50 mg of vanadyl sulfate, twice daily for 4 weeks. Six patients continued in the study and received a placebo for an additional 4 weeks. The improvement in fasting plasma glucose (decreased fasting plasma glucose concentrations by 20%) and hepatic glucose output, which were noted during vanadyl administration, was also maintained during the administration of placebo. However, there were also side effects. Thus, it was reported that some patients suffered diarrhea, flatulence, slight nauseas and abdominal cramps. For the first time, these researchers clearly remarked that the effects of long-term treatment of vanadyl sulfate, as well as administration of high doses of this compound, must be carefully examined before its potential use in diabetes therapy. In another study carried out by Goldfine et al. (2000), the efficacy of oral vanadyl sulfate was investigated in 16 type 2 diabetic patients, before and after 6 weeks of treatment, at 75, 150 and 300 mg/day, which were equivalent to 25, 50 and 100 mg of vanadium per day. It was found that although glucose metabolism during a euglycemic insulin clamp did not increase at 75 mg/day, it improved in 3 of 5 patients, and 4 of 8 patients given 150 and 300 mg/day of vanadyl sulfate, respectively. The authors concluded that vanadyl sulfate was apparently well tolerated at the administered doses. However, they also stated that the long-term safety of administration of this compound had not