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Mini-review

# Vanadium (V) and magnesium (Mg) - *In vivo* interactions: A review☆

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ABSTRACT

Vanadium (V) and magnesium (Mg) arouse interest of many research centres worldwide. Many aspects of their action have already been recognized but some of them have not been fully elucidated yet. Relatively little is known about the mechanisms of absorption, transport, and excretion of V. There is also a lack of sufficient data about the most sensitive biomarkers of V toxicity and the mechanisms of its toxic action, which have not been fully explained yet. There is also a lack of comprehensive research on the consequences, character, and mechanisms of mutual interactions of V (which has strong pro-oxidant properties) with elements with an antioxidant potential such as Mg, the recognition of which, besides the cognitive value, may have great practical importance. It should be highlighted that the question of interactions between elements is always up to date and it is still an important issue in toxicology. A comprehensive research on interactions of V with Mg can be particularly important in the studies of the usage of V (which has a narrow margin of safety) in the treatment of certain diseases in humans, especially diabetes, which is accompanied by changes in the level of Mg in the tissues and weakening of the antioxidant barrier and oxidative stress. Therefore, the aspect concerning the possible interaction of V (as a potent pro-oxidant) with Mg (as an antioxidant) was the subject of our special interest. In addition, the examination of the effects of the interactions between V and Mg is very important especially for extending the knowledge of the mechanism of the influence of V on the organism and a potential role of Mg (which is characterized by a wide therapeutic window) in prevention of V toxicity. This review summarizes the most important results obtained from our experiments in a rodent model referring to the interactions of V with Mg on the background of the *in vivo* experimental data published by other researchers of this issue. Our studies have shown that V and Mg supplied in combination are able to modulate the response in an interactive manner to produce a specific effect that is distinct from that observed during separate administration thereof. The present report also provides the most important information about the effects of the action of V and Mg with other metals.



*Abbreviations:* ALB, albumin; ALP, alkaline phosphatase; AMV, ammonium metavanadate; BMOV, bis(maltolato)oxovanadyl(IV); BP, blood pressure; BW, body weight; CAT, catalase; CH, cerebral hemisphere; Cyt-PTK, cytosolic protein tyrosine kinase; d, day; DMT-1, divalent metal transporter 1; DPGM, diphosphoglyceromutase; dw, drinking water; exg, exogenous; F, feces; FD, femoral diaphysis; FER, ferritin; FRs, free radicals; GGT, γ-glutamyl transpeptidase; GLU, glucose; GLUT 4, glucose transporter type 4; GR, glutathione reductase; GSH, reduced glutathione; GSH-Px, glutathione peroxidase; GSSG, oxidized glutathione; GST, glutathione transferase; g.v., gavage; Hb, hemoglobin; Ht, hematocrit; IA, intestinal absorption; InsR-PTK, insulin-receptor protein tyrosine kinase; i.p., intraperitoneally; K, kidney; KS, kidney supernatants; L-AA, L-ascorbic acid; L, liver; L-E rats, Long-Evans rats; LPO, lipid peroxidation; $LPO_{spont.}$, spontaneous lipid peroxidation; LS, liver supernatants; MCV, mean corpuscular volume; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; MDA, malondialdehyde; MetfDeca, metforminium decavanadate; MO, magnesium oxide; MS, magnesium sulfate; NEUT, neutrophils; NPY, neuropeptide Y; OS, oxidative stress; P, plasma; $PM_{2.5}$, Particulate matter; PCV, packed-cell volume; Phosphate-TP, phosphate transport protein; R, ribosomes; RAS, renin-angiotensin system; RBC, erythrocytes; RDW, red cell distribution width; RET, reticulocytes; ROS, reactive oxygen species; RVW, relative ventricle weight; S, spleen; Sa, mean roughness; S-D rats, Sprague-Dawley rats; Sdq, mean square of the surface slope; Sdr, developed interfacial area ratio; Sku, kurtosis; SMV, sodium metavanadate; SOD, superoxide dismutase; Sq, root mean square roughness; Ssc, mean summit curvature; Ssk, skewness; Sz, ten-point height; TAS, total antioxidant status; Tf, transferrin; TIBC, total iron binding capacity; TMe, transition metal; TS, transferrin saturation; U, urine; UA, uric acid; UIBC, unsaturated iron binding capacity; $V_{Absorb}$, absorbed vanadium; $V_{Absorp}$, absorption of vanadium; $V_F$, fecal vanadium excretion; $V_I$, vanadium intake; $V_{Ret}$, retained vanadium; $V_U$, urinary vanadium excretion; Vit. C, vitamin C; WB, whole blood; wk, week; W rats, Wistar rats; W-K rats, Wistar-Kyoto rats; 1,3-DPG, 1,3-diphosphoglycerate; 3-PGA, 3-phosphoglyceric acid; 2,3-DPG, 2,3-diphosphoglycerate.

☆ Part of the results referring to the interaction of vanadium with magnesium was presented in the form of a poster presentation at the 5th International Symposium on *Metallomics* in Beijing (China).

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**Contents**



## 1. Vanadium and magnesium – biological role

Vanadium (V) and magnesium (Mg) are biologically important elements involved in numerous physiological processes. The most important functions of both these metals are illustrated in Scheme 1, which has been elaborated on the basis on literature data [1–8].

As presented, both V and Mg (a) affect carbohydrate and lipid metabolism, (b) have an effect on bone/teeth mineralization, (d) take part in the transport of glucose (GLU) into skeletal muscles, liver, and adipose tissue, (e) affect glucose transporter type 4 (GLUT 4), and (e) activate insulin-receptor protein tyrosine kinase (InsR-PTK) and non-receptor cytoplasmic protein tyrosine kinase (Cyt-PTK).

Besides the above-mentioned effects, V also (a) reduces tooth decay, (b) modulates intracellular signal transduction, (c) positively affects thyroid metabolism, and (d) regulates the affinity of Hb to oxygen through its influence on the activity of diphosphoglyceromutase (DPGM) in erythrocytes. DPGM catalyzes the conversion of 1,3-diphosphoglycerate (1,3-DPG) into 2,3-diphosphoglycerate (2,3-DPG) (the Rapoport-Luebering glycolytic shunt), which is able to bind to Hb. The binding of 2,3-DPG to Hb leads to a fall in the affinity of this molecule to oxygen. Causing inhibition of the DPGM activity, V leads to a decrease in the level of 2,3-DPG and, thereby, the affinity of Hb to oxygen rises (Scheme 1).

Mg, i.e. the second most abundant element in the cellular system, is an important modulator of intracellular ion concentrations and is essential for normal functioning of anaerobic/aerobic and extracellular/intracellular metabolism. It plays a structural and regulatory role in the organism participating in all reactions involving formation and utilization of adenosine triphosphate (ATP). One of the most important functions of this macro-element is to act as an ion activating a large number of enzymes. Mg also plays a pivotal role in (a) regulating membrane structure and permeability, (b) maintaining membrane integrity, (c) activating the synthesis of membrane phospholipids, and (d) regulating cell growth, reproduction, as well as Ca transport and accumulation. In addition, Mg (a) determines the integrity of mitochondria, chromosomes, DNA, RNA, lysosomes, and ribosomes, (b) affects protein and nucleic acid synthesis, (c) influences hormone response, (d) increases mineral bone density, (e) regulates functions of osteoblasts, osteoclasts, and osteocytes, and (f) affects the physicochemical properties of teeth. The essentiality of Mg to proper function of many systems within the organism (*inter alia*, neuromuscular, cardiovascular, and immune systems) has been reported as well.

## 2. Reasons for which V and Mg were selected for testing in our *in vivo* experimental conditions during separate and combined administration

Having in mind (a) the growing pollution of the environment with V, which has a narrow margin of safety and strong pro-oxidant potential, (b) the ability of this metal to accumulate in certain internal organs/tissues, and (b) reports suggesting the ingestion of V from dietary supplements at a dose above 18 mg/day (particularly by individuals who want to improve their muscle mass) and those that describe the adverse symptoms of supplementation with V in animals (mainly in rats) and in humans, as well as (c) the extremely elevated levels of V in the feces of children aged 1–4 years and in the blood of hemodialysis patients on the one hand, and (d) the attempts to use V against world's threatening diseases such as diabetes, together with (e) the promising results indicating the possibility of V use in the treatment of other illnesses like osteoporosis, certain types of cancer and some parasitic and infectious diseases on the other hand [1,9–39], it is still valid to carry out studies on the toxicity of V and on the mechanisms of its toxic action. This type of research is very important, as it may help to understand and elucidate fully the toxicology of V and the modes of its action. Many researchers constantly focus on investigation of the toxicity of this metal [40–42], which depends on many different factors such as the type of the compound, the kind of diet, the administration/exposure route and duration, the dose, and the sensitivity of the individual organism. The valence of V is not without significance either.

It should be highlighted that pentavalent V, which was examined in our study, is the most toxic form. The risk of poisoning with this form of V is still increasing, since this metal is widely used in industry, among others, in the chemical and refining industry. V is also a component of many dyes (used in a wide variety of applications), liquid and solid fuels, and various metal alloys used in the construction of jet engines, space technology, and nuclear industry. It should also be emphasized that V-containing steel (characterized by greater hardness, strength, elasticity, and abrasion resistance) is used for construction of many machinery and aircraft parts and in manufacture of various types of instruments and orthopedic implants. Noteworthy, relatively high pollution with V (in the +5 oxidative state) is caused by dust and fumes originating from burning of liquid and solid fuels as well as by oil refineries and power plants heated with coal or mazout, which results in an increased risk of exposure of anyone present in the area of their influence. In turn, V-containing dusts (falling with rain) may cause