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Vanadium: A Review of its Potential Role in the Fight Against Diabetes

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ABSTRACT

The potential role of vanadium in human health is described as a building material of bones and teeth. However, another very interesting and promising application for vanadium in human health emerges from recent studies that evaluated the role of vanadium in the management of diabetes. Vanadium is present in a variety of foods that we commonly eat. Skim milk, lobster, vegetable oils, many vegetables, grains and cereals are rich source of vanadium (>1 ppm). Fruits, meats, fish, butter, cheese, and beverages are relatively poor sources of vanadium. The daily dietary intake in humans has been estimated to vary from 10 μg to 2 mg of elemental vanadium, depending on the environmental sources of this mineral in the air, water, and food of the particular region tested. In animals, vanadium has been shown essential (1–10 μg vanadium per gram of diet). There is only circumstantial evidence that vanadium is essential for humans. However, in doses ranging from 0.083 mmol/d to 0.42 mmol/d, vanadium has shown therapeutic potential in clinical studies with patients of both insulin-dependent diabetes mellitus (IDDM) and noninsulin-dependent diabetes mellitus (NIDDM) type. Although vanadium has a significant biological potential, it has a poor therapeutic index, and attempts have been made to reduce the dose of vanadium required for therapeutic effectiveness. Organic forms of vanadium, as opposed to the inorganic sulfate salt of vanadium, are recognized as safer, more absorbable, and able to deliver a therapeutic effect up to 50% greater than the inorganic forms. The goal is to provide vanadium with better gastrointestinal absorption, and in a form that is best able to produce the desired biological effects. As a result, numerous organic complexes of vanadium have been developed including bis(maltolato)oxovanadium (BMOV), bis(cysteinamide N-octyl)oxovanadium known as Naglivan, bis(pyrrolidine-N-carbodithioato)oxovanadium, vanadyl-cysteine methyl ester, and bis-glycinato oxovanadium (BGOV). The health benefits of vanadium and the safety and efficacy of the available vanadium supplements are discussed in this review.

INTRODUCTION

The insulin-like properties of vanadium salts have attracted much attention from the research community in recent years for 2 reasons: first, vanadium presents a promising complementary approach to the management of diabetes in cases of insulin resistance and insulin deficiency (Boden et al., 1996; Cohen et al., 1995; Goldfine et al., 1995; Halberstam et al., 1996),

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The authors are employees of Sabinsa Corporation which is a manufacturer of the organic vanadium complex, and therefore have a commercial interest in vanadium.

and second, vanadium salts have been useful in elucidating the molecular mechanism underlying pathology in diabetes (Sekar et al., 1996).

Despite the benefits of insulin therapy, especially in insulin-dependent diabetes mellitus (IDDM) patients, many of those suffering from diabetes have found that insulin is far from being an ideal drug, primarily because of the frequent incidences of insulin resistance. In addition, oral drug therapy aimed at controlling hyperglycemia in noninsulin-dependent diabetes mellitus (NIDDM) patients often fails, and most patients require insulin treatment late in the course of their disease. This progressive deterioration in glucose metabolism is due, in part, to worsening insulin sensitivity that may be ameliorated by the glucose-lowering effect of exogenous insulin therapy (Yki-Jarvinen, 1992). Therefore, agents that could lower the requirements for insulin or augment insulin sensitivity may be useful in treatment of both forms of diabetes mellitus. Another important reason to search for new antidiabetic treatments has to do with the evolving definition of diabetes, which is now perceived not so much as a "high blood sugar" disease, but a "small vessel" disease.

The history involving the discovery of vanadium as a chemical element is complicated. By some accounts the first to discover and describe this element was Del Rio in 1801, who called it erythronium, but then changed his mind, thinking that he was dealing with a form of chromium (Schroeder et al., 1963). Rediscovered as a new element by Swedish chemist Nils Sefstrom in 1830, vanadium as a sodium vanadate was first considered therapeutically useful in the management of a variety of infectious and debilitating diseases, including diabetes, in the late nineteenth century (Schroeder et al., 1963; Willsky, 1990). This early 1899 observation revealed that the administration of sodium vanadate to diabetic patients resulted in a decrease in urinary glucose levels. The insulin mimetic action of vanadium was first reported in *in vitro* experimental model in 1979 by Tolman and colleagues (Tolman et al., 1979). In 1985, Heyliger and colleagues published a similar observation derived from their *in vivo* experiments (Heyliger et al., 1985). Since those discoveries, vanadium has been considered as an insulin-mimicking compound, which may control glucose metabolism either by an insulin-dependent and/or independent biochemical pathway(s) (Shechter, 1990; Sekar and Shechter, 1996).

VANADIUM: NUTRITIONAL ESSENTIALITY

Vanadium belongs to the biologically important group of transition elements. These elements have the ability to exist in a number of different oxidation states and possess the tendency to form complex ions. This latter property enables these elements to form biologically important complexes called coordination compounds with organic carriers, such as proteins. Vanadium has an extremely complex chemistry; it can readily alter its oxidation state and exist in an anionic or cationic form. The +5 oxidation state (anionic form) is predominant under physiological conditions. Under these conditions, vanadium exists as metavanadate (VO^{3-}) or orthovanadate (H_2VO^{4-}), which resembles phosphate. The +4 oxidation state manifests in the cationic vanadyl form (VO^{2+}), which resembles Mg^{2+}.

Coordination compounds play several important roles in plants and animals. Functionalities identified include:

- Storage and transportation of oxygen, eg, iron heme complex in hemoglobin;
- Role as electron transfer agents, eg, iron heme complex in cytochromes;
- Role as catalysts, eg, cobalt in cobalamine, and
- Role in photosynthesis, eg, magnesium in chlorophyll.

Vanadium is relatively abundant in nature (approximately 0.02%) (Brichard et al., 1995; Schroeder et al., 1963). Theoretically, vanadium meets several criteria for being considered an essential nutrient (Hopkins and Mohr, 1974; Schroeder et al., 1963).

- Low molecular weight (atomic weight 50.94);
- Excellent catalytic activity;
- Ubiquity in the geosphere and possibly in the biosphere;

- Homeostatic regulation by controlled accumulation, and
- Low toxicity on oral intake.

The influence of vanadium on biological systems was first demonstrated in 1977 through its effects on ion transport pathways (Cantley et al., 1977). Vanadium was shown to inhibit Na^+/K^+ transport adenosine triphosphatase (ATPase) *in vitro*. Later researchers determined that vanadium salts can also inhibit other transport ATPases (Nechay et al., 1986). However, the physiological essentiality of vanadium in the regulation of these ion pumps was not established (Brichard and Henquin, 1995).

The essentiality of vanadium has been established for some plants and animals. Green algae, for example, were found to require vanadium as a micronutrient for growth (Arnon and Wessel, 1953). The essentiality of vanadium for plants has been confirmed by recent discoveries of naturally occurring vanadium containing enzymes, haloperoxidases (De Boer et al., 1986), ie, bromoperoxidase and iodoperoxidase in algae and lichens and nitrogenase (Robson et al., 1986) in azotobacter. Nitrogenase reduces dinitrogen to ammonia; bromo-iodoperoxidase facilitates the formation of a carbon-halogen bond.

Some haloperoxidase enzymes also function in higher animals and humans, eg, thyroid peroxidase. Haloperoxidases may have some relevance in further studies of vanadium essentiality because vanadium deprivation in rats affected the response of thyroid peroxidase activity (Uthus and Nielsen, 1989).

For a nutrient to be recognized as being essential for humans and/or animals, its deficiency has to be linked to a well-documented pathology. Symptoms of vanadium deficiency in animals have been described and include impaired reproduction, characterized by higher abortions and perinatal mortality, bone abnormalities, and changes in thyroid metabolism (Alexander, 1984; Anke, 1986; Uthus and Nielsen, 1989). In vanadium deprivation studies on goats, animals receiving 2 ng of vanadium per gram of diet compared to controls fed 10 μg vanadium per gram of diet showed a higher abortion rate and produced less milk during the first 56 days of lactation (Anke, 1986). Approximately 40% of newborn goats from vanadium-deprived mothers died between day 7 and 91 of life, while only 9% of the newborns died in the vanadium supplemented group. Developmental skeletal deformations were seen in the forelegs and forefoot tarsal joints in the vanadium-deprived group. Biochemical signs of vanadium deprivation in goats included elevated serum creatinine and β-lipoproteins, with depressed blood glucose levels.

Vanadium deprivation in rats resulted in impaired reproductive performance, ie, decreased fertility and increased perinatal mortality, which became apparent only in the fourth generation of vanadium-deprived animals (Hopkins and Tilton, 1966). Low vanadium in diets fed to chicks resulted in depressed growth, elevated hematocrits, and plasma cholesterol. Adverse effects on the animal's bone development was also observed (Nielson and Ollerich, 1973).

The effects of vanadium deprivation including growth retardation and skeletal abnormalities could be explained by vanadium's role in thyroid functions. As compared to control rats (receiving 1 μg vanadium per gram of diet), vanadium-deprived rats fed 2 ng vanadium per gram of diet showed increased thyroid weight and thyroid/body weight ratio and a tendency toward slower body growth (Uthus and Nielsen, 1989). Thyroid hormones affect bone metabolism, and hypothyroidism can reduce both bone formation and resorption. Thyroid hormones may also enhance the production of somatomedins, which regulate cartilage growth and maturation.

The potential role of vanadium in thyroid metabolism may possibly be explained by nutrients that interact with vanadium, and that also play an important role in thyroid functions, eg, iodide, iron, and sulfur amino acids. Interestingly, vanadium levels in experimental diets were shown to influence the metabolism of a number of nutrients including chloride (Hill, 1985), iodide (Uthus and Nielsen, 1989), chromium (Hill, 1979a), iron (Nielsen, 1983), copper (Shuler and Nielsen, 1995), ascorbic acid (Hill, 1979b), cysteine (Nielsen, 1984), methionine (Nielsen, 1985), riboflavin (Hill, 1988), and protein (Hill, 1979c). Rats fed less than 100

ng vanadium per gram of diet showed slower growth, higher plasma and bone iron, and higher hematocrits than controls fed 500 ng vanadium per gram of diet (Strasia, 1971).

The above examples prove that conditions related to vanadium deficiency in animals exist, and therefore, vanadium has been established as an essential trace element for animals. At present there is only a circumstantial evidence that suggests that vanadium is an essential trace element for humans, mostly because vanadium has broad pharmacological activity both *in vitro* and *in vivo*, which point to the biological importance of this mineral (Verma et al., 1998).

BIOLOGICAL EFFECTS OF VANADIUM

The basic mechanism underlying biological versatility of vanadium could be related to the effect of vanadium on bioenergetic processes such as phosphorylation/dephosphorylation and the activation/deactivation of various key enzymes. After the initial discovery of the inhibitory effect of vanadium on Na, K-ATPase, it was thought that this action of vanadium may be specific to this enzyme alone (Cantley et al., 1977). Soon it was discovered that several enzymes including Ca-ATPase (O'Neal et al., 1979), Mg-ATPase (O'Neal et al., 1979), and myosin ATPase (Goodno, 1979) were also inhibited by vanadium.

Mechanism of enzyme inhibition by vanadium

The inhibitory mechanisms of vanadate are relatively well understood for enzymes having a phosphoprotein intermediate in their catalytic cycle (Willsky, 1990). Vanadate's close resemblance to phosphate enables it to inhibit many of the enzymes involved in phosphate metabolism and subsequently in the processes of phosphorylation and dephosphorylation (De Master and Mitchell, 1973).

Mechanism of stimulation/inhibition of biological processes by vanadium

The mechanisms by which vanadate stimulates biological processes is less understood than the mechanisms of inhibition by vanadate (Willsky, 1990). Vanadate is known to increase activity of adenylate cyclase and intracellular levels of cyclic adenosine monophosphate (cAMP) (Hackbarth et al., 1980). Treatment with metavanadate increased the cAMP concentration in intact cat heart muscle preparations, concomitant with increases in the force of contractions of heart muscles (Hackbarth et al., 1980). A possible mechanism for vanadium increasing intracellular levels of cAMP has been described where vanadate-glutathione complex inhibited the cAMP disposing enzyme phosphodiesterase (PDE) type IV (Souness et al., 1992). Vanadium may exert a complex regulatory effect on levels and activity of cAMP through the activation of tyrosine kinase and protein kinase C-mediated processes (Ueki et al., 1992).

Theoretically, the regulatory effect of vanadium on cAMP levels and activity may affect a broad range of functions in the body, which are known to result from the "second messenger" role of cAMP in hormonal interactions. The physiological principle of cAMP as second messenger may cause inhibition of platelet aggregation, increased lipolysis in adipocytes, increased force of contraction of heart muscles, potentiation of insulin secretion, increased production of thyroid hormones, increased synthesis of steroids, increased secretion of pituitary hormones, ie, adrenocorticotrophic hormone (ACTH), and decreased intraocular pressure. Vanadium thus appears to be a very active and versatile substance from a pharmacological point of view.

Insulin-like effects of vanadium

There are several insulin-like or insulin-mimetic effects of vanadium confirmed by *in vitro* studies and *in vivo* experiments on animal models. There are also reported effects of vanadium that have not been compatible with the metabolic actions of insulin. In some tissues, vanadate simulated some of the actions of insulin, while failing to mimic others. Both biologically active forms of vanadium, vanadyl, or vanadium in tetravalent state, and vanadate, or vanadium in pentavalent state have been demonstrated to possess insulin-like effects (Heyliger et al., 1985; Ramanadham et al.,

1990a). Vanadate stimulated glucose uptake (Tolman et al., 1979), glucose transport and oxidation (Curran and Castello, 1956; Duckworth et al., 1988; Shechter and Karlish, 1980), decreased lipolysis (Degani et al., 1984) and increased lipid synthesis (Castro et al., 1984). Vanadate also activated glycogen synthase in adipose tissue, liver, and muscles (Tamura et al., 1984; Duckworth et al., 1988); enhanced potassium uptake in cardiac muscle cells (Werden et al., 1982), inhibited Ca/Mg ATPase (Delfert and McDonald, 1985), elevated intracellular pH (Cassel et al., 1984), and suppressed secretion of apoliproprotein B from rat hepatocytes (Jackson et al., 1988). In the livers of streptozotocin (STZ)-diabetic rats, vanadate restored levels of mRNA for glycolytic enzymes, glucokinase, L-type pyruvate kinase, increased levels of glycogen synthase, glycogen phosphorylase, and restored liver glycogen (Gil et al., 1988; Rosetti and Laughlin, 1989; Sekar et al., 1990a, 1990b), while decreasing levels of phosphoenolpyruvate carboxykinase (PEPCK) and glucose transporter in liver (GLUT2) and muscles (GLUT4) (Brichard et al., 1993). Glucokinase and phosphotyrosine carboxykinase gene activation have also been attributed to vanadium (Brichard et al., 1993).

Despite similarities between vanadium and insulin biological actions, it becomes obvious that vanadium may also produce actions different from insulin. Furthermore, there are many inconsistencies in experimental results by different researchers evaluating the insulin-mimetic action of vanadium. For example, it has been found that vanadate may increase PEPCK mRNA levels, which is contrary to the findings by others, and opposite to the known mechanism of insulin, which results in suppression of PEPCK mRNA levels (Ferber et al., 1994). Additionally, vanadate seems to have a different central nervous system (CNS) mechanism than the insulin does (Meyerovitch, 1989). The rise in brain glucose levels is a recognized feature of insulin action and vanadate as well, resulting in suppressed food intake in experimental animals. However, it seems that this food-intake suppressing effect is mediated by 2 independent mechanisms, 1 characteristic for insulin the other for vanadium (Meyerovitch, 1989).

Effect on lipid metabolism

The potential importance of vanadium's biological role can also be seen in its effects on lipid metabolism, which may or may not resemble the action of insulin. Vanadium compounds in isolated rat adipose tissue may activate lipogenesis (Castro et al., 1984), inhibit lipolysis (Degani et al., 1984) and also increase lipoprotein lipase activity (Ueki et al., 1989). Liver biosynthesis of cholesterol, fatty acids, and phospholipids were inhibited in rats by vanadyl sulfate both in *in vitro* and *in vivo* conditions (Snyder and Cornatzer, 1985). In addition, vanadium compounds may produce lipid peroxidation in isolated hepatocytes (Younes and Strubelt, 1991). Vanadate added to the diet as V_2O_5, was able to induce mobilization of predeposited aortic cholesterol in rabbits (Curran, 1954), and to decrease deposition of cholesterol and phospholipids in rabbits (Mountain, 1956) and chickens (Eades and Gallo, 1957) fed high-cholesterol diets. It has been postulated that the inhibition of lipid biosynthesis by vanadium compounds may be due to the vanadium caused decrease in levels of coenzymes Q (Aiyar and Sreenivason, 1961), and inhibition of at least 2 steps in the mevalonic acid pathway to cholesterol synthesis (Azarnoff and Curran, 1957; Menon et al., 1980).

Vanadium effect on protein metabolism

Vanadate may differ from insulin in its effect on metabolism of proteins. Insulin is an anabolic hormone, and when isolated muscle was perfused with different concentrations of insulin, protein degradation was inhibited and correlated well with a lower ratio of glycolysis to glucose uptake, measured as lactate release (Clark, 1985). Insulin increased protein synthesis by 60% and inhibited total and net protein degradation by approximately 24%. On the other hand, vanadate, unlike insulin, did not change the ratio of glycolysis to glucose uptake in the incubated muscle, and had no effect on either muscle protein synthesis or total protein degradation. Yet vanadate can inhibit lysosomal proteolysis in hepatocytes (Seglen and Gordon, 1981) and the adenosine triphosphate (ATP)-dependent proteolysis in reticulocytes (Tanaka et al., 1984). It was also found that

vanadate administered to diabetic rats can upregulate the depleted levels of hepatocyte nuclear factor-1 (HNF1), and albumin mRNA, which in turn increases albumin gene transcription and albumin production (Barrera-Hernandez et al., 1996).

Other important biological effects of vanadium

In addition to its insulin-mimetic properties, another well-known effect of vanadium discovered in the latter 1800s was its digitalis-like action on the cardiovascular system (Ramasarma and Crane, 1981). Dogs that were intravenously injected with metavanadate were found to have increased strength of heart muscle contractions, as measured by changes in their electrocardiogram (Lewis, 1959). The effects of vanadium on heart muscle was also observed *in vitro* in the presence of propranolol, cimetidine and mepyramine indicating a lack of participation of β-adrenergic and histamine receptors in the mechanism of vanadium (Grupp et al., 1979). It has been concluded that vanadium's effect on heart muscle is produced by alteration of transmembrane potential and/or due to the inhibition of cardiac Na/K ATPase (Borchard, 1979). The latter mechanism has been described for cardiac glycosides like digitalis.

The cardiovascular effect of vanadium may in part be linked with the increased diuresis obtained within a few minutes after intravenous injections of orthovanadate in rats (Balfour, 1978). Excretion of sodium in urine increased, which could be explained by possible inhibition of sodium reabsorption. The diuretic and natriuretic effects of vanadium were not accompanied by increased glucose or protein excretion, indicating that the vanadium treatment did not result in damage to the kidney, and in particular to the nephrons. In fact, after vanadium administration, urine flow returned to normal after only a few hours, indicating the reversible effect of vanadium.

In addition, vanadium may exert an antioxidant effect on the isolated heart muscle by quenching free radicals, thus preventing potential injury to the heart (Matsubara et al., 1995). Vanadium compounds may behave as antioxidants and pro-oxidants, depending on experimental conditions and the dose of vanadium, with the lower doses predisposing antioxidant mechanisms (Sekar et al., 1990a,b).

Mechanisms of insulin-mimetic action of vanadium

The classic pathway activating insulin receptor. The role of vanadium in regulating the activities of key enzymes involved in insulin action has been researched extensively. Vanadate may enhance activity of the cell membrane-associated tyrosine kinase (component of the insulin receptor) by inhibitory action on phosphotyrosine phosphatase (Hei et al., 1992; Sekar et al., 1996; Tracey and Gresser, 1986). This classic mechanism of vanadate leads to an increase in phosphotyrosine content of the insulin receptor and its subsequent activation. The 3-day administration of vanadate to BB- and STZ-diabetic rats resulted in the inhibition of a specific fraction of the phosphotyrosine phosphatase, which has been associated with normalization of blood glucose levels (Meyerovitch et al., 1989). The *in vitro* studies indicate that although vanadate and insulin caused similar changes in glucose metabolism, the magnitude of these changes differed significantly (Clark, 1985; Tamura et al., 1984). Insulin generated several-fold higher levels of stimulation of glucose uptake, glycogen synthesis and glycolysis than did the vanadate (Tamura et al., 1984), however, vanadate had a 2-fold greater effect on lactate and glucose oxidation (Clark, 1985; Tamura et al., 1984). These differences can possibly be explained by different patterns of insulin-receptor phosphorylation by these 2 compounds (Tamura et al., 1983). Insulin has been shown to activate phosphorylation of serine, threonine, and tyrosine residues in the 95,000 dalton β-subunit of the insulin receptor, while vanadate facilitated similar phosphorylation of tyrosine and a slight phosphorylation of threonine only.

Relevant to the direct action of vanadium on insulin receptor is also the finding that vanadate augments insulin binding, as assessed in the vanadate-treated placenta tissue from women with gestational diabetes mellitus (Al-Attas et al., 1995). It was also found that vanadium, in form of bis-glicynato oxovanadium

(BGOV), can enhance biological action of insulin, as measured by increased glucose utilization by the rat epididymal cells *in vitro* (Leigh Broadhurst, Nutrient Requirements and Functions Laboratory, USDA, Beltsville, Pennsylvania, personal communication, 1998).

The alternative pathway independent of insulin receptor. Vanadium compounds can also operate independent of the insulin receptor pathway, precipitating insulin-like biological effects (Strout et al., 1989). Unlike in the classic pathway, where vanadate facilitates action of the cell membrane-associated tyrosine kinase or the insulin receptor, in the insulin receptor-independent or alternative mode of action vanadate activates the cytoplasm soluble form of the kinase (Shechter and Shisheva, 1993; Shisheva and Shechter, 1992; Sekar et al., 1996). As proof of this alternative mode of action, it has been demonstrated that vanadium diminished insulin resistance in diabetic animals, increased the number of the insulin receptors and the receptor affinity to insulin, all without changes in the activity of the classic kinase activity (Boden et al., 1996; Meyerovitch et al., 1991; Ramanadham et al., 1990a, 1990b).

Distal to the membrane-associated kinase, cytoplasm soluble protein-tyrosine kinase has a molecular weight of 53 kd (membrane associated kinase, 350–400 kd), its exogenous substrate or $PolyGlu_4Tyr$ (a random copolymer 30 kd) is common to both varieties of kinases, the cofactor is cobalt (for membrane associated kinase-manganese), unlike the membrane-associated kinase the cytoplasm soluble kinase is not inactivated by N-ethylmaleimide, and more sensitive to inhibition by staurosporine (Sekar et al., 1996; Yki-Jarvinen, 1992).

An alternative insulin-like pathway via the activation of cytosolic kinase seems very specific for vanadate. Other compounds tested *in vitro* on intact rat adipocytes, ie, insulin, isoproterenol, dibutyryl cAMP, okadaic acid, hydrogen peroxide and the phorbol ester, did not alter cytosolic kinase as compared to vanadate (Shisheva and Shechter, 1992). Other possible mechanisms of induction of insulin-like biological effects, but independent of the classic insulin-dependent pathway, may be a result of vanadium mediated changes in the intracellular pH or Ca ion concentration (Roden et al., 1993). In addition, postreceptor effects such as enhanced activity of mitogen-activating protein (MAP) kinase have been postulated (Goldfine et al., 1995). The alternative pathway of vanadate may explain the effectiveness of vanadium in adipocytes that have lost approximately 60% of their membrane-associated insulin receptors and are less responsive to insulin (Green, 1986). It has been suggested that the predominance of either the classic or alternative mode of action of vanadate in experimental conditions *in vivo* may depend on the doses of administered vanadium, duration of treatment, clinical status of treated animals and the interspecies differences (Sekar et al., 1996).

The finding that vanadate bypasses the insulin receptor is of particular interest as a potential modality in the management of insulin-independent diabetes, and in cases of insulin resistance (including defects in the insulin receptor itself). Vanadium therapy in insulin-independent diabetes (Brichard et al., 1990) and insulin-dependent diabetes (Ramanadham et al., 1990a, 1990b) in rodents has been studied, using genetically conditioned models of the disease in mice and rats. Vanadium was found effective in those animals whose insulin-responsive tissues have lost their capability to metabolize glucose in response to the hormone (Brichard et al., 1992; Meyerovitch et al., 1991). On the other hand, vanadium therapy in the experimental model of insulin-dependent diabetes was only 30% effective as compared to conventional insulin therapy (Kohn and Shechter, 1989).

Participation in physiological reactions of oxidation-reduction. The insulin-mimetic action of vanadium is further understood by its participation in physiological reactions of oxidation converting vanadyl to vanadate that may generate H_2O_2 (Ramasarma et al., 1990). Hydrogen peroxide has been shown to mimic several of the metabolic actions of insulin, including enhanced glucose transport, glucose oxidation and inhibition of lipolysis (May and De Haen, 1979). Thus hydrogen peroxide is sometimes referred to as the "second messenger" for insulin action (Mukherjee, 1980).

The fact that vanadium can exist in many ox-

idation states enables the element to function as an electron transfer catalyst in a wide variety of reactions. Vanadyl has the potential to catalyze the disproportionation of superoxide. During this process, the ion is oxidized to vanadate and forms hydrogen peroxide (Rush and Bielski, 1985).

$$V^{IV} + HO_2 \rightarrow V^{V} + H_2O_2$$

Oxidation of vanadyl to vanadate in the biological systems containing NADH also results in production of hydrogen peroxide (Ramasarma et al., 1990). Two interdependent reactions are involved in the simultaneous oxidation of NADH and vanadyl (Ravishankar and Ramasarma, 1995). $NADH \rightarrow NAD^{+}$ supplies hydrogen peroxide essential for vanadyl oxidation.

In addition to H_2O_2 producing insulin-like effects *per se*, interaction of vanadium with H_2O_2 showed a synergistic effect in activating the insulin receptors *in vitro* (Fantus et al., 1989). As a result of the reaction between vanadate and H_2O_2, peroxides of vanadium are being formed that have been found to be approximately 100 times more potent than vanadate in mimicking the biological effects of insulin *in vitro* (Shisheva and Shechter, 1993). These effects have been shown to occur via the insulin-dependent pathways (Shisheva and Shechter, 1993). The promise of peroxides of vanadium maybe limited nevertheless, due to their oxidizing nature that could deplete the antioxidant reserves of the body, especially the glutathione system (Li et al., 1995).

Vanadate oxidation may be an important step in understanding the insulin-mimetic action of the compound (Sekar 1990a). Vanadate does not exert an instant activation of the insulin receptor in the *in vitro* cell culture, while peroxovanadium does (Shisheva and Shechter, 1993). On the other hand, according to one report, prolonged incubation of vanadate in the cell culture may result in oxidizing the vanadate to peroxovanadium (Sekar et al., 1996). Oxidation of vanadium may also be facilitated by interaction with the amine oxidases. An *in vitro* experiment with rat adipocytes, which have substantial amine oxidase activity, showed that tyramine was readily oxidized, and this reaction in turn potentiated the effects of vanadium on glucose transport through release of hydrogen peroxide (Marti et al., 1998). Therefore, the inhibition or stimulation of the activity of a broad range of enzymes in the *in vitro* and *in vivo* conditions by vanadyl or vanadate, producing insulin-mimetic effects, may be a result of a gradual biological activation of the vanadium compound via the complex oxidation cascade. Some of the resulting reactions are as listed:

- Vanadate and vanadyl ions were shown to inhibit Ca/Mg ATPase (Delfert and McDonald, 1985). This action may lead to an increase in the intracellular Ca, the occurrence of which has been associated with effects of insulin in various tissues, including increased rates of glucose transport activity (GTA) and glucose metabolism (Shechter, 1991).
- The vanadate mediated inhibition of Na/K ATPase has been associated with the *in vitro* secretion of insulin from incubated rat pancreatic tissue (Fagin et al., 1987).
- The inhibitory effect of vanadate ions on transmembrane transport may also result in increased intracellular pH, which subsequently stimulates glucose metabolism (Shechter, 1991).

SAFETY AND POTENTIAL ROLE OF VANADIUM IN THE TREATMENT OF DIABETES

Vanadium is present in a variety of foods that we commonly eat. Rich dietary sources of vanadium (>1 ppm) include gelatin, skim milk powder, grapenuts, dried lentils, dried Navy beans, lobster, hickory, pea green, radishes, buckwheat, hazel nuts, cabbage, oats, potato, turnip greens, rye seed, squash, lettuce, vegetable oils, especially soybean, olive, corn, peanut, cedar, safflower and cottonseed (Schroeder et al., 1963). Relatively little vanadium is found in fruits, wheat, millet, meats, fish, butter, and cheese (Schroeder et al., 1963). The daily dietary intake in humans has been estimated to vary from 10 μg to 2 mg, depending on environmental levels in the region

studied (Nielsen and Uthus, 1990; Ramasarma and Crane, 1981).

Vanadium belongs to a group of microelements, long recognized for their nutritional and medicinal qualities. As previously mentioned, it was widely used for therapeutic purposes at the turn of the century in France for treatment of anemia, tuberculosis, chronic rheumatism and diabetes (Brichard and Henquin, 1995; Schroeder et al., 1963). It was also recommended to increase appetite, strength and weight in a dose of up to 5 mg/d in the form of sodium metavanadate (Schroeder et al., 1963; Willsky, 1990). In recent years, termed the "nutraceutical revolution," vanadium compounds have become popular among body builders as an addition to multivitamin nutritional supplements. Also, vanadium, like chromium, is being used increasingly as nutritional intervention in management of diabetes (Sekar et al., 1996). On the other hand, despite its popular use as a nutritional supplement, there is only circumstantial evidence on vanadium's essentiality for humans, and relatively little evidence from human studies on its potential therapeutic role.

Safety of vanadium in therapeutic and nutraceutical applications

The regimen for supplementation with a trace element like vanadium, in addition to clinical or nutritional indication, has to be based on the therapeutic index for the compound, its biochemical fate in the organism including absorption rate, retention time, excretion route, and any risks of untoward effects.

The mechanism of toxicity of vanadium is likely due to its pro-oxidant activity (Djordevic and Wampler, 1985). In an *in vivo* experiment, intraperitoneal administration of vanadium to rats at a dose of 1.5 mg/kg for a period of 12 days resulted in increased lipid peroxidation in the brain cells, together with a decrease in nonprotein sulfhydryl groups in the brain (Haider et al., 1998). A concurrent selenium treatment in these animals prevented oxidative effect of vanadium, and depression in the sulfhydryl groups.

These pro-oxidant activities of vanadium can possibly cause the local irritation of mucosal membranes, which may be responsible for a frequently reported transient gastroenteritis in patients treated with vanadium compounds (Cohen et al., 1995). Also the pro-oxidant activities of vanadium fumes may induce inflammatory changes in the eye conjunctiva and mucosal lining of the respiratory tract in humans and animals leading to conjunctivitis, pharyngitis, rhinitis, chronic cough and tightness of the chest (Nechay, 1984).

The acute toxicity study of vanadium in rodents showed that both vanadyl and vanadate are toxic, and that toxicity increases with higher valency of vanadium (Llobet and Domingo, 1984). The orla median lethal dose (LD_{50}) dose of vanadyl sulphate pentahydrate (V+4) for rats is 448 mg/kg and mice is 467.2 mg/kg. However, the same route LD_{50} with sodium metavanadate (V+5) for rats is 98 mg/kg and mice is 74.6 mg/kg. The affected animals had diarrhea, irregular respiration, and neurological symptoms within the first 24 hours. These symptoms disappeared within the next 7 days among the survivors. A short-term, (3-month) toxicity study done in rats receiving sodium metavanadate in drinking water at concentrations of 0, 5, 10, and 50 ppm did not affect physical appearance, behavior, or food and water consumption (Domingo et al., 1985). The element accumulated in the kidneys and spleen resulting in mild histopathological changes in those organs. Plasma concentrations of urea and uric acid were increased in the group receiving the 50 ppm dose. Vanadium administered orally in form of vanadyl sulphate pentahydrate was evaluated for its embryotoxic, fetotoxic, and teratogenic potential in pregnant Swiss albino mice (Paternain et al., 1990). The NOEL (no observable effect level) dose of vanadium was established in this experiment at 37.5 mg/kg/d. In another experiment, the NOEL dose for sodium ortovanadate was established for mice at 15 mg/kg per day (Sanchez et al., 1991). According to one source, the toxic dose of vanadium for sheep via oral administration is in the range of 400–600 mg/kg per day (McNeill et al., 1992).

The therapeutic index for vanadium varies greatly, depending on species, and as previously mentioned, on the form of vanadium that directly affects the absorption rate and meta-

bolic fate of vanadium. For example, the therapeutic oral dose of vanadyl sulfate for diabetic rats is approximately 45 mg/kg, which is 10 times less than the estimated LD_{50} dose (Sekar et al., 1996). On the other hand, the biologically effective dose for humans is estimated to be up to 40 times less than that for a rat (McNeill, 1992). The potentially useful dose range of vanadium for man is estimated at 0.0007 to 2.0 mg/kg per day (McNeill, 1992).

It has been estimated that no more than 1% of vanadium normally ingested with the diet is absorbed (Byrne and Kosta, 1978; Hopkins and Tilton, 1966). Most ingested vanadium is excreted via the feces; estimated excretion is 141–2210 μg per 24 hours. The absorbed vanadium is excreted mainly in the urine; the remainder is excreted in the feces (Byrne and Kosta, 1978). At 96 hours after an intravenous injection of radiolabelled vanadium in rats, 30% to 46% of the dose had been excreted in the urine and 9% to 10% in the feces (Hopkins and Tilton, 1966).

Under conditions where vanadium is not supplemented, very little vanadium is retained in the body. Most tissues contain less than 10 ng vanadium per gram wet weight (Byrne and Kosta, 1978) (Table 1).

Hair from scalp in adults contain from 433 pg/g to 90 ng/g (Byrne and Kosta, 1978). Human serum vanadium levels range from 0.016 to 0.939 ng/mL, with most values below 0.1 5 ng/mL (Cornelis and Versieck, 1981).

Animal studies indicate that tissue vanadium is markedly elevated in animals fed high dietary vanadium, especially in the kidneys, bones, and liver (Bodgen et al., 1982; Domingo et al., 1991; Honsard et al., 1978). In rats, liver vanadium increased from 10 to 55 ng/g wet weight when dietary vanadium was increased from 0.1 to 25 μg/g (Domingo et al., 1985). In sheep, bone vanadium was increased from 220 to 3320 ng/gm dry weight when dietary vanadium was increased from 10 to 220 μg/g (Honsard et al., 1978).

TABLE 1. VANADIUM LEVELS IN HUMAN TISSUES

Tissue	*Concentration of vanadium (ng/g wet weight)*
Fat and Muscle	0.55
Heart	1.1
Kidney	3
Liver	7.5
Lung	2.1
Thyroid	3.1

Hair from scalp in adults contain from 433 pg/g to 90 ng/g (Byrne and Kosta, 1978). Human serum vanadium levels range from 0.016 to 0.939 ng/mL, with most values below 0.1 5 ng/mL (Cornelis and Versieck, 1981).

According to clinical studies this tendency for accumulation of supplemental vanadium in the body does not have obvious toxic effects (Boden et al., 1996; Cohen et al., 1995; Goldfine et al., 1995; Halberstam et al., 1996). In fact, accumulated vanadium in diabetic human subjects and the experimental animals acts like a "time-released" vanadium compound that maintains the therapeutic effects up to several weeks after termination of vanadium supplementation (Cam et al., 1997; Cohen et al., 1995; Cross et al., 1995).

Clinical studies of vanadium in lowering cholesterol and in management of diabetes

To date, human studies used vanadium in the form of vanado-tartrate, vanadyl sulfate, and sodium metavanadate for oral administration (Boden et al., 1996; Cohen et al., 1995; Curran, 1959; Dimond et al., 1963; Goldfine et al., 1995; Halberstam et al., 1996; Somerville and Davies, 1962). In the late 1950s and in 1960s vanadium attracted interest due to its anticholesteremic potential. In 1 human study, 5 healthy, normocholesteremic male medical students received orally 100–125 mg of diammonium oxytartaratovanadate in 3 divided doses per day with a multivitamin for a period of 6 weeks with a 3-week follow-up period (Curran, 1959).

The results showed that the total cholesterol and the free cholesterol levels of the serum decreased significantly, and the subjects who remained on a standard diet throughout the study lost 1–4 pounds of weight. Cholesterol/phospholipid ratio showed a significant decline, while serum triglycerides rose significantly during the period of vanadium administration. However, the altered levels of blood lipids returned to pretreatment values during the recovery period. Based on urinary vanadium levels analyzed after termination of vanadium

administration the investigators suggested that a relationship exists between retained vanadium and the lowering of serum cholesterol. In addition, it was estimated that a concentration of approximately 1 μg vanadium per pound of body weight is necessary for a maximal cholesterol lowering effect. No side effects were reported, with the exception of some subjects noticing transient green discoloration of the tongue. Complete blood work remained unchanged, as well as the 24-hour urinary 17-ketosteroids and 17, 21-dihydroxy-20-ketosteroid excretions were unchanged in the course of 6 weeks of vanadium administration.

This initial study on hypocholesterolemic action of vanadium was in agreement with another contemporary observation involving 32 middle-aged men, industrial workers, who were exposed to higher than normal levels of environmental vanadium and had significantly lower levels of serum cholesterol than controls from the same area (Lewis, 1959). Those exposed to vanadium also experienced a slightly green discoloration of the tongue and elevated urinary excretion of vanadium as compared to the control group.

The early 1960s human study evaluated the effect of diamonium vanado-tartarate on cholesterol when administered for 6 months to 12 patients with ischemic heart disease (Somerville and Davies, 1962). Nine patients had persistent hypercholesterolemia and in 7 of these the condition was familial. The vanadium compound was administered 3 times daily in a total daily dose ranging from 75–125 mg. There was no significant effect on serum cholesterol, no changes in the lipoprotein pattern, blood urea, hemoglobin, and no patient developed albuminuria during administration of vanadium. Five patients had persistent upper abdominal pain, anorexia, nausea, green discoloration of the tongue, and loss of weight. Symptoms improved in three patients after the dose was reduced, and in the other 2 cases the treatment was discontinued after 4 months.

In another 1960s study concentrating on the potential of vanadium as a cholesterol lowering compound, 5 middle-aged female and 1 male, borderline to hypercholesterolemic ambulatory patients received 50–125 mg of ammonium vanadyl tartarate in 3 divided daily doses for a minimum of 6 weeks (Dimond et al., 1963). A slight decrease in total serum cholesterol was observed in 2 subjects, with this lower level of cholesterol being maintained 1 week after therapy was discontinued. There was no apparent trend in serum levels of phospholipids, triglycerides, and cholesterol/phospholipid ratio after the administration of vanadium. The urinary excretion of vanadium evaluated in this study showed wide variations in the excreted microelement, which suggested poor absorption of the compound. All patients did experience purple-green discoloration of the tongue, gastrointestinal difficulties, black and loosened stools and cramps. The gastrointestinal symptoms were lessen with a cholinergic-blocking drug. In addition, three participants noted increased dysmenorrhea, and two of the participants reported greater fatigue than usual while on vanadium. Blood work did not show altered values during the vanadium regimen, and the urinary 17-ketosteroids and 17-hydroxycorticosteroids were unchanged as a result of the treatment.

As previously mentioned the therapeutic role of vanadium in management of diabetes was evaluated in relatively few human studies. A blinded study evaluated effect of therapy with vanadyl sulfate administered to 5 patients with NIDDM in poor metabolic control, who were not using insulin, and who were treated with an oral hypoglycemic agent, and 1 subject treated with diet alone (Cohen et al., 1995). The following study design was implemented: 2 weeks placebo, followed by 3 weeks of 100 mg dialy of vanadyl sulfate, followed by 2 weeks of placebo administration. Besides clinical and routine laboratory tests patients' status was evaluated by examining activities of skeletal muscle glycogen synthase, phosphorylase and whole-body glucose metabolism during euglycemic hyperinsulinemic clamps. The biological effects of vanadium as a result of the microelement accumulation during the 3 week treatment was evaluated in the follow-up, second placebo period.

Glycemic control was significantly improved as a result of the treatment with plasma glucose lowered from average 210 mg/dL at the baseline to 181 mg/dL after treatment, and glycosylated hemoglobin was significantly low-

ered from an average baseline value of 9.6%, to a post treatment value of 8.8%. The Michaelis-Menten rate constant (Km) value of skeletal muscle glycogen synthase, which is inversely correlated with the rates of glycogen synthesis, was lowered significantly by 26%–29% as a result of vanadyl sulfate treatment. The glucose infusion rate during the hyperinsulinemic clamp was increased by approximately 88% during the vanadium treatment as compared to the pretreatment placebo period. Carbohydrate oxidation estimated during the clamp increased significantly from an average 1.43 mg/kg/min in the pretreatment period to 1.96 mg/kg per minute during the vanadyl sulfate treatment phase. A significant decrease in free fatty acids levels was noted during the hyperinsulinemic clamp at the time of vanadium administration, average 0.23 mM, vs the pretreatment average 0.36 mM. Plasma lactate levels were significantly lowered after vanadyl sulfate treatment, average 1.10 mM, versus average 1.30 mM in the pretreatment period.

The described biochemical improvement in diabetic patients was sustained for up to 2 weeks after discontinuation of the vanadyl sulfate treatment. While plasma vanadium concentrations were undetectable prior to the treatment, vanadyl sulfate administration resulted in the plasma concentrations of vanadium of average 73.3 μg/L. The plasma vanadium remained detectable 2 weeks after discontinuation of treatment at an average value of 9.5 μg/L. Compliance with the treatment regimen was excellent, this despite that in the first week of the 3-week treatment, patients experienced mild diarrhea and gastrointestinal cramps. Vital signs were unchanged in all study periods. With the exception of hematological indices showing decline in hemoglobin concentration in all subjects after vanadium treatment, an average 1 gm/dL, other laboratory parameters, ie, liver function tests, renal function tests and blood lipid profile were without change.

Another clinical study compared response to vanadyl sulfate treatment of NIDDM diabetic patients with overweight but nondiabetic subjects (Halberstam et al., 1996). The experimental regimen provided for 2 weeks of placebo administration, followed by 3 weeks of vanadyl sulfate supplementation at 100 mg daily. This study confirmed previously described benefits for NIDDM diabetics taking 100 mg of vanadyl sulfate daily for 3 weeks, with no effects of vanadium administration on nondiabetic individuals. None of the parameters of glycemic homeostasis were altered in nondiabetics treated with vanadyl sulfate as compared to the placebo phase of the study. This was in contrast to NIDDM diabetic subjects whose glycemic control improved statistically significant in the course of treatment with vanadium as compared to the pretreatment placebo phase. The authors of this study suggest that vanadyl sulfate may improve an important aspect of NIDDM based on the defect in signaling insulin action in the body. Both study groups reported a mild gastrointestinal side effects at the beginning of vanadium treatment including nausea, diarrhea, and cramps, and some of the subjects reported a dark discoloration of stool. Stool examinations were negative for occult blood. Blood pressure, liver function tests, and renal function tests were similar for both groups, as compared before and after vanadium administration. As in the previous study hematological indices indicated a small decline in hematocrit, approximately 1%, and only in NIDDM subjects.

The clinical application of vanadium was also evaluated in patients with NIDDM as well as IDDM form of diabetes (Goldfine et al., 1995). Unlike in the previous studies, sodium metavanadate rather then vanadyl sulfate was used in a daily dose of 125 mg for 2 weeks. This regimen improved glucose metabolism during the hyperinsulinemic clamp by 29% with low dose of insulin, and by 39% with high dose of insulin in NIDDM patients. This change in glucose metabolism was mostly due to nonoxidative glucose disposal. On the other hand, glucose metabolism was not improved by vanadium treatment in IDDM patients. Nevertheless, vanadium treatment was beneficial to those patients by lowering the insulin requirements statistically significantly from the average 39.1 U/d before treatment to 33.8 U/d after the treatment. As in the previous study, the major inconvenience in treatment with sodium metavanadate was transient gastrointestinal intolerance, including nausea and diarrhea, and in singular case episode of vomiting and in-

creased salivation. There was a single episode of hypoglycemia requiring assistance in treatment in subject with IDDM. No biochemical evidence of vanadium treatment toxicity was detected based on assessment of blood electrolytes, blood urea nitrogen, creatinine, liver function studies, thyroid functions, urinanalysis, and complete blood cell count.

The safety and efficacy of vanadium in form of vanadyl sulfate was also evaluated in a single-blind, placebo-controlled study involving 4 men and 4 women with NIDDM diabetes (Boden et al., 1996). These patients received 50 mg of vanadyl sulfate twice daily for 4 weeks, and the laboratory and clinical parameters including the euglycemic-hyperinsulinemic clamps results were evaluated during the course of the study. The regimen with vanadyl sulfate produced previously described, transient, gastrointestinal symptoms. The treatment resulted in a 20% decrease in fasting glucose and significantly decreased hepatic glucose output during hyperinsulinemia. This objective improvement was maintained 4 weeks after termination of therapy.

Providing vanadium in a safer form with enhanced bioavailability

In view of the biological potential of vanadium being diminished by its toxicity, attempts have been made to reduce the dose of vanadium required for therapeutic effectiveness, thereby reducing the risk of toxicity (McNeill et al., 1994). The goal was to provide vanadium with better gastrointestinal absorption, and in a form that is best able to produce the desired biological effects.

The following data have been considered in designing a more bioavailable and safer form of vanadium. It has been found that vanadium in the form of vanadate permeates cells and is converted intracellularly by glutathione to vanadyl (Rubinson, 1981). Both vanadyl and vanadate are biologically active. Theoretically, providing vanadyl, as opposed to vanadate, would save the mammalian cell the trouble of converting vanadate to intracellular vanadyl. Vanadyl is, however, poorly absorbed from the gastrointestinal tract and also poorly bioavailable to the body cells (Rubinson, 1981). Furthermore, it is well recognized that vanadium, a member of the family of transition metals, has the natural capability to form chemical complexes, primarily with organic compounds, which theoretically would be better absorbed than inorganic compounds of vanadium (McNeill, 1992).

Based on the above considerations, various organic chelators of vanadium were used to bind vanadyl and surround it, so that it could be carried via the hydrophobic surface of the biological membrane. Increased potency of vanadium using organic ligands lead to the synthesis of many organic compounds of vanadium (Cam et al., 1993; McNeill, 1992; McNeill et al., 1992, Nandhini et al., 1993; Sakurai et al., 1990). One of the better studied forms of vanadium has been organic compound of vanadium bis(maltolato) oxovanadium or BMOV, a complex of vanadyl with the common food additive maltol in a 1:2 ratio (McNeill, 1992; McNeill et al., 1992).

BMOV was investigated in spontaneously hypertensive rats (Bhanot et al., 1994) and rats treated with STZ, which subsequently developed diabetes (McNeill et al., 1992, 1994; Yuen et al., 1993a, 1993b). BMOV was proven effective in lowering plasma glucose in STZ-diabetic rats, when administered in drinking water over a 25-week period. The effective therapeutic dose of BMOV was calculated to be 0.45 mmol/kg (Yuen et al., 1993a), compared with 0.55 to 0.64 mmol/kg for vanadyl sulfate (Ramanadham et al., 1990b). The maintenance dose of BMOV of 0.18 mmol/kg per day was approximately 50% of that required for vanadyl sulfate, ie, 0.18 mmol/kg per day versus 0.4 mmol/kg per day (Yuen et al., 1993a). The effective dose of BMOV also compares favorably with the corresponding doses obtained in other experiments with inorganic forms of vanadium, ie, effective dose for sodium metavanadate ($NaVO_3$) (0.26–1.02 mmol/kg per day) and sodium orthovanadate (Na_3VO_4) (0.20–0.65 mmol/kg per day) (Domingo et al., 1991).

Studies with the inorganic forms of vanadium indicated that administration to the diabetic animals reduced food and fluid intake, or polyphagia and polydipsia the 2 characteristic symptoms of diabetes (Brichard et al., 1988). A similar effect was observed with organic forms of vanadium therapy. However, there was no

incidence of the diarrhea that had previously been attributed to the gastrointestinal toxicity of vanadium therapy (Yuen et al., 1993a).

BMOV as well as vanadyl sulfate affected insulin secretion in spontaneously hypertensive and hyperinsulinemic rats (Bhanot et al., 1994; Bhanot and McNeill, 1994). This resulted in lowering insulin levels, as well as systolic blood pressure, and enhanced insulin sensitivity in the treated animals. The treatment also resulted in weight loss.

The role of BMOV in the prevention of secondary complications of diabetes such as cardiovascular disease and eye cataracts formation was also studied (Yuen et al., 1993a, 1993b). The 25-week administration of BMOV normalized heart function in STZ-diabetic rats, as measured by the left atrial filling pressure (Yuen et al., 1993b). This normalization might be due to improved glucose homeostasis, since treated rats had lower plasma glucose and percent of glycosylated hemoglobin, an integrated measure of blood glucose control.

During this study, 60% of untreated STZ- diabetic animals developed cataracts as compared to 8% in the BMOV-treated group (Yuen et al., 1993b). It has also been found that the administration of BMOV to STZ-diabetic rats resulted in the alleviation of a broad range of pathologies that characterize diabetic rats, ie, elevated levels of urea, creatinine, alanine aminotransferase, and a high incidence of histological abnormalities in kidneys (Dai S, Yuen VG, Orvig C, McNeill JH Prevention of Diabetes-Induced Pathology in STZ-Diabetic Rats by Bis(Maltolato)Oxovanadium (IV); Division of Pharmacology and Toxicology, University of British Columbia, Vancouver, Canada; unpublished data, 1993).

Another form of organic vanadium complex, BGOV, was studied in a rat model of streptozotocin induced diabetes (Nandhini et al., 1993). BGOV was administered for 15 days to diabetic rats and to healthy controls in drinking water, in a dose of 30 mg per 100 mL. As a result of the 15-day regimen, diabetic rats decreased fluid intake from an average pretreatment 584 mL/kg per day to 270 mL/kg per day, blood glucose levels decreased from pretreatment 254 to 118 mg/dL; cholesterol decreased from a pretreatment 204 to 107 mg/dL and triglycerides decreased from a pretreatment 164 to 97 mg/dL. In addition, glycogen and hexokinase levels increased significantly, while lactate dehydrogenase and fructose-1, 6-bisphosphatase decreased significantly in the course of treatment with BGOV. In the BGOV treated diabetic animals, the level of tissue glycogen was doubled as compared to the untreated diabetic control. Interestingly, the healthy controls receiving BGOV also gained in tissue glycogen levels as compared to the untreated healthy controls.

Other organic compounds of vanadium besides BMOV and BGOV that have been evaluated in the experimental model of diabetes include bis(cysteinamide N-octyl)oxovanadium (IV) also known as Naglivan (Cam et al., 1993), bis(pyrrolidine-N-carbodithioato) oxovandium (IV) (Nakai and Sakurai, 1994), and vanadyl-cysteine methyl ester (Sakurai et al., 1990).

In general, treatment of STZ-diabetic rats with organic forms of vanadium is considered more effective and advantageous, particularly from a safety point of view compared to the inorganic vanadium treated animals (Nandhini et al., 1993; Yuen et al., 1993a, 1993b).

CONCLUSION

Vanadium in the form of organic complexes appears in many ways to be superior to the inorganic vanadate or vanadyl; particularly since equal therapeutic effects are accomplished with a significantly lower dose of the organic vanadium compounds. The safety of vanadium therapy should be of primary consideration, because, as was previously mentioned, it already is extensively used in nutritional therapy and as a nutritional supplement in humans. Recent findings indicate that vanadium may be of importance in human nutrition, and therefore overall guidelines as to its use should be developed.

The daily dietary requirement, if any, for vanadium is very small, probably 10 μg/d is sufficient (Tamura et al., 1984). Most diets supply between 15 to 30 μg of vanadium. The question remains, how much vanadium do humans need daily, and how much of the daily dietary value of vanadium is absorbed and utilized in

the body? It should also be kept in mind that the environmental ubiquity of vanadium is not equal with the useful dietary vanadium, available to our body.

Nutritional therapy with nutraceuticals like vanadium should be well defined for a very important reason: we can hardly afford to waste the vast therapeutic potential of vanadium. The history of medicine is littered with misused therapies. For example, if antibiotic therapy was applied more discriminately in the past, it would have left us with much more effective antimicrobial treatments today.

Vanadium promises to provide an improved therapy and possibly prevention of diabetes—a disease that is the seventh leading cause of death in the United States, resulting in more than 36,000 deaths each year. Obesity and diabetes are 2 major contributors to the number one cause of death in the industrial countries: cardiovascular disease.

Clearly our long-term fascination with vanadium in medicine approaches a critical point, especially when you consider what was learned about its biological potential since the early 1960s. Back then, Dr. Henry Schroeder and his research colleagues implied that there were few examples of other trace metals, with so many biological activities claimed, that had not y et been proven essential (Schroeder et al., 1963). Thus the opportunity of employing vanadium in disease prevention and treatment should not be missed.

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