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Basic information about vanadium 'ultra-trace element or occasionally beneficial element' and its various functions in animals: A review article

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Abstract
Minerals are broadly classified as macro (major) or micro (trace) elements. The third category of minerals that includes vanadium, chromium, boron, lithium, molybdenum, nickel, rubidium and silicon are the *'ultra trace elements or occasionally beneficial elements'*. Among several metals, vanadium has emerged as an extremely potent agent with insulin-like properties. These insulin-like properties has been demonstrated in isolated cells, tissues different animal models of type I and type II diabetes as well as a limited number of human subjects. Effect of vanadium on bio energetic processes such as phosphorylation/dephosphorylation and activation and deactivation of various key enzymes. Bone tissue is an important reservoir of growth factors (GFs) and proteins related to bone development. The GFs act locally to modulate bone formation by stimulating osteoblast proliferation and differentiation. According to recent study on Hariana heifers - the activity of SOD was significantly higher ($p< 0.001$), whereas mean values of LPO decreased linearly ($p < 0.05$), plasma total antioxidant status (TAS) also increased linearly ($p < 0.05$), plasma IgG levels increased linearly ($p < 0.05$) and plasma IGF-1 concentrations showed significant effect ($p < 0.05$) in V supplemented groups and plasma T4 concentration increased linearly ($p < 0.05$). According to these results, V supplementation may play a role in modulating the immunity and antioxidant status of growing Hariana heifers.

Keywords: vanadium**,** ultra trace element, antioxidant, growth, immunity

Introduction
Minerals are inorganic substances, present in all body tissues and fluids and their presence is necessary for the maintenance of certain physicochemical processes, which are essential to life. They are the chemical constituents used by the body in many ways. They have important roles to play in many activities in the body [62, 33]. Minerals are broadly classified as macro (major) or micro (trace) elements. The macro-minerals include calcium, phosphorus, sodium and chloride, while the micro-elements include iron, copper, cobalt, potassium, magnesium, iodine, zinc, manganese, molybdenum, fluoride, chromium, selenium and sulfur [33]. The macro-minerals are required in amounts greater than 100 ppm and the micro-minerals are required in amounts less than 100 ppm [69]. The third category of minerals that includes vanadium, chromium, boron, lithium, molybdenum, nickel, rubidium and silicon are the *'ultra trace elements or occasionally beneficial elements'*. These minerals are classified so, because based on some studies it was evident that deprived animals were unhealthy and showed physiological responses to the supplementation thus indicating that homeostatic mechanism is there. All these criteria are suggestive of essentiality of these minerals. Ultra trace minerals are those elements with estimated dietary requirements usually less than 1 µg/g and often less than 50 ng/g of diet for laboratory animals [71].

Vanadium (V) is a group V transition element, which exists in several valence states (-3, −1, 0, and +1 to +5). Under physiological conditions, it is found in either an anionic form (vanadate) or a cationic form (vanadyl) (Brichard and Henquin, 1995) [17], the cationic (pentavalent) form is six to ten times more toxic for animals and humans [30, 82]. The essentiality of vanadium for algae species is unquestionable. It is essential for several species of green, yellow green and brown algae. Vanadium at very low concentrations (0.1-1 mg V/l stimulates growth, but at higher concentrations stimulates both growth and to a greater extent also chlorophyll formation [6]. In the brown alga *Ascophyllum nodosum*, the activity of the enzyme bromoperoxidase is essentially influenced by vanadium [7, 95, 28].

The role of vanadium in higher biological systems has long been elusive and controversial, and since 1980 the nutritional essentiality of vandium for animals was not clear and no specific deficiency symptoms were reported. The most substantive evidence for vanadium essentiality in higher animals was reported in goats by Anke *et al*. (1983) [2] and Nielsen *et al.* (1983) [72] in rats. To establish the nutritional essentiality and specific deficiency sign for V in ruminant animals the long term experiments inducing V deficiency in growing, pregnant, and lactating goats over 15 generations using the semi synthetic feed ration by the University Jena team were conducted. It was reported that there was decrease feed intake and milk yield, along with reduced survival rate and reproduction efficiency accompanied by high abortion rate [46]. Based on these experimentations, the authors (Haenlein and Anke, 2011) [46] claimed that V was a nutritionally essential element at 2.0 mg per kg DM feed for goats and that no deficiency sign could occur under normal farm conditions. Drebickas (1966) [31] reported that 0.1 mg V per kg of diet could optimize growth in calves. Farm species vary widely in their susceptibility to V toxicity, being poultry the most and sheep the least susceptible species [89].

A role for vanadium in bone formation has been demonstrated (Anke, 2004; Barrio and Etcheverry, 2006) [6, 12] but mechanisms of action have remained largely unexplored. *In vitro* studies, using calvaria primary cultures Canalis, (1985) [21] and bone-derived cell lines (Tiago *et al*., 2008) [91] have evidenced the regulation of bone-related enzymes activity (e.g. alkaline phosphatase (ALP) and protein tyrosine phosphatases, the stimulation of bone-related protein synthesis (e.g. type I collagen), the alteration of bone-related cell proliferation and extracellular matrix (ECM) mineralization, and the activation of insulin and insulin-like growth factor 1 (IGF-1) signalling mechanisms (Tiago *et al*., 2008) [91] by vanadium compounds. Another studies in which skeletal deformities in forelegs, swollen tarsal joints and pain (symptoms similar to P, Mn or vitamin D deficiency) were observed in goats kept on V deficient diet (Anke *et al*., 2005; Haenlein and Anke, 2011) [5, 46] points towards possible role of V in bone metabolism with respect to calcium and phosphate utilization.

Vanadium as an ultra trace element has been reported to have insulin mimetic/enhancing effects on type 2 diabetic rats and humans [61, 47, 27]. These studies have correlated the direct effect of vanadium treatment with a reduction in blood glucose levels while both Ramanandham *et al.* (1991) and Pederson *et al*. (1989) [84,81] have further determined that a vanadyl induced normoglycemic state can persist for at least 3 months after withdrawal from treatment. Srivastava and Mehedi (2005) [88] reported that vanadium compounds inhibit gluconeogenesis and the activities of some gluconeogenic enzymes (phosphoenol pyruvate, carboxykinase and glucose-6- phosphatase in the liver and kidney) as well as lipolysis in fat cells, which illustrates the potential mechanisms to its antidiabetic insulin-like effects. A recent study conducted by Heidari *et al*. (2016) [53] on vanadium supplementation in periparturient cattle suggested role of vanadium in modulation of the action of insulin and metabolic biomarkers related to energy metabolism during the critical periparturient period.

The potential role of vanadium as antioxidant is studied by Francik *et al*. (2011) [39] who reported increase activity of GSH and possible role of V in mitigating the effect of reactive oxygen species. Vanadyl sulfate protected the rats from lipid peroxidation and hypertriglyceridemic effects and also decreased the level of TBARS (Harati and Ani, 2006). Kim *et al*. (2012) [50, 58] suggested that vanadium-containing Jeju water produces antioxidant effect by enhancing the activities of antioxidant enzymes *in vitro*. Kim *et al*. (2012) [58] studied the effect of consumption of jeju ground water containing vanadium components on oxidative stress in obese mice and reported decreased generation of oxidative stress induced-lipid peroxidation in the liver. It also enhanced the enzymatic antioxidant defense system by increasing the protein expression and activity of superoxide dismutase, catalase, and glutathione peroxidase in liver tissues of mice by induction of Nrf2 gene. Vanadium is also a potent inhibitor of Na^+/K^+-ATPase enzymes (Cantley *et al*., 1977) [22] involved in many physiological systems [85].

Review of literature

Mineral nutrition particularly plays crucial role in normal metabolism, reproduction, production, and in certain physiological processes of animal system. Large animal populations in the world, particularly in the tropics suffer from mineral imbalances or deficiencies (McDowell *et al*., 1993) [64] and deficiency of essential minerals may result in failure of the homeostasis mechanism, affecting the productive and reproductive performances of animals [41]. The physiological functions of both major and minor minerals and their role in optimum production performance of livestock are well established. Recently, the other category Possibly/Occasionally essential minerals are also being focused. In the similar context, Vanadium is the one of such potential trace elements with promising role in bone growth, antioxidant and immune modulation. Basic information about vanadium and its various functions are reviewed under following sub heads:

3.1 Physicochemical properties of Vanadium
3.2 Distribution of Vanadium in soil, water and feeds
3.3 Dietary requirements and maximum tolerable levels for Vanadium
3.4 Metabolism of vanadium
3.4.1. Absorption and Excretion
3.4.2. Storage and transportation
3.4.3. Interaction of vanadium with other nutrients
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3.5.1. Insulino-mimetic and anti-diabetic effects of vanadium compounds
3.5.2. Activation and inhibition of enzymes
3.5.3. Modulation of thyroid hormones
3.5.4. Bone growth
3.5.5. Action as Antioxidant
3.6 Effect of Vanadium supplementation on animal performance
3.6.1 Effect of Vanadium supplementation on Growth
3.6.2 Effect of Vanadium supplementation on Blood Biochemicals
3.6.3 Insulin like effect of Vanadium
3.6.4. Effect of vanadium on immunity and antioxidants defense

3.1 Physicochemical properties of Vanadium

Vanadium (V) is a group (5) transition element that, exists in several valance states (-3, -1, 0, and +1 to +5). It is found in either an anionic form (vanadate) or a cationic form (vanadyl) [17]. Its pentavalent form is toxic for animals and humans [30]. Cationic form is 6-10 times more toxic than anionic form [82].

It is widely distributed in earth' crust at an average concentration of 100 ppm (approximately 100 mg/kg), similar to that of zinc and nickel [18]. It is the 22nd most abundant element in earth crust [11]. Vanadium is primarily used in the production of rust-resistant, spring, and high-speed tool steels; vanadium pentoxide is used in ceramics. Vanadium is released to the environment by continental dust, marine aerosols, volcanic emissions, and the combustion of coal and petroleum crude oils. It is naturally released into water and soil as a result of weathering of rock and soil erosion. It is found in about 65 different minerals; carnotite, roscoelite, vanadinite, and patronite are important sources of this metal along with bravoite and davidite [11]. Vanadium pentoxide is an industrially important vanadium compound [60].

Some other properties of vanadium:

a. Description: Yellow to rust-brown orthorhombic crystals [78, 60]; yellow-orange powder or dark-gray flakes [13, 70]
b. Boiling-point: 1800 °C, decomposes [60]
c. Melting-point: 670 °C [60]; 690 °C [78]
d. Density: 3.36 [78, 60]
e. Solubility: Slightly soluble in water (0.1−0.8 g/100 cm^3); soluble in concentrated acids and alkalis; insoluble in ethanol [96, 78]
f. Stability: Reacts with chlorine or hydrochloric acid to form vanadium oxytrichloride; absorbs moisture from the air [34]

3.2 Distribution of Vanadium in soil, water and feeds

Vanadium is found in a wide range of food, usually in the form of VO^{2+} (vanadyl, V^{4+}) or HVO_4^{2-} (vanadate, V^{5+}) [73]. Natural foodstuffs contain vanadium mostly in the form of vanadyl (VO^{2+}) [75]. The dietary sources of vanadium are an eclectic group of foods. Particularly rich in vanadium are mushrooms, parsley, dill and black pepper [54]. Dairy milk has an average value of 1.1 µg/kg vanadium whereas powdered milk shows a value as a high a 25 µg/kg [97]. Wheat grain contains 3.6µg/kg while vanadium levels in milled flour can climb as high as 40µg/kg [97]. Each of these differences is directly attributed to the refining processes concerned. Vanadium is abundant in soils, particularly in the finer clay fraction (65-200 mg /kg DM), but only small fraction (<10%) is extractable (Berrow *et al*., 1978) [15] and level in pasture and crops are usually low (<.1 mg/kg DM). Since grazing animals cannot avoid consuming soil when they graze and contamination of herbage varies from approximately 25 % in summer to 10% or more of dry matter intake in winter, soil ingestion is a major source of vanadium intake for pastured animals.

Generally, seeds, cereal products, bread, cake and pastries, tubers and fruits have, on average, a low vanadium content (5 to 40 µg/kg DM). Mushrooms, red radish, leafy vegetables (lettuce, spinach) as well as herbs contain much higher levels of vanadium (100-2,400 µg V/kg DM) [3, 4]. Animal foodstuffs deliver on average lower vanadium amounts in the food chains. Especially cow's milk (12 µg/kg DM), and cheese (3-14 µg/kg DM) provide lower vanadium amounts to humans [6, 5]. Breast milk (34 µg V/ kg DM) contains more vanadium than cow's milk. Formulas for babies deliver 2 to 17 µg V/kg DM [56].

3.3 Dietary requirements and maximum tolerable levels for Vanadium

Vanadium shows essentiality at low concentrations and toxicity at high doses. Limited information about nutritional significance is available. But the studies conducted are suggestive of the potential for this newer trace element on performance of animals, as the studies conducted on V deficient diets have shown that performance was adversely affected thus pointing towards its essentiality. Vanadium at 0.1mg/kg of diet optimized growth in rats (Schwartz and Milne, 1971) [87] and calves [31]. How it acts is unknown. Preliminary studies indicate ruminal function (DM digestibility) in lambs was disrupted with just 7mg V /kg of diet. Average basal and normative requirements for V are not documented for any species in any feeding standard as sufficient data required to do so are not available, though the maximum tolerance level for cattle and sheep (NRC, 2001; Van Paemel *et al*., 2010) [76, 94] has been documented as 50 ppm.

3.4 Metabolism of Vanadium

3.4.1. Absorption and Excretion

Most of the ingested vanadium remains unabsorbed by the gastrointestinal tract and is excreted in the faeces. Hansard *et al*., (1975) [48] reported that less than 1% of vanadium is absorbed in sheep.

Very low level of the Vanadium in urine in comparison to the estimated dietary intake and fecal levels of the Vanadium indicate that ≤ 1% of Vanadium ingested is absorbed [19]. This level is lower than the estimated absorption of 5 to 12% of vanadium given a salt (Faulkner- Hudson, 1964) [35], but the availability or absorption of the vanadium is markedly affected by food and dietary composition. For example, vanadium toxicity in chicks was alleviated by corn, dehydrated grass, cottonseed meal, ascorbic acid, EDTA, chromate and protein [55]. Parker and Sharma, (1978) [79] found that the tissue residue of the vanadium was always higher in animals fed 50µg of vanadium as sodium orthovanadate/g of diet than in those given the same dose as vanadyl sulphate.

3.4.2. Storage and transportation

Vanadium is stored mostly in the liver, kidney and bone. Bone is the long-term storage of the vanadium [49]. Blood play a pivotal role in exchanging dietary or intravenous vanadium with body tissue, the gastrointestinal tract and the kidney [80]. About 95% of the vanadium transported in the blood is bound of transferrin as the vanadyl ion (VO^{+2}) [80]. Vanadium is known to bind transferrin intracellularly (Harris *et al*., 1984) [52] and may therefore compete with iron for gastrointestinal absorption and cellular receptor sites. There is some evidence that vanadium can complex with lactoferrin and be transported to suckling infants during breastfeeding [32]. Hansard *et al*. (1975) [48] conducted studies in sixteen ram lambs fed on 0, 50 or 200 ppm supplemental vanadium daily as ammonium metavanadate (NH_4VO_3) for 90 days and found that vertebral vanadium content was elevated after exposure to 200 ppm added vanadium in the diet for 15 days in sheep, but non significant increase occurred thereafter. Increasing dietary vanadium increased bone ash vanadium concentration from 0.4 to 1.7 and 3.8 ppm. In a balance study, urinary concentrations of the element also were related directly to dietary intake.

The vanadium concentration in the serum may be a good indicator of exposure to higher dietary V concentration. Cornelis, (1981) [24] reported serum concentration to be in range of 0.016-0.939 ng/ml most value being below 0.15 ng/ml, it was suggested that concentration above 1.0 ng/ml

possibly indicates excessive exposure. In case of cow's milk, the concentration of V is very low usually less than 10 -12 µg V/kg DM and around 3-14 µg V/kg DM in cheese [6, 5].

3.4.3. Interaction of vanadium with other nutrients

The interaction of vanadium with iron was studied by Sabbioni and Rade, (1980) [86] the relationship between Fe and V metabolism was studied by incubating the bovine milk with radio isotopes of Fe and V i.e $^{48}VO^{2+}$ and $^{59}Fe^{3+}$ ions. It was found that ^{48}V was incorporated into lactoferrin, the milk protein which contains iron. This suggests that lactoferrin may play a role in the bioavailability of vanadium during lactation, as vanadium is an essential element for the growth of some animal species. The binding properties of vanadium with lactoferrin further support the possible biochemical role of Fe-containing non hemoproteins in the metabolism of vanadium.

Vanadium-organoligand complexes have been used to examine the structure and activity of many proteins, taking opportunity of spectroscopic techniques [23]. There are naturally appearance ligands that bind vanadium, such as the iron binding siderophores. Siderophores are involved in iron homeostasis, and their binding of vanadium occurs to be a secondary function [16]. Vanadate does inhibit the transport of iron-siderophore complexes (Cornish and Page, 2000) [25] showing that there is an interaction of vanadium with iron transport systems. Many natural metabolites, including glutathione, cysteine, ascorbic acid, nucleotides, and carbohydrates, form complexes with vanadium that have been characterized by the different authors in [10, 38].

3.5 Biological effects of vanadium

3.5.1. Insulino-mimetic and anti-diabetic effects of vanadium compounds

Vanadium mimics insulin like action. The first step in insulin action consists in binding of the hormone to specific cell surface receptors. This receptor displays two functional domains: an extracellular alpha-subunit containing the majority or the totality of the hormone binding site and an intracellular beta-subunit possessing insulin-stimulated tyrosine kinase activity. Concerning the mechanism of transmembrane signalling, the interaction of insulin with the receptor alpha-subunit triggers a conformational change, which is propagated to the beta-subunit which in turn results in activation of tyrosine kinase. This is followed by phosphorylation of insulin receptor substrate (IRS-l) which increases a cascade of phosphorylation and dephosphorylation and produces biological response. In muscle and fat cells, activation of IRS-l causes translocation of GLUT4 glucose transporter from intracellular pool to the plasma membrane, thereby allowing rapid uptake of glucose by these tissues. Vanadium (V) may increase the phosphorylation of the β subunit. It may also activate insulin-independent cytosolic tyrosine kinases [9].

Among several metals, vanadium has emerged as an extremely potent agent with insulin-like properties. These insulin-like properties has been demonstrated in isolated cells, tissues different animal models of type I and type II diabetes as well as a limited number of human subjects. Vanadium treatment has been found to improve abnormalities of carbohydrate and lipid metabolism and of gene expression in rodent models of diabetes. In isolated cells, it enhances glucose transport, glycogen and lipid synthesis, and inhibits gluconeogenesis and lipolysis. The molecular mechanism responsible for the insulin-like effects of vanadium compounds have been shown to involve the activation of several key components insulin-signaling pathway that include the mitogen-activated-protein kinases (MAPKs) extracellular signal-regulated kinase ½ (ERK1/2) and p38MAPK, phosphatidylinositol 3-kinase (P13-K)/protein kinase B (PKB). It is interesting that the vanadium effect on these signaling systems is independent of insulin receptor protein tyrosine kinase activity, but it is associated with enhanced tyrosine phosphorylation of insulin receptor substrate-1. These actions seem to be secondary to vanadium-induced inhibition of protein tyrosine phosphatases. Because MAPK and P13-K/PKB pathway are implicated in mediating the mitogenic and metabolic effects of insulin, respectively, it is plausible that mimicry of these pathway by vanadium serve as a mechanism for its insulin-like responses [66].

3.5.2. Activation and inhibition of enzymes

Vanadium might have a role in the regulation of Na+-K+-ATPase, phosphoryl transfer enzymes, adenyl cyclase and protein kinase [73]. Effect of vanadium on bio energetic processes such as phosphorylation/dephosphorylation and activation and deactivation of various key enzymes. Initially the inhibitory effect of vanadium on Na^+, K^+-ATPase enzyme was discovered [22]. Later it was found that several other enzymes including Ca-ATPase [77], Mg –ATPase [77], myosin ATPase [42] was also inhibited by vanadium. Vandate'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 [29]. Vanadate also increases the activity of adenyl cyclase and intracellular level of cyclic adenosine monophosphate (cAMP) [45]. 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 the pituitary hormone i.e. adrenocorticotrophic hormone (ACTH).

3.5.3. Modulation of thyroid hormones

Thyroxin (T4) and tri-iodothyronine (T3), hormones of the thyroid gland, are major regulators of metabolic rate, growth and development of animals [57]. Thyroid hormones have a positive correlation to body weight gain or production (Page *et al*., 1993). A higher metabolic rate is associated with increased secretion of the hormone thyroxine (T4), which is deiodinated to triiodothyronine (T3) in the periphery, mainly in the liver and kidneys. Vanadium compounds were reported to modulate thyroid hormone levels in blood. Vanadium deficiency affects thyroid metabolism, decreased thyroid weight and thyroid weight-body weight ratio [8]. Plasma tri iodothyronine was higher in vanadium-supplemented rats [8]. Triiodothyronine is the main metabolic stimulating hormone [65, 40].

On supplementation of Vanadium in Hariana heifers, there is dose dependent linear increase in plasma IGF-1 and T4 concentration [44].

Uthus and Nielsen (1989) [93] reported that vanadium might affect thyroid and iodine metabolism. In these study rats were supplemented with vanadium at a dose of 0 or 1 µg/g and iodine at 0 or 0.33 or 25 µg/g. Vanadium deficiency increased thyroid weight and thyroid weight/body weight ratio and decreased the concentration of vanadium in liver. V and

iodine interacted in such a manner that, as dietary iodine was increased, plasma glucose increased in vanadium deficient rats but decreased in vanadium supplemented rats. Similar results were also found when dietary iodine was increased thyroid peroxidase activity was decreased. In vanadium supplemented rat, decreased thyroid peroxidase activity was more marked.

3.5.4. Bone growth

Vanadium compounds behave as growth factor mimics in bone-related cells; cellular model studies in culture are of great importance in understanding the intracellular signaling pathways involved in the biological and pharmacological effects of vanadium derivatives. IGFs belong to a group of peptides that play an important role in the growth and development of bone as well as other tissues. IGFs are the most abundant GFs synthesized and accumulated in bone [90]. Vanadium compounds stimulate DNA and collagen synthesis and also promote osteoblastic differentiation in bone-related fibroblasts cells [21].

Bone tissue is an important reservoir of growth factors (GFs) and proteins related to bone development. The GFs act locally to modulate bone formation by stimulating osteoblast proliferation and differentiation. Among the GFs synthesized by osteoblasts and stored in the ECM are insulin like GFs IGF-I, IGF-II, transforming GFs (TGFb1 and TGFb2), acid FGF, basic FGF, platelet-derived GF (PDGF), and bone morphogenetic proteins (BMPs) [14, 67].

3.5.5. Action as Antioxidant

Vanadium complexes have been demonstrated to exert various insulin-mimetic, anti-diabetic effects, improved lipid and protein metabolism and antioxidant properties without apparent signs of liver and kidney toxicity. Vanadyl ion may act as a scavenger of oxyradicals and prevent liver (Koyuturk *et al*., 2005) [59] and heart dysfunctions [63].

Harati and Ani, (2006) [50] conducted studies in four different fed rats fructose fed rats (FF), vanadyl sulfate treated fructose fed treated rats (FV), control rats (C), and vanadyl sulfate treated control rats (CV) and reported that low doses of vanadyl sulfate (0.2mg/ml for 7 days) protected rats from lipid peroxidation and hypertriglyceridemic effects of fructose-enriched diet by significant normalizing plasma insulin and triglyceride levels and also by significantly decreasing TBARS (thiobarbituric acid reactive substance) than untreated and fructose-fed rats.

The LPO concentration in plasma was significantly lower in 5.0 mg of V/kg DM-supplemented group in comparison to control in Hariana heifers. In V-supplemented groups lower values of LPO in suggest lower lipid peroxidation. Antioxidant enzyme SOD in plasma increased linearly ($p < 0.05$) on V supplementation in Hariana heifers [44].

3.6 Effect of Vanadium supplementation on animal performance

3.6.1 Effect of Vanadium supplementation on Growth

Female goats given a diet containing <10 µg V/kg DM had a higher abortion rate, produced less milk and reared fewer offspring than control goats given 2mg V/kg DM [1]. In the rat vanadium deprivation tends to decrease growth while increasing thyroid weight [74]. Vanadium-nutrition of rats showed increased thyroid weight and thyroid-to-body weight ratios, and depressed growth. This study also showed that stress factors, which change the thyroid status or iodine metabolism, enhance the response to vanadium deprivation [73]. Supplementation of vanadium can improve glucose production and availability and that can suppress lipolysis to improve insulin sensitivity and enhance response to insulin may have significant production and health responses during the periparturient period [43].

3.6.2 Effect of Vanadium supplementation on Blood Biochemicals

Pharmacological uses of vanadium include lowering of cholesterol, triglycerides and glucose levels, diuretic and natriuretic effects, anti-carcinogenic effect, contraction of blood vessels, enhancement of oxygen-affinity of hemoglobin and myoglobin. Man beings, V acts as a cofactor that enhances or inhibits enzymes and plays some roles in metabolism, including cholesterol and triglyceride metabolism, hepatic glucose and glycogen metabolism, and blood cell integrity [51]. Fawcett *et al*. (1997) [36] studied the effects of oral vanadyl sulfate (0.5 mg/kg per day) for a period of 12 weeks in 31 weight training-athletes on their hematological parameters, including red and white cells, platelet counts, haemoglobin level, haematocrit, plasma viscosity, blood viscosity, lipids and indices of liver and kidney function. It was reported that there was no effect of $VOSO_4$ treatment on hematological indices and biochemistry of the organs studied. The concentrations of creatinine and triglycerides and the activity of gamma glutamyl transferase were significantly higher in vanadium-deficient compared to control animals [5].

Heidari *et al*. (2016) [53] conducted studies in 32 multiparous Holstein cows from 4 week prior to calving to 4 week postpartum fed 4 levels of vanadium in the form of vanadyle sulfate (0.04, 0.08, and 0.12 mg of V /kg of $BW^{0.75}$) and reported that plasma glucose concentration increased whereas plasma NEFA concentration decreased in a quadratic fashion in a response to increasing supplemental vanadium level. The insulin: glucose ratio decreased quadraticaly in early lactation but not in late gestation.

3.6.3. Insulin like effect of Vanadium

Vanadium does not replace insulin from its action but it activates cellular insulin receptor either by phosphotyrosine phosphorylation or via inhibition of phosphotyrosine phosphatase enzymes leading to an increase in glucose transporter proteins (Glut-1) in the plasma membrane [68].

Srivastava and Mehedi (2005) [88] reported that vanadium compounds inhibit gluconeogenesis by decreasing the activities of the gluconeogenic enzymes (phosphoenol pyruvate carboxykinase and glucose-6-phosphatase) in the liver and kidney as well as lipolysis in fat cells which contributes as potential mechanisms to their antidiabetic insulin-like effects. They reported that at the cellular level, vanadium activates several key elements of the insulin signal transduction pathway, such as the tyrosine phosphorylation of insulin receptor substrate-1, and extracellular signal-regulated kinase 1 and 2, phosphatidylinositol 3-kinase and protein kinase B activation. These pathways are involved in the metabolic actions of insulin as protein tyrosine phosphatases (PTPases) are considered to be negative regulators of the insulin-signalling pathway, it was suggested that vanadium can enhance insulin signalling and action by inhibition of PTPase activity and increase tyrosine phosphorylation of substrate proteins.

After administration of vanadium compounds in insulin

dependent diabetic rats and human the blood glucose concentration was normalized. Vanadium salt reduced hyperglycemia and improved insulin action by increasing the glucose transporters activity via insulin receptor substrates 1 and 2 (IRS1/2), phophatidylinositol 3-kinase (PI 3-kinase) [20].

3.6.4. Effect of vanadium on immunity and antioxidants defense

Preet *et al.* (2005) [83] conducted studies in diabetic rats treated with insulin (2 IU/day), sodium orthovanadate (SOV, 0.6 mg/ml), Trigonella foenum graecum seed powder (TSP, 5%) and TSP (5%) in combination with lower dose of vanadium SOV (0.2 mg/ml), for a period of 3 weeks found that vanadium at lower doses given in combination with Trigonella was the most effective in controlling the altered glucose metabolism and antioxidant status in diabetic rats by significantly decreasing the activity of the enzymes, hexokinase, aldose reductase, sorbitol dehydrogenase, TBARS (thiobarbituric acid reactive substance) level and by increasing significantly the activity of glucose-6- phosphate dehydrogenase, glutathione peroxidase, glutathione reductase. High level of dietary vanadium can induce the depression of superoxide dismutase (SOD), glutathione peroxidase (GSH-Px) activities and an increase in malondialdehyde (MDA) content in the muscles of rats [37].

In the Hariana heifers, plasma IgG increased significantly ($p < 0.05$) in V supplemented groups, this study shows it may triggers the immune response [44].

Dietary vanadium can affect the antioxidant function. Dietary vanadium in the range of 30~60 mg/kg is found to cause inhibition in the activities of antioxidant enzymes, enhancement of lipid peroxidation and finally induction of oxidative damage in the spleen. Thus, oxidative stress induced by vanadium plays an important role in the pathogenesis and toxicity of vanadium. At the same time, dietary vanadium in the range of 5 ~ 10 mg/kg is relatively safe for the spleens of young chickens [26].

Upreti *et al*. (2014) [92] conducted studies in diabetic rats fed insulin, vanadate (0.6mg/ml), A. indica with combined dose of vanadate (0.2mg/ml) and A. indica and reported that the combined dose of vanadate and A. indica was most effective in normalizing altered of antioxidant enzyme level (Superoxide dismutase, catalase, glutathione peroxidase and glutathione reductase).

Conclusion

According to different studies we can say, Vanadium play important role in bone growth antioxidant and immune modulation. Vanadium play role in bio energetic processes such as phosphorylation/dephosphorylation and activation/deactivation of various key enzymes. By decreasing the activities of the gluconeogenic enzymes (phosphoenol pyruvate carboxykinase and glucose-6-phosphatase) in the liver and kidney, Vanadium compounds inhibit gluconeogenesis as well as lipolysis in fat cells which contributes as potential mechanisms to their antidiabetic insulin-like effects. At the cellular level, vanadium activates several key elements of the insulin signal transduction pathway. It may play role in modulating the immunity and antioxidant status of growing Hariana heifers because in present study on Hariana heifers the plasma LPO concentration was significantly lower in 5.0 mg of V/kg DM-supplemented group in comparison to control. Lower values of LPO in V-supplemented groups suggest lower lipid peroxidation. The plasma activity of antioxidant enzyme SOD increased linearly ($p < 0.05$) on V supplementation. Vanadium deficiency may affects thyroid metabolism because Vanadium compounds were reported to modulate thyroid hormone levels in blood. From the collected literature it might be concluded that most of the researches elucidating the beneficial effect of V are conducted in humans and monogastric animals but very few studies have been conducted in ruminant system.

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