Diabetes, Metabolic Syndrome and Obesity

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REVIEW

# Exploring the Biological Effects of Anti-Diabetic Vanadium Compounds in the Liver, Heart and Brain

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**Abstract:** The prevalence of diabetes mellitus and diabetes-related complications is rapidly increasing worldwide, placing a substantial financial burden on healthcare systems. Approximately 537 million adults are currently diagnosed with type 1 or type 2 diabetes globally. However, interestingly, the increasing morbidity rate is primarily influenced by the effects of long-term hyperglycemia on vital organs such as the brain, the liver and the heart rather than the ability of the body to use glucose effectively. This can be attributed to the summation of the detrimental effects of excessive glucose on major vascular systems and the harmful side effects attributed to the current treatment associated with managing the disease. These drugs have been implicated in the onset and progression of cardiovascular disease, hepatocyte injury and cognitive dysfunction, thereby warranting extensive research into alternative treatment strategies. Literature has shown significant progress in utilizing metal-based compounds, specifically those containing transition metals such as zinc, magnesium and vanadium, in managing hyperglycaemia. Amongst these metals, research carried out on vanadium reflected the most promising anti-diabetic efficacy in cell culture and animal studies. This was attributed to the ability to improve glucose management in the bloodstream by enhancing its uptake and metabolism in the kidney, brain, skeletal muscle, heart and liver. Despite this, organic vanadium was considered toxic due to its accumulative characteristics. To alleviate vanadium's toxic nature while subsequently manipulating its therapeutic properties, vanadium complexes were synthesized using either vanadate or vanadyl as a base compound. This review attempts to evaluate organic vanadium salts' therapeutic and toxic effects, highlight vanadium complexes' research and provide insight into the novel dioxidovanadium complex synthesized in our laboratory to alleviate hyperglycaemia-associated macrovascular complications in the brain, heart and liver.

**Keywords:** diabetes mellitus, hyperglycaemia, dioxidovanadium, toxicity

## Introduction

The prevalence of diabetes mellitus (DM) poses a significant challenge to global health.[1] Despite the generation of new pharmaceuticals and the advancement of clinical treatment, diabetes is becoming increasingly prevalent.[1] Approximately 537 million people are diagnosed with type 1 or type 2 diabetes globally, with drastic predicted increases in middle and low-income countries.[2,3] DM accounts for approximately 8.5% of worldwide mortality rates, and 20% of mortalities result from multiple micro and macrovascular organ systems dysfunctions.[3,4] However, this review will focus on the ramifications of diabetes and current treatment strategies on the organ systems, viz., the brain, liver and heart, which possess large blood vessels, and the effects of vanadium compounds on them.[2,5] Hyperglycaemia induced injury to vasculature in organs such as the liver, heart and brain has been shown to result in the formation of atherosclerotic plaques in these blood vessels, resulting in cardiovascular disease, stroke, or organ failure.[6–8] Current DM treatment involves using four main classes of drugs; however, insulin remains the mainstay treatment.[9,10]

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However, these pharmacological drugs have several detrimental side effects. These drugs are known to be involved in the progression of heart disease, hepatocyte injury and brain dysfunction, contributing to the high morbidity and mortality rates.[11,12] Research into alternative treatment strategies is warranted. Literature has shown significant progress in utilizing metal-based compounds, specifically those containing transition metals such as zinc, magnesium and vanadium, in managing hyperglycaemia.[13] Vanadium's insulin-mimicking ability to increase insulin sensitivity, enhanced cellular glucose transport, and glycogen synthesis have made it the most extensively researched metal for anti-diabetic efficacy.[14] In this review, we assess the pharmacological and toxicological effects of some vanadium compounds that have been shown to manage hyperglycaemia and evaluate their success in attenuating diabetes-associated complications, as diabetes is a polygenic disease. Although the anti-hyperglycaemic effects of vanadium were elucidated decades ago, no vanadium salt or vanadium compounds have entered markets for diabetes management. Drug properties must be scrutinized, especially with ADME (absorption, distribution, metabolism and excretion) in silico tools at our disposal.

Studies have shown that exposure to vanadium in excess or accumulative amounts results in the generation of reactive oxygen species and adverse cellular reactions which may lead to necrosis and organ dysfunction.[15,16] These observations limit the efficacy of vanadium as an anti-diabetic treatment. Organic ligands have been utilized and envisaged to reduce toxic accumulation in tissues whilst retaining their anti-diabetic activity to attenuate the toxicity associated with vanadium.[17] These advancements have yielded positive outcomes in ameliorating associated toxicity and have been demonstrated by several organic vanadium compounds.[17]

In our laboratory, we have also made efforts to attenuate the toxicological effect of vanadium through organic ligands.[18–20] Organic heterocyclic ligands were used to synthesize the novel vanadium complex, cis-[VO2 (obz)py] (Hobz=2 hydroxyphenyl-1H-benzimidazole and py=pyridine), which provides thermodynamic stability and effective transport of vanadium to target tissues. Vanadium complex, dioxido(V)vanadium complex, cis-[VO2(obz)py] (Hobz=2 hydroxyphenyl-1H-benzimidazole and py=pyridine), was synthesized using organic heterocyclic ligands which provide thermodynamic stability and efficient vanadium transport to target tissues.[18,19] This provided greater potency, stability and safety to the complex.[19] This organic complex was shown to have anti-diabetic properties on the liver, heart and skeletal muscle without toxicity.[18,21,22] Further studies are being conducted on the effects of the complex on the brain.[19]

Accordingly, this review seeks to appraise the readers on the biological observation of vanadium compounds in diabetes mellitus, focusing much on macrovascular complications. Further, we will highlight potential hazards of vanadium accumulation in the heart, liver and brain.

## Metal-Based Complexes

Since the 1980's numerous researchers have endeavoured to identify alternative anti-diabetic compounds.[23] Medicinal plants and metal-based compounds have shown promising attributes as future anti-diabetic treatments. Currently, a plethora of studies have illuminated the effectiveness of metal-based compounds, such as zinc, ruthenium (II), copper and vanadium, in managing hyperglycaemia.[13] Copper complexes have been found to reduce reactive oxygen species (ROS) production in diabetic individuals by improving antioxidant enzyme function.[24]

Zinc complexes have been shown to reduce glucose levels in the blood and decrease glycated haemoglobin.[25,26] Ruthenium (II) complexes have been found to have anti-diabetic properties through mechanisms that exhibit anti-inflammatory and vasodilatory properties.[27–29] Vanadium complexes have been found to mirror insulin's mechanism of action by phosphorylating signalling proteins in the insulin signalling pathway.[26,30] However, these metallic compounds are toxic or non-compatible with biological systems due to their unwanted deposition in cells.[31] To remedy these complications, research into the therapeutic properties of these compounds was further investigated, hence growing the scientific pool of knowledge regarding the various properties and mechanisms of these metal-based compounds.[31] Groups 3–12 on the periodic table represent transition metals well known for displaying different oxidation states due to possessing partially filled d-shells.[32] This allows these metals to interact with negatively charged molecules, synthesizing metal-based complexes.[13] Metal-based complexes refer to chemical compounds composed of a central metal atom coordinated with a group of ligands.[32,33] These ligands act as electron donors and form bonds with the central metal atom, thus stabilizing the complex.[33] This coordination results in a potent structure that exhibits heightened chemical reactivity and catalytic activity.[33]

## The Nature of Vanadium in Biological Systems and Its Insulin-Mimetic Characteristics

Vanadium is a transition metal with oxidation states of −1 to 5+ that has been reported to possess anti-inflammatory, antioxidant and anti-diabetic qualities.[14,15,34] The anti-diabetic effects of vanadium are achieved through its insulin-mimetic properties.[15,35] Two common vanadium salts are vanadyl (VO2+), with a +4 oxidation state and vanadate (VO2+), with an oxidation state of +5.[36] The therapeutic effects of vanadium salts warrant its use in medicine as an antiseptic, anti-anaemia and anti-diabetic drug.[37] Vanadium-derived compounds have been reported to have a systemic circulating half-life of between 2 to 12 days.[38] To study the in-vitro insulin-mimetic activity of vanadium, less toxic vanadyl compounds are preferred over vanadate.[30] Vanadyl compounds have been found to significantly improve glucose absorption in adipocytes and inhibit lipolysis, restoring normo-glycaemia in animal models.[15,30] Short-term clinical studies of 2 to 4 weeks reported that administering vanadyl at doses of 33 to 50 mg daily improved glycemia with decreased fasting glucose and improved insulin sensitivity during euglycemic-hyperinsulinemic clamp studies.[39,40]

The mechanism by which vanadium acquires its insulin-mimetic effects has been shown to involve the activation of critical components of the insulin signalling pathway, such as the tyrosine phosphorylation of insulin receptor substrate-1 (IRS), extracellular signal-regulated kinase (1/2), phosphatidylinositol 3-kinase (PI3-K) and protein kinase B activation (Figure 1). [30,37] In doing so, vanadium increases glucose uptake through insulin-dependent glucose transporter GLUT4.[30,41] These pathways have been shown to be responsible for the metabolic actions of insulin.[30]

Despite its therapeutic effects, a major drawback of vanadium compounds is their ability to toxically accumulate in organs such as the heart, brain and liver.[43] Consequently, promoting oxidative stress, metabolic dysregulation and cellular degeneration (Table 1). [43] Alternate vanadium complexes were synthesized by attaching organic ligands to improve clearance and reduce the toxicity of vanadium.

## Dioxidovanadium

In our laboratory, the anti-diabetic properties displayed by novel vanadium complexes have been proven to be a viable source for improving glucose uptake and insulin resistance caused by diabetes.[18,21] The complex showed improved independent glucose uptake in skeletal muscle and liver cell line cultures.[55] The anti-diabetic effects of vanadium were envisaged through its insulin-mimetic properties as increased GLUT-4 expression was observed in skeletal muscle.[30,55]

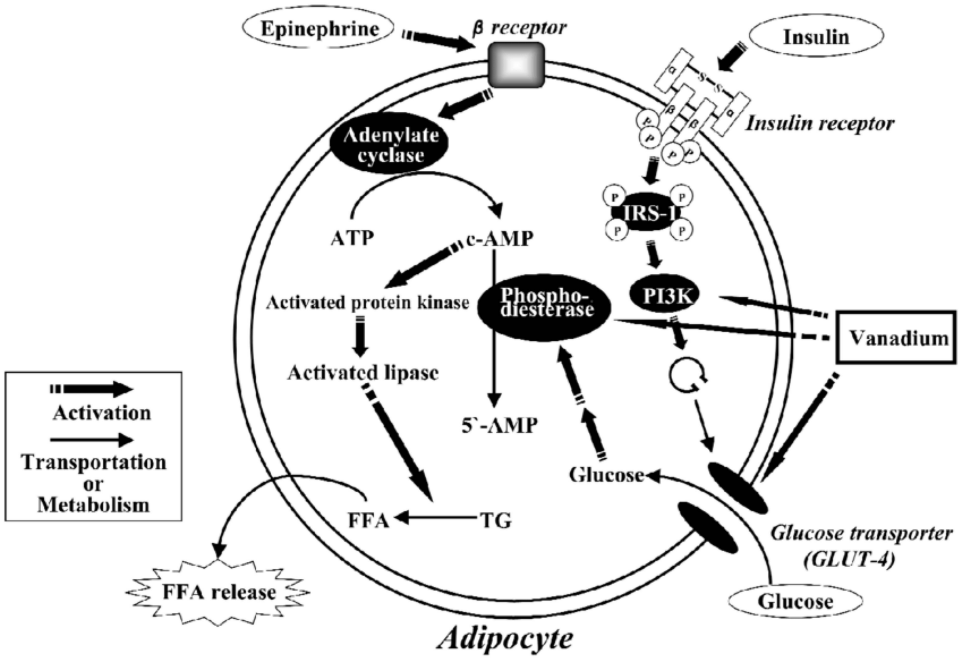


**Figure 1** Effects of vanadium on the insulin signalling pathway.
**Notes**: Reprinted from Sakurai H, Funakoshi S, Adachi Y. New developments of insulinomimetic dinuclear vanadyl (IV)-tartrate complexes. *Pure and applied chemistry*. 2005;77(9):1629–1640.[42]

**Table 1** The Side Effects and LD50 Values of Some Common Vanadium Salts and Compounds

| Vanadium salts and compounds | $LD_{50}$ | Side effects | References |
|---|---|---|---|
| Sodium Metavanadate | Oral: 98mg/kg b.w (rats), Intraperitoneal: 12mg/kg b.w (rats) | Gastrointestinal intolerance (vomiting, diarrhea) and excessive hypoglycaemia. Neurobehavioral changes were reported in long-term studies | [44–46] |
| Bis(maltolato)oxovanadium (BMOV) | Oral: 220mg/kg b.w (mouse) | Gastrointestinal tract discomfort and toxic accumulation in bone tissue | [47–49] |
| Bis (ethylmaltolato) oxovanadium(IV) (BEOV) | No defined $LD_{50}$ available | Long-term usage during clinical trials led to renal complications | [49–51] |
| Vanadyl sulphate | Oral: 448 mg/kg b.w (rats) | Clinical trials: Nausea, mild diarrhea, and abdominal cramps. Pregnancy: maternal toxicity and embryo or fetal toxicity | [45,52] |
| Orthovanadate | Estimated oral: 300 mg/kg b.w (mouse) | Gastrointestinal discomfort (hypermotility, diarrhea) | [45,53,54] |

However, the toxicity associated with inorganic vanadium limits its potential as a therapeutic agent for diabetes in the near future.[43] Therefore, to remove this toxicity, our laboratory has synthesized an organic vanadium complex using heterocyclic ligands designed to enhance absorption, potency, and therapeutic safety.[18,21,22] Organic dioxidovanadium complex [VO (Hpybz) 2SO4.H2O] was synthesized with 2:1 molar ratio reactions of the heterocyclic ligand 2-pyridylbenzimidazole (Hpybz) with vanadyl (IV) sulphate, a derivative of vanadium.[18,22,55] Pyridylbenzimidazole (Hpybz) is a well-established promising heterocyclic ligand with various therapeutic attributes such as antimicrobial, antibacterial, and anti-diabetic traits.[22,55] Hypothetically, the appropriate fusion of Hpybz with a vanadium compound will amplify its glucose-lowering capacity, thereby improving the value of vanadium as a medicinal drug.[55] Since the heterocyclic ligand Hpybz is a stable compound, it was expected to provide thermodynamic stability and efficient transport of vanadium to target locations in the body.[21] The resulting compound produced a more stable and safer potential anti-diabetic drug than inorganic vanadium salts.[18,21] The dioxidovanadium complex exhibited no cytotoxic effects in skeletal muscle cell lines, indicating that using heterocyclic ligands may have curbed vanadium toxicity.[38] Furthermore, Sprague Dawley rats treated with dioxidovanadium did not present with any side effects and showed improved body weight compared with the diabetic rats.[18,22,38] The absence of side effects combined with the alleviation of hyperglycemia suggests that the strategy employed in synthesizing our vanadium complex attenuated the vanadium toxicity without altering its anti-diabetic effects. Therefore, removing the toxicity associated with vanadium salts is an ideal choice.

## The Pathophysiological Relationship Between Hyperglycaemia and Vanadium in the Heart, Brain and Liver

### Hyperglycaemia-Induced Cardiovascular Disease

The heart is a vascular organ of vital importance as it is responsible for maintaining adequate blood circulation to body systems.[21] Cardiovascular disorders are caused by hypertension, hyperlipidaemia and hyperglycaemia.[21,56] The mechanisms of cardiovascular disease in DM are related to epigenetic, genetic, and cell signalling defects in interrelated metabolic and inflammatory pathways.[57] The cardiac muscle is well-suited to utilize all metabolic substrates and can easily switch between free fatty acids and glucose based on environmental changes.[58] Typically, cardiac cells use free fatty acids at rest and switch to glucose during stressful conditions, namely pathological hypertrophy and myocardial ischemia, which are often observed in diabetes.[59]

In cardiovascular tissues, two distinct glucose transporters are accountable for glucose transfer; namely, GLUT1 and GLUT4.[60] Nonetheless, GLUT4 occurs more predominantly in a healthy and fully matured heart.[60,61] The glucose is metabolized through physiological pathways such as glycolysis, oxidative phosphorylation and citric acid cycle.[57] Hyperglycaemia disrupts the physiological and metabolic function of the heart and, as a result, increases lipid formation in cardiac cells, causing the downregulation of the GLUT4 gene.[62] This alters GLUT 4 receptor expression, decreasing glucose transport to cardiac cells and resulting in cardiomyocyte death.[62]

Furthermore, studies have shown that chronic oxidative stress in diabetic humans is related to the metabolism of excess glucose and fatty acids in hyperglycemia.[63.] Excessive production of oxidative stress-related factors such as reactive oxygen species (ROS) can give rise to atherosclerosis, myocardial infarction, and cardiac injury.[63] In normal physiological conditions, ROS functions as signalling substances that regulate vascular smooth muscle growth, contraction, and relaxation.[64] Pathophysiological states lead to a perturbation in the balance between ROS and antioxidants, significantly contributing to endothelial dysfunction and several cardiovascular ailments.[64,65]

When the endothelium is healthy, it functions efficiently to regulate blood vessel tone, platelet activation, thrombogenesis, leukocyte adhesion, and inflammation; however, in diabetes, the endothelium is dysfunctional due to the increased secretion of the vasoconstrictor endothelin-1 and decreased levels of the vasodilator nitric oxide (NO).[66] The enhanced biodegradation of NO is caused by ROS called superoxide anions.[65,66]

These abnormalities are also associated with the release of pro-inflammatory cytokines.[67] Elevated levels of inflammatory cytokines such as interleukin 1 and interleukin 6, Tumor Necrosis Factor-α (TNF-α) and leptin have been shown to directly affect the cardiomyocytes, causing inflammation of cardiac cells and cellular apoptosis.[67,68] The elevated release of these cytokines exacerbates injury in blood vessels and induces the formation of atherosclerotic plaques.[66] Atherosclerotic plaques narrow the diameter of the vessel and reduce blood supply, resulting in nutrient deficiency and rupturing of the plaque resulting in the occlusion of coronary arteries.[69] This reduces myocardial blood flow, causing a spontaneous myocardial infarction.[68]

## The Interaction Between Vanadium and the Heart

Literature has reported on the cytoprotective effects of vanadium compounds on cardiomyocytes, both in vitro diabetic cells and in vivo diabetic animals.[21,70] In several studies, the overall cardiac function in diabetic patients improved upon the intake of vanadium salts.[17,71] Moreover, enhanced nitric oxide synthase activity in the blood vessels of rodents was reported after oral administration of organic vanadium chelate Bis (1-oxy-2-pyridinethiolato) oxovanadium.[65,70]

Vanadium decreases the activity of enzymes associated with free radical generation by alleviating the levels of antioxidants such as glutathione peroxidase, superoxide dismutase and catalase.[21] Enzyme lipoprotein lipase activity was significantly reduced, restoring phospholipids' levels and controlling lipid peroxidation.[17] Endothelin levels were brought to a physiological level which promoted vascular health.[72] A study by Bhuiyan et al reported that activation of tyrosine kinase as a result of intraperitoneal vanadium administration was found to reduce mitochondrial apoptosis and the extent of myocardial infarction, thereby exhibiting a cardioprotective effect against hypoxia.[73] However, it is speculated that vanadate-induced improvement of the contractile activity of the heart is caused by changes in $Ca^{2+}$ homeostasis within the cardiac muscle cell.[72] It is also noted that vanadium, as with the brain, is associated with accumulation over long-term exposure.[15,65] In contrast to its beneficial effects, this accumulation is toxic and favours the formation of ROS and free radicals such as hydrogen peroxide.[43] Thus, given the discordant results, the mode of action of vanadium compounds in cardiomyocytes remains ambiguous.[43]

Furthermore, Bis (maltolato) oxovanadium (BMOV) was shown to be a slightly less potent anti-diabetic drug; however, this complex showed remarkable abilities to suppress both the apoptotic and pro-survival unfolded protein response signalling induced by endoplasmic reticulum stress present in diabetic cardiomyopathy suggesting cardioprotective traits.[74] Mbatha et al, exhibited the dioxido(V) vanadium complex's role in lowering hyperglycaemia and regulating mean arterial pressure and lipid metabolism.[22] This attenuated the hyperglycaemia-induced cardiovascular dysfunction.[22] Therefore, this suggests a potential role that dioxidovanadium might play in cardioprotective effects and DM management.[21]

## Diabetes and the Brain

The global prevalence of diabetes and comorbid brain disorders is increasing at an alarming rate.[75] Diabetes has been linked to various neurological conditions, such as cognitive dysfunction and impaired cerebrovascular perfusion.[75] Studies show that 40% of late-stage diabetics suffer from cognitive impairment, ranging from mild cognitive impairment to dementia.[76] Glucose metabolism provides neuronal and non-neuronal brain cells with glucose to produce ATP and neurotransmitter synthesis.[77,78] The tight regulation of glucose metabolism is critical for normal brain physiology as it has been shown to play a significant role in neuroenergetics, neurotransmission, biosynthesis and oxidative defence.[79]

Excessive exposure to glucose and ROS is shown to disrupt the blood-brain barrier (BBB) by disrupting proteins in tight junctions between its micro-endothelial cells, thereby making the BBB porous and allowing toxic amounts of glucose to enter the brain.[77] Activation of the polyol pathway and oxidative stress from AGE and RAGE binding promotes the degeneration of neuronal tissue and glial cells such as astrocytes.[80,81] Astrocytes are damaged during hyperglycemia and release protein S100, which is released into the bloodstream due to the damage caused to the BBB.[81] Despite metabolism being independent of insulin, an absence of insulin in the brain has been shown to promote the formation of amyloid beta, which binds to the RAGE receptor and causes further oxidative stress, resulting in neuron degradation.[77] PKC's presence induces chitin scaffolding formation in neurons in the brain, thereby disrupting cognitive function.[82]

Hyperglycemia-induced hypoxia initiates anaerobic glucose metabolism, which increases lactate formation.[83] Despite lactate being required as an energy source and for memory skills, increased levels increase cell acidity.[84] Increased lactate production from pyruvate also decreases its availability for conversion to acetyl CoA. Therefore, the critic acid (TCA) cycle is downregulated.[85,86]

Several studies have reported that Streptozotocin (STZ) induced diabetic rats displayed deficits in performance during cognitive tasks used to assess brain function, such as memory analysis during the Morris water maze.[87] STZ-induced diabetes resulted in the altered function of NMDA and AMPA-type glutamate receptors, intermediates of the TCA cycle required for neurotransmitter synthesis.[80] Since glutamate is associated with memory and learning, deficiencies are associated with cognitive dysfunction.[77]

Evidence of Tau proteins has also been presented in diabetic patients.[82] These Tau proteins are found in the Locus coeruleus, a nucleus that projects neurons onto various brain regions. These regions include the hippocampus and amygdala, key areas responsible for memory.[83] Cleavage of the tau proteins in these hippocampal and amygdala neurons induces the apoptotic cascade, impairing spatial memory and cognitive function.[83]

### Vanadium-Related Brain Toxicity

Vanadium and its derivatives can cross the BBB and have neurologic and neuropathological consequences through different routes of administration.[36] Multiple studies have reported neurobehavioral changes, neuropathology, and increased brain vanadium content after intraperitoneal administration.[83,88]

After vanadium exposure, specific biochemical changes studied in the brain reveal processes that support oxidative stress and lipid peroxidation as the significant sequelae of vanadium administration.[89,90] Once accumulated in the brain, it promotes the depletion of the antioxidant glutathione, thereby catalyzing the formation of ROS.[36] Acute exposure to vanadium results in the activation of the microglia inflammatory pathway in the hippocampus and cerebellar area, by which cytokines such as AP-1 and IL-1β are released.[15,88]

The large amounts of lipid substances in the mammalian brain cause it to be susceptible to free radical attack.[90] Though proteins, carbohydrates and nucleic acids are damaged in the brain, lipid membranes are ROS's primary targets.[91] The brain has a high content of polyunsaturated fatty acids and aerobic catabolism; therefore, it is the most vulnerable target for peroxidative attack.[91] Morphological alterations due to vanadium exposure induced demyelination in the cerebellum and the corpus callosum, making demyelination one of the significant phenotypes of vanadium-induced neurotoxicity.[89] Furthermore, prolonged vanadium exposure was reported to result in CA-1 pyramidal neuron degeneration and dendritic spine loss.[89] These neurons are responsible for spatial memory.[89]

In contrast, short-term use of vanadium significantly decreased lipids, phospholipids, cholesterol, cerebrosides and protein in various brain regions.[92] These observations warrant further investigation into the most effective dose and duration of exposure required for vanadium to exhibit its therapeutic properties.

### Vanadium Complexes and Cognition

BMEOV and BMOV complexes have been previously considered as a treatment for Alzheimer's disease as it has been shown to improve spatial memory in diabetic and non-diabetic rats.[50] At present, no research has documented the effects of this novel dioxidovanadium complex on brain function. However, since the complex has successfully been shown to alleviate hyperglycaemia and associated complications in the liver and the heart, with little toxicity, we speculate that treatment with this complex might be beneficial in alleviating hyperglycaemia-induced brain dysfunction.

## Effects of Hyperglycaemia on Liver Function

The liver is one essential macrovascular organ that responds to changes in blood glucose.[93] It controls glycogenesis, glycogenolysis and gluconeogenesis, all processes that significantly influence glucose levels in the blood.[94] DM has been shown to induce liver damage via several pathways.[95,96] Insulin resistance is the predominant causative factor of hyperglycaemia-induced liver damage.[95–97] The liver is a collection of insulin-sensitive tissues and is one of the main organs susceptible to hyperglycaemia-induced inflammation and oxidative stress, possibly leading to liver tissue injury.[97,98] Together, oxidative stress and inflammatory responses act as damaging agents in exacerbating the pathological state of DM.[98,99]

During diabetes, there are elevations in the release of mediators of inflammation, oxidative stress and coagulation.[100] These mediators promote the release of fetuin-A.[97,101] Fetuin-A is a protein responsible for regulating.[101,102] Upon secretion, fetuin-A binds to insulin receptor tyrosine kinase, inhibiting insulin binding and signalling transduction.[101,102] To accommodate this lack of glucose uptake due to insulin resistance, the liver produces glucose from glycogenolysis.[103] Hormone-sensitive lipase, usually regulated by insulin, breaks down adipose tissue into free fatty acids (FFA) for de novo lipogenesis for further glucose production.[103,104] Elevated levels of unesterified fatty acids lead to lipotoxicity, which promotes low-grade inflammation.[100,105] The FFA overload the hepatic mitochondrial β-oxidation system, leading to the generation of free radicals, peroxisomes, and the accumulation of triglycerides in the liver.[106] The intracellular accumulation of triglycerides in the liver is further exacerbated by insulin resistance in skeletal muscle, which acts synergistically with adipose tissue leading to systemic inflammation, which causes the release of proatherogenic and nephrotoxic factors.[100]

Adipokines and tumour necrosis factor (TNF- α) partially regulate lipid metabolism.[107] TNF-α is an important pro-inflammatory cytokine as it plays a dual role in the insulin signalling pathway.[97,108] Excessive chronic production of TNF-α favours steatosis and contributes to the pathogenesis of the inflammation present in Non-alcoholic steatohepatitis.[107] Non-alcoholic fatty liver disease (NAFLD) is a chronic condition characterized by insulin resistance and hepatic fat accumulation.[97,102] NAFLD is one of the most prevalent complications in T2DM, with a reported incident rate of 40–70%.[102,109]

### The Effects of Vanadium on the Liver

The liver is the main accumulation site of vanadium and a vital role player in maintaining glucose homeostasis.[18,110] Cusi et al reported that vanadium complexes such as Vanadyl sulphate and Bis (ethylmaltolato) oxovanadium (IV) (BEOV) improved glucose homeostasis in T1DM and T2DM.[111]

Streptozotocin-induced diabetic rats treated with Vanadyl sulphate presented increased insulin sensitivity in the liver, kidneys, adipose tissue, and skeletal muscle.[43,111] Additionally, in a similar experimental model, BEOV increased the concentration of high-density lipoproteins (HDL) and reduced glycosuria, total cholesterol and triglyceride levels.[43,112] BEOV administration on rat models of type 2 diabetes decreased the synthesis of very low-density lipoproteins and reduced adipocyte lipolysis and the subsequent uptake of FFA by the liver.[20,50,112]

In in-vitro studies, vanadium salts, sodium orthovanadate, and vanadyl sulphate accelerate glucose transport and oxidation in the liver and skeletal muscles, inhibit lipolysis, and accelerate lipogenesis in hepatocytes.[111] These

observations confirm the beneficial role of vanadium compounds in alleviating the pathological and physiological consequences of diabetes.

In contrast to its insulin-mimetic properties, excessive vanadium accumulation in the liver results in hepatotoxicity.[113] Hepatotoxicity induced by vanadium has been well-established both in vivo and in vitro.[43,114] Vanadium disrupts the cell cycle and initiates apoptosis of hepatocytes.[113] Abnormal destruction of hepatocytes exacerbates the development of liver diseases.[115] Literature states that vanadium induces hepatocyte degeneration, structural damage, and inflammation.[52]

Furthermore, in vivo and in vitro studies strongly suggest that vanadium-induced liver toxicity is associated with the metal's effects on mitochondrial respiratory complexes I, II, and III.[116] These cause ROS formation and ATP depletion in hepatocytes.[116,117] This ultimately leads to programmed cell death signalling by mitochondrial pore opening and cytochrome c release.[30,117]

Vanadyl acetylacetonate (Vac) is a potent anti-diabetic drug shown to reduce blood glucose by inhibiting gluconeogenesis and lipolysis in the body.[110] The compound has been shown to favour delivery to the bone, kidney and liver. It has been demonstrated to accumulate and release its insulin-mimetic effects over extended periods.[110] Adding the organic ligand has significantly reduced its accumulation in the liver but has increased its accumulation in bone.[110,118] There is also evidence of reversal induced by BMOV treatment in morphological changes caused by diabetes in the liver.[119] However, accumulation and distribution patterns of BMOV were bone > kidney > liver in a 24 h trial, and the concentrations detected were three times higher than vanadyl sulphate.[111,120] A study by Sibiya et al reported that the ligands bound to the novel complex dioxido(V) vanadium aided in the clearance of excess vanadium from the liver, preventing accumulation and hepatotoxicity.[18] This was evident via a significant attenuation in malondialdehyde concentrations.[18] Furthermore, the vanadium complex was shown to increase liver function enzymes, alanine transferase and aspartate transferase, improving liver function and injury brought about by diabetes.[18] Hence, the dioxidovanadium complex is an effective hypoglycaemic for managing liver damage in DM.[18]

## Conclusion

Extensive experimental research has shown compounds of a vanadyl nature to improve insulin sensitivity and glycaemic control via increasing glucose uptake in vital organs such as the brain, heart and liver. Although vanadium's medicinal features have shown promising results in controlling hyperglycaemia, most studies have reported on the toxic accumulation of vanadyl compounds and the resulting detrimental side effects in the heart, liver and brain. To mitigate the toxicity associated with current vanadium compounds, researchers have synthesized vanadium complexes to manipulate the therapeutic impact of vanadium whilst alleviating its toxic effects. Our laboratory has produced a novel vanadium complex, Dioxidovanadium, by manipulating organic ligands to contribute to vanadium research. The novel Dioxidovanadium compound has proven to be non-cytotoxic and has been shown to alleviate hyperglycaemia, as evidenced by the compound's insulin-mimetic properties. However, this was a result of short-term dioxidovanadium use. Based on previous evidence and the promising results from existing research, further investigations into vanadium complexes and specifically dioxidovanadium regarding overall therapeutic potency are also warranted so that limitations such as duration of exposure are investigated. Taken together, the pros and cons associated with vanadium compounds presented in this review encourage further investigations into the biological activity of these compounds and their potential in diabetes mellitus management.

## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

## Disclosure

The authors report no conflicts of interest in this work.

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