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Vanadium as potential therapeutic agent for COVID-19: A focus on its antiviral, antiinflamatory, and antihyperglycemic effects

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ABSTRACT

An increasing evidence suggests that vanadium compounds are novel potential drugs in the treatment of diabetes, atherosclerosis, and cancer. Vanadium has also demonstrated activities against RNA viruses and is a promising candidate for treating acute respiratory diseases. The antidiabetic, antihypertensive, lipid-lowering, cardioprotective, antineoplastic, antiviral, and other potential effects of vanadium are summarized here. Given the beneficial antihyperglycemic and antiinflammatory effects as well as the potential mechanistic link between the COVID-19 and diabetes, vanadium compounds could be considered as a complement to the prescribed treatment of COVID-19. Thus, further clinical trials are warranted to confirm these favorable effects of vanadium treatment in COVID-19 patients, which appear not to be studied yet.

1. Introduction

As the number of confirmed cases of the Coronavirus disease 2019 (COVID-19) overpassed 230 million and almost 5 million people have lost their lives due to this devastating disease, significant efforts are being made to efficiently treat COVID-19 and prevent its progression to the serious stage of disease, particularly in the patients with the preexisting conditions. The most reported comorbidities in patients with severe COVID-19 include hypertension, diabetes, and obesity [1–3]. The diabetic patients are exposed to an enlarged risk of serious complications, such as cardiac and neurological complications [4,5], as well as to an increased severity of this disease [6]. Based on recent clinical findings, pathophysiological mechanisms associated with the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), such as cytokine storm and hypercoagulation, appear to make the diabetic patients more susceptible to these COVID-19 complications [6,7]. Furthermore, this multifaceted disease may also predispose the patients to difficult-to-treat hyperglycemia [8,9] as well as to lowered sensitivity to insulin and perturbed insulin secretion [10].

The potential role of the trace metals, such as zinc and selenium, in the prevention and treatment of COVID-19 has recently been suggested [11–15]. Supplementation with zinc and selenium was reported to be crucial for the resistance to viral disease, immune function, and alleviated inflammation, particularly if it was administered during the early phase of a viral infection [11]. A recent study also indicated that based on clinical evidence, the trace elements should be added to the treatment of the early stages of COVID-19 as an immunoprotection strategy and for an efficient elimination of the virus [16].

Vanadium is a trace, ubiquitous element with a potentially unique biological function. It is widely distributed in nature, it can be found in

Abbreviations: ACE2, angiotensin-converting enzyme; BEOV, bis(ethylmaltolato)oxovanadium(IV); BK, bradykinin; B1R, BK type 1 receptors; B2R, BK type 2 receptors; BMI, body mass index; BMOV, bis(maltolato)oxovanadium(IV); COVID-19, Coronavirus disease 2019; COX-2, cyclooxygenase-2; CREB, cyclic AMP response binding element; DPP-IV, dipeptidyl peptidase IV; EGFR, epidermal growth factor receptor; ERK, extracellular signal-regulated kinase; FFA, free fatty acid; GLUT4, glucose transporter 4; GS, glycogen synthase; HbA1c, hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; HIV, human immunodeficiency virus; HOMA-IR, homeostasis model assessment-insulin resistance; IBV, infectious bronchitis virus; IL-1, interleukin-1; IL-4, interleukin 4; IL-6, interleukin-6; IFN-I, type I interferons; IFN-γ, interferon-γ; JAKs, Janus kinases; MAPK, mitogen-activated protein kinase; M^{pro}, SARS-Cov-2 main protease; NF-kappa B, transcription factor nuclear factor kappa B; PI3K, phosphatidylinositol 3′-kinase; PIP3, phosphatidylinositol 3, 4, 5 triphosphate; PLC, phosphoinositide phospholipase C; PP1, protein phosphatase-1; PTP, protein tyrosine phosphatases; PTP1B, protein tyrosine phosphatase 1B; RAS, renin-angiotensin system; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; STATs, signal transducers and activators of transcription; STZ, streptozotocin; Th1, T-helper 1; TNF-α, tumor necrosis factor-α; TYK2, tyrosine kinase 2.

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certain algae, sea squirts, fungi, and mammalian tissues [17,18], and it has been recognized to be essential for animal development [18]. Vanadium-dependent enzymes, such as vanadate-dependent haloperoxidases and vanadium nitrogenases, have been described in different microorganisms, including bacteria [19]. In humans, it is mainly present in liver, kidney, and bones, while its concentration in blood is reported to be around 200 nM [20]. Vanadium is present in a variety of foods, including vegetable oils, skim milk, grains, cereals, and vegetables such as beans, peas, and squash [21,22]. It has been reported that only about 1% of vanadium contained in the diet is absorbed [23] and that this percentage of absorbed vanadium, as well as its disposition, therapeutic and toxic effects, are affected by its biotransformation into different vanadium species upon oral digestion [20]. This led to the development of inorganic and organic vanadium compounds containing ligands to protect the compound from speciation, to increase its absorption, and to conserve its pharmacological properties [20].

The reported effects of both, inorganic and organic vanadium compounds, include antihyperglycemic and insulin-enhancing actions, lipid-lowering, antihypertensive, cardioprotective, and antineoplastic effects [18,24,25]. Furthermore, vanadium derivatives are being used as a nutritional supplement for the enhancement of performance by body builders, weight management, and the prevention of obesity [18,26]. These biomimetic functions and mechanisms of vanadium actions will be reviewed in this article, including its potential use against viruses, with a particular focus on SARS-CoV-2. Given the significance of the puzzling link between COVID-19 and diabetes as well as the observed antihyperglycemic, insulin-enhancing, and antiinflammatory effects of vanadium compounds, further clinical studies have a high potential to open additional avenues for the treatment of both of these pandemic diseases.

2. Vanadium treatment of diabetes and other diseases

2.1. Beneficial vanadium effects

A large amount of evidence demonstrated vanadium's antidiabetic and insulin-mimicking effects, as well as its ability to counteract insulin resistance [18,20,27–29]. Heyliger et al. were the first to demonstrate vanadium effects in streptozotocin (STZ)-induced diabetic rats [30], which reduced blood glucose levels to normal and prevented the diabetes-induced deterioration of cardiac function [30,31], even three months after withdrawal from an oral vanadium treatment [32]. Furthermore, recently it was suggested that the antihyperglycaemic effects of vanadium may improve kidney dysfunction in diabetes [33]. In addition, a recent report showed that a peroxyvanadate compound activated insulin-signaling cascade and improved insulin sensitivity [34], while Naglah et al. (2020) reported antidiabetic effects of vanadyl (IV) folate-amino acid-complexes in animal models of diabetes [35]. A recent study demonstrated the capability of the oxidovanadium complexes to target the active site and inhibit dipeptidyl peptidase IV (DPP-IV), which is target of recently introduced antihyperglycaemic agents used to treat T2D [36]. Vanadium compounds were also reported to be effective in the prevention of Type 2 diabetes development in animal models of diabetes [37].

The effects of vanadium salts, such as vanadyl sulfate, sodium orthovanadate and peroxovanadium compounds, as well as organic vanadium complexes, including bis(maltolato)oxovanadium(IV) (BMOV), have been investigated in diabetes treatment (Fig. 1). These studies have found that organic vanadium compounds have improved the bioavailability and safety profile as compared to the inorganic salts [38–40]. The BMOV and its ethylmaltol analog, bis(ethylmaltolato) oxovanadium(IV) (BEOV), were shown to have similar effects on the diabetic traits in Zucker Fatty rats and STZ-diabetic Wistar rats [41,42]. BEOV demonstrated the improved characteristics for pro-drug use, so it was selected for phase 1 and phase 2 clinical trials [43]. It was demonstrated that its use in T2D subjects was associated with reduction

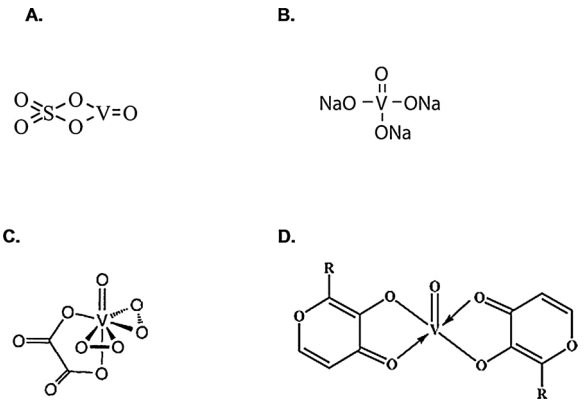

Fig. 1. Chemical structures of: **A.** Vanadyl sulfate; **B.** Sodium orthovanadate; **C.** Peroxovanadium complex; **D.** Bis(maltolato)oxovanadium(IV) (BMOV), R = CH_3, and bis(ethylmaltolato)oxovanadium(IV) (BEOV), R = C_2H_5.

in fasting glucose and hemoglobin A1c (HbA1c) levels, as well as with an improved response to the oral glucose tolerance test [43]. Similarly, other clinical trials also demonstrated that in both, Type 1 and Type 2 diabetic subjects, vanadium treatment decreased the need for exogenous insulin, suggesting an enhancement of insulin sensitivity [44,45] and its potential to treat diabetes [46]. Interestingly, an oral administration of vanadium compounds appears not to cause hypoglycemia, a serious potential side effect in insulin-treated diabetic patients [47]. Furthermore, vanadium treatment did not affect C-peptide levels in Type 1 diabetic patients, suggesting that restored insulin secretion was not responsible for the decreased need for insulin administration in these individuals [48]. Eriksson et al. [49] demonstrated that vanadium treatment significantly increased insulin binding capacity at the cell surface of normal and insulin-resistant cells.

In addition to antihyperglycemic and insulin-enhancing effects, vanadium compounds also demonstrated antihyperlipidemic action. Recently, decavanadate showed insulin-mimicking effects in human adipocytes, including the inhibition of lipolysis and the activation of glucose transport, thus limiting lipotoxicity associated with obesity and insulin resistance [50]. The inhibition of lipolysis and activation of glucose uptake by different vanadium compounds was also demonstrated in other studies [26,51–53]. Nakai et al. [54] showed that vanadium was incorporated into most organs, including the adipose tissues of the STZ-induced diabetic rats, which was accompanied by the normalization of increased glucose and free fatty acid (FFA) levels. The gene-array study reported that oral administration of vanadyl sulfate, which alleviated diabetic hyperglycemia and hyperlipidemia, also corrected diabetes-altered gene expression in skeletal muscle of STZ-induced diabetic rats [47]. This study showed that diabetes altered the expression of about 130 genes, and the expression of 30 % of these genes was normalized by vanadyl sulfate [47]. Interestingly, these genes, whose expression appeared to be affected by vanadium treatment, include those related to the lipid metabolism, signal transduction, oxidative stress, and the complement system [47]. A recent study demonstrated that vanadium exposure appeared to be associated with increased high-density lipoprotein cholesterol (HDL-C) and apoA-I levels as well as decreased atherogenic indexes, indicating further the beneficial effects of vanadium in the treatment of atherosclerosis [55]. Interestingly, recent genome-wide CRISPR screens in SARS-CoV-2-infected cells have reported that inhibition of cholesterol homeostasis reduced the replication of coronavirus, which suggested the development of therapies targeting those intracellular pathways [56].

In addition to diabetes and atherosclerosis, vanadium compounds have been also investigated as potential medication for the treatment of other diseases, including its potential antirheumatic [57] and anticancer effects [18,58,59]. A recent novel use of vanadium compounds to stimulate viral oncolytic and systemic anticancer immunity was also

demonstrated [60]. Furthermore, previous studies indicated an application of vanadium treatment in cardiac and neuronal diseases, parasitic, bacterial [61], and viral infections, such as influenza, HIV, and SARS [18].

2.2. Adverse effects of vanadium

Despite these beneficial outcomes, vanadium treatment resulted in adverse effects, including gastrointestinal symptoms, hepatotoxicity, nephrotoxicity [61,62], and neurotoxicity [63], which represent the major obstacle for more efficient transfer of vanadium compounds in the clinical use for long-term diabetes treatment, as reviewed by Domingo et al. [64,65]. Recently, different factors have been recognized to be associated with the vanadium toxicity, including the structure of the vanadium compound (inorganic/organic) and the characteristics of ligands attached to vanadium complexes, valence, dose, route of administration, duration of action/exposure, as well as an individual sensitivity to vanadium action [18]. A recent study that used highly dispersible and water-soluble graphene quantum dots as nano-platform/delivery system for vanadium, demonstrated its improved pharmacokinetic characteristics, hypoglycemic effects, and β-cell protection *in vivo* [66]. Furthermore, another recent study demonstrated no toxic effects in animals after their sub-chronic treatment with vanadium nanoparticles [67]. In addition, the combinatory treatment of vanadium with several supplements also showed the protective effects against the adverse effects of vanadium [35,62,68–70]. Thus, further development of vanadium-based drugs, including the formation of nanoparticles and other drug-formulation strategies, should be employed to develop vanadium compounds with alleviated pharmacological properties and decreased adverse effects.

3. Rationales for potential use of vanadium compounds in COVID-19 treatment

3.1. Mechanisms of antiviral vanadium effects

As shown in the Table 1, previous studies demonstrated that vanadium compounds affected the human immunodeficiency virus 1 (HIV-1) gene expression, thus suggesting their use in therapy of viral infections [71]. The mechanism of anti-HIV action of vanadium appears to include an effect on HIV binding to the cell membrane [72]. Ross et al. [73] reported the vanadium complexes docked into the human chemokine receptor CXCR4 model, thus affecting the function of these coreceptors essential for HIV-1 entry into CD4+ cells. This appears to prevent viral multiplication and to protect against the development of infection [18]. Vanadium complexes also inhibited the activity of viral reverse transcriptase [74], which are responsible for the integration of viral DNA into the host cell genome, thereby preventing viral replication [18]. Furthermore, physiologically stable vanadium porphyrins demonstrated a high potency in inhibiting HIV-1 replication in cultured cells, thus representing a new class of anti-HIV agents [75]. In addition, previous *in vitro* and *in vivo* studies demonstrated a broad spectrum and non-toxic anti-RNA virus activity of vanadium containing polyoxotungstate, which was suggested to be employed as a novel first-line treatment in acute respiratory diseases, including infections with the SARS coronavirus [76].

As described earlier, COVID-19 is caused by the RNA virus SARS-CoV-2, which employs angiotensin-converting enzyme 2 (ACE2) receptor, the transmembrane serine protease TMPRSS2, and the SARS-Cov-2 main protease (M^{pro}) to enter the host cell [77,78]. Viral binding to ACE2 and the other two proteases lead to the virus replication and spreading throughout the body. The recent computational studies emphasized the favorable physicochemical properties of vanadium compounds, including M^{pro} targeting, which could be potentially employed in treatment of SARS-CoV-2 infection [79,80].

ACE2 exerts its major role in the renin-angiotensin system (RAS), consisting of the classical ACE-Ang-II-AT1R axis and non-classical, recently discovered ACE-2-(A1-7)-Mas axis [81]. It is suggested that the ACE2 expression is modified during diabetes and that this may affect glucose homeostasis and insulin sensitivity [82]. It is also proposed that the ACE-2-(A1-7)-Mas, which is already distressed in diabetes/insulin resistance, is additionally strained due to ACE2 use for the viral entry [83].

Table 1
The rationales for potential use of vanadium compounds in prevention and treatment of COVID-19.

General Effects of Vanadium	Effects Observed in Selected Studies	References
Antiviral effects	Affected HIV-1 gene expression and viral entry	[71,72,73,74]
	Inhibited the activity of viral reverse transcriptase	[74]
	Prevented viral replication	[18,75]
	Showed a broad spectrum and non-toxic anti-RNA virus activity.	[76]
	Computational analysis indicated the favorable physicochemical properties of vanadium, including targeting of the SARS-Cov-2 main protease (M^{pro}) used by virus to enter the host cell.	[79,80]
Antiinflammatory & anticoagulation effects	Affected the secretion/expression/function of inflammatory cytokines, including IFNγ, TNFα, IL-1α and IL-1β.	[57,117,118,119,120]
	Demonstrated the inhibition of D-dimer formation, suggesting that the vanadium compounds could potentially relieve a hypercoagulative state in diabetic patients.	[100]
	Lowered levels of kallikrein which has a crucial role in the molecular mechanisms of vasodilation and blood coagulation.	[135,136]
Antihyperglycemic & insulin-enhancing effects	Decreased high levels of glucose and insulin as well as body weight in animals.	[84]
	Affected the activity of members of the insulin receptor signaling pathway, including but limited to TYK, PI3K, and PTP1B.	[95,96,97,98]
	Showed insulin-mimetic/enhancing action	[41,42,43,44,45,86,87,88,89,90,91]
	Demonstrated antidiabetic effects and counteracted insulin resistance.	[18,20,27,28,29]
	Corrected diabetes-altered gene expression in skeletal muscle of STZ-induced diabetic rats.	[47]
	Normalized blood glucose levels and prevented the diabetes-induced deterioration of cardiac function	[30,31,32]
	Showed antihyperglycaemic effects and improved kidney dysfunction in diabetic animals.	[33]
	Demonstrated the capability to inhibit DPP-IV, which is target of recently introduced antihyperglycaemic agents used to treat T2D.	[36]

3.2. Mechanisms of antihyperglycemic and insulin-enhancing vanadium effects

The capability of vanadium to stimulate insulin signaling pathways

appears to be an important mechanism responsible for its glucoregulatory effects and its insulin-mimicking characteristics. It was demonstrated that vanadium treatment of genetically diabetic mice decreased high levels of glucose and insulin, as well as their body weight [84]. In addition, vanadium appears to regulate appetite by promoting glucose uptake in the brain [85], thus preventing an increase of body weight and obesity.

As suggested by the previous studies, vanadium promotes insulin action by a direct insulin-mimetic action and by an enhancement of insulin sensitivity [86–88]. It was suggested that vanadium achieves its effects by enhancing insulin action [89–91] through the activation of the phosphatidylinositol 3'-kinase (PI3K), stimulated synthesis of phosphatidylinositol phosphates, such as phosphatidylinositol 3, 4, 5 triphosphate (PIP3), that mediates the phosphorylation of its downstream targets regulating glucose transport, glycogen synthesis, and gluconeogenesis [92]. Semiz et al. [42] showed that vanadium treatment improved an impaired insulin sensitivity in the Zucker fatty rats, resulting in an increased muscle glucose metabolism through enhanced glycogen synthase (GS) and insulin-stimulated protein phosphatase-1 (PP1) activity. Interestingly, recent genome-wide CRISPR screens in SARS-CoV-2 infected cells have recognized phosphatidylinositol phosphate biosynthesis as a critical pathway supporting the coronavirus infection and that the inhibition of phosphatidylinositol kinases decreased the coronavirus replication [56]. Furthermore, Kawabe et al. [93] indicated that the insulin-mimetic activity of vanadium compounds includes an inhibition of FFA release and that this effect is probably regulated by the inhibition of the glucose transporter 4 (GLUT4) and members of the insulin receptor-signaling pathway, such as tyrosine kinase and PI3K. The adipogenic potential of vanadium was also attributed to the activation of the cyclic AMP response binding element (CREB) transcriptional factor [94]. In addition, a recent review reported that the mechanisms of vanadium action include protein tyrosine phosphatases (PTP), mitogen-activated protein kinase (MAPK), epidermal growth factor receptor (EGFR), transcription factor nuclear factor kappa B (NF-kappa B), phosphoinositide phospholipase C (PLC) γ, and cyclooxygenase-2 (COX-2), which are associated with the insulin signaling network [95]. This is in line with the other studies, which also implicated the activation of NF-kappa B and MAPK2 in vanadium action [96–98]. In addition, the extracellular signal-regulated kinase (ERK) belonging to the MAPK family, has also been reported to be involved in pathogenesis of different viral infections [99]. A recent study reported that the inhibition of ERK1/2 signaling restricted the replication of the infectious bronchitis virus (IBV), which is the representative strain of gammacoronavirus, suggesting that the components of the ERK pathway may denote excellent targets for the novel antiviral drugs development [99].

Furthermore, previous studies also implicated the inhibition of the protein tyrosine phosphatase 1B (PTP1B) as potential mechanism of vanadium action [100,101]. Accordingly, additional studies confirmed the role of potent and selective PTP1B inhibitors in diabetes management [86,102–104]. It was suggested that these inhibitors could also potentially target a hypercoagulative state in diabetic patients [100] and that sensitivity of PTP inhibition and glucose transport to vanadate is probably mediated by the cellular redox state [96,97,105].

3.3. Mechanisms of antiinflammatory vanadium effects

Following viral infection by SARS-CoV-2, the levels of proinflammatory cytokines (interleukin-1 (IL-1), interleukin IL-1β, interleukin-6 (IL-6), interferon-γ (IFN-γ), and tumor necrosis factor-α (TNF-α)), and chemokines are elevated, leading to the COVID-19-associated vascular inflammation, coagulopathy [106] and severe forms of this disease [107]. Recently, Smith et al. indicated that ACE2 is an interferon-stimulated gene upregulated by viral infections [108]. A recent GWAS reported the genome wide significant associations of interferon receptor *IFNAR2* gene in seriously ill COVID-19 patients [109]. Furthermore, type I interferons (IFN-I) have been indicated as key players in an effective antiviral response [110]. Recent findings suggested that IFN-I signaling is affected by genetic variations of tyrosine kinase 2 (TYK2) [111], which was reported with the genome wide significant association in severe cases of COVID-19 [109]. This kinase is a Janus kinases (JAKs) family member, involved in the cytokine receptors' downstream signaling, whose activation leads to phosphorylation of the signal transducers and activators of transcription (STATs) and increased production of inflammatory mediators, triggering the cytokine storm and inflammation in COVID-19 patients [112]. With an effort to alleviate excessive inflammation, JAK/STAT inhibitors, including the first-generation ruxolitinib, tofacitinib, and baricitinib, have been reported to act via suppression of cytokine signaling and protein tyrosine phosphatases activity [112]. The effects of vanadium on expression and activities of JAK/STAT pathway was investigated in the recent study, which appeared to demonstrate a trend of reduced STAT phosphorylation by vanadium [113].

An accumulating amount of evidence suggests that adipose tissue inflammation is an important risk factor for the development of insulin resistance and Type 2 diabetes in obese subjects [114,115], which may lead to increased proinflammatory cytokine levels [116]. As mentioned earlier, vanadium compounds acting as PTP inhibitors, inhibited the formation of D-dimer, a fibrin degradation product and a marker of coagulation activation [100]. This suggests a potential relieving effect of vanadium on a hypercoagulative state in diabetes [100] as well as in similar inflammatory and coagulative processes described above in COVID-19 patients. Recently, it was reported that vanadium modulated the effect of IFNγ on chemokine secretion [117]. It was also demonstrated that vanadium compounds were able to stimulate the secretion of T-helper 1 (Th1) chemokines, synergistically increasing the effect of key Th1 cytokines, including IFNγ and TNFα [118]. Previous studies have also showed that vanadium affected the macrophage IFNγ-binding and -inducible responses [119], which were associated with lower DNA methylation of IFNγ and interleukin 4 (IL-4) [120]. Deregulated signaling of interleukin 1α (IL-1α) and IL-1β inflammatory cytokines has been reported to cause the devastating diseases associated with severe inflammation [121]. Recent systematic review/meta-analysis identified IL-1α as one of the novel therapeutic targets for COVID-19 treatment [122]. Interestingly, Oliver et al. [57] showed that BMOV therapy strongly reduced synovial mRNA expression of IL-1α and alleviated symptoms of clinical arthritis in BMOV-treated rats as compared to controls. Vanadium compounds may also affect the expression of the inducible form of cyclooxygenase COX-2 [98] and regulate its activity [123], which appears to be increased during acute and chronic inflammation contributing to the excessive cellular production of reactive oxygen species and tissue damage [124].

In addition to these interferon-regulated processes, it was also reported that ACE2 can affect the kinin-kallikrein system, which has a crucial role in the molecular mechanisms of vasodilation and blood coagulation [125–127]. ACE2 regulates both bradykinin (BK) receptors, the BK type 1 (B1R) and BK type 2 (B2R) receptors. Recently, Garvin et al. [128] performed the gene expression data analysis in bronchoalveolar lavage fluid cells from COVID-19 patients and showed increased levels of ACE2, RAS, renin, angiotensin, bradykinin receptors, kinogen and several kallikrein enzymes, as compared to the control subjects. Similarly, other recent studies showed that the virus binding to ACE2 increases bradykinin levels, leading to the systemic inflammation, coagulation, the complement system induction, and the cytokine storm in COVID-19 patients [7,78,129]. These bradykinin-driven pathological processes appear to be associated with many of the symptoms observed in the COVID-19 patients [128], with an extensive release of proinflammatory cytokines and with a decrease in T cell counts [78,129]. Recently, it was proposed that blocking the kallikrein-kinin system with lanadelumab, a monoclonal antibody against the plasmatic kallikrein, should prevent the inflammatory and coagulation storm in these patients and thus, should be used in parallel with antiviral therapy [78].

Another inhibitor of the kallikrein-kinin system is conestat alfa, which is a recombinant human C1 esterase inhibitor (C1INH). It also inhibits serine protease activity [130], which was reported to be elevated in T2D patients and to be positively associated with HbA1c levels, homeostasis model assessment-insulin resistance (HOMA-IR) and body mass index (BMI), thus supporting the potential role of serine protease in T2D development [116]. Previous studies demonstrated that vanadium compounds inhibited serine proteases [131,132]. Furthermore, a recent study demonstrated that treatment with the conestat alfa also resulted in reduced levels of complement activation products and decreased viral loads in nasopharyngeal swabs, leading to alleviation of the severe COVID-19 cases [133]. Furthermore, van de Veerdonk et al. [134] recently proposed that blocking the B2R and plasma kallikrein activity might produce beneficial effects in the early stages of disease caused by SARS-CoV-2 and prevent acute respiratory distress syndrome. Interestingly, it was reported that vanadate treatment lowered levels of urine kallikrein in animal models [135,136], suggesting its potential action on the coronavirus infection via regulation of kallikrein levels.

Therefore, vanadium treatment seems to modulate major risk factors for severe COVID-19, including its alleviating effect on hyperglycemia and dysregulated immune and inflammatory responses. Furthermore, as suggested by the recent computational studies, vanadium may also affect the SARS-CoV-2 viral entry. Thus, the potential of vanadium compounds as an adjuvant therapeutic agent in the treatment of COVID-19 should be explored in further studies, which appear to have not been investigated sufficiently.

4. Conclusions

In conclusion, an increasing evidence suggests that vanadium compounds may represent new potential medications in therapy of diabetes, cancer, atherosclerosis, and other diseases. Vanadium compounds have also demonstrated a broad spectrum and non-toxic activities against RNA viruses and are promising candidates for treating acute respiratory diseases. Given those benefits and the important relationship between COVID-19 and diabetes as well as the observed beneficial antiviral, antihyperglycemic, insulin-enhancing, and anti-inflammatory effects, vanadium compounds could be considered as an adjuvant therapy to the prescribed treatment of COVID-19. Furthermore, vanadium might be used to complement efforts in managing difficult-to-treat hyperglycemia in COVID-19 patients. Thus, a further clinical trials are warranted to confirm these beneficial effects of vanadium treatment of COVID-19, which seem to have not been studied yet.

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Ethics approval and informed consent

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Availability of data

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Declaration of Competing Interest

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