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# Reducing obesity and inflammation in mice with organically-derivatized polyoxovanadate clusters

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ABSTRACT

Obesity, characterized by the dysregulation of energy balance in adipose tissue and other metabolic organs, is frequently accompanied by chronic low-grade inflammation. As long-acting insulin sensitizers, the organically-derivatized polyoxovanadates (POVs), can extend the dosing interval of antidiabetic drugs from hourly to almost daily. In this work, the protective activity of POVs is investigated by an eight-week *in vivo* experiment, in which a small amount of POVs was administrated orally to a mouse model of diet-induced obesity every day. The present study shows that administration of POVs significantly decreases the body weight of mice, reduces adipose tissue accumulation, and simultaneously reduces adipose tissue inflammation. In addition, the anti-obesogenic population of iNKT cells is protected potentially by POVs, which subsequently alleviates visceral adipose tissue inflammation in high-fat-diet (HFD)-fed mice against diet-induced obesity. By contrast, the change in body weight after POV treatment is the result of a substantial reduction in fat mass, with no obvious effects on lean body mass. These findings demonstrate that supplementary of POVs would be an effective way to combat obesity and metabolic disorders while lowering metabolic inflammation.



Obesity is linked to dysregulation of nutrition metabolism, insulin resistance, inflammation, and cancer [1,2]. Classical cellular pathways activated by various proinflammatory cytokines play key roles in the disease development. Suppression of c-Jun N-terminal protein kinases (JNK) phosphorylation alleviates inflammation-related symptoms, such as obesity and insulin resistance, and has shown the positive effects on tumorous and neurodegenerative diseases [3]. A central regulator of inflammatory cell function, receptor-interacting serine/threonine-protein kinase 1 (RIPK1), has been reported that it not only coordinates with inflammation, apoptosis and necroptosis in response to inflammatory stimuli but also genetically associates with obesity [4]. In addition, a recent study showed a high frequency of obesity among patients admitted in intensive care for SARS-CoV-2 [5]. One of the characteristics of obesity is the increased triglycerides and lipid droplet accumulation in viscera, which increases the risk of developing type 2 diabetes [6,7]. All these mentioned metabolic disorders are largely associated with a deranged cellular and serum metal ion homeostasis. Serum levels of free Fe are elevated in patients with diabetic ketoacidosis [8]. Insulin resistance is associated with an increase in intracellular $Ca^{2+}$ and a decrease in intracellular $Mg^{2+}$ [9,10]. In spontaneously and chemically induced diabetic animals, vanadium administration reverses insulin resistance and lowers blood glucose levels [11–13]. The antidiabetic activity of vanadium mainly comes from the inhibition of protein tyrosine phosphatase 1B (PTP1B) [11–14], a negative regulator of the insulin signaling pathways. PTP1B was also found to suppress LepRb signaling *in vivo* by directly dephosphorylating JAK2 at Tyr1007 and Tyr1008 [15], which is a potential mechanism contributing to leptin resistance in obesity. Nevertheless, pharmacotherapy of obesity has a checkered history. Certain drugs are recommended only for short-term uses due to their potential side effects [16]. Several other drugs or drug combinations were withdrawn shortly after regulatory approval because of various serious acute or chronic

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adverse effects [16–18]. Therefore, the application of vanadium compounds in targeting obesity-related proteins would be an effective strategy for pharmacological interventions in obesity.

Decavanadate, a member of the polyoxometalate (POM) family, has also shown the effectiveness on several enzymes and proteins [19,20], most of which could be ascribed to its high affinity to positively charged sites of proteins and the accompanied oxidation of thiol groups nearby. Inevitably, the highly negatively charged decavanadate ions will non-specifically bind to proteins in biological systems before functioning at a particular site. Unlike other POMs, the Lindqvist-type isopolyoxovanadate species $\{V_6O_{19}\}$ is structurally unstable due to its unusually high negative charge density [21]. In fact, hexavanadates could be isolated as alkoxo derivatives, in which some of the bridging oxygens in $\{V_6O_{19}\}$ cores are replaced by organic caps including alkoxy groups, such as tris(alkoxo) ligands. These polyoxovanadates (POVs) are good post-functionalization facilities for the design of covalently integrated organic-inorganic hybrid molecules [22,23], thereby modulating their physicochemical properties and expanding their applications in catalysis [24,25], materials science [26], and bioinorganic chemistry [23]. In a recent study, a new organic-inorganic hybrid POM compound was demonstrated its high stability in physiological buffers and remarkable antibacterial activity against *Staphylococcus aureus* and *Escherichia coli* [27]. In our previous studies, we have found that Lindqvist-type POVs covalently functionalized with myristic acids ($Na_2[V_6O_{13}\{(OCH_2)_3CCH_2OCO(CH_2)_{12}CH_3\}_2$, abbreviated as V6-C14) improve insulin sensitivity and remit insulin resistance in streptozotocin (STZ)-induced diabetic mice [23]. In therapeutic applications, the main transporter in blood for anionic vanadate species is transferrin [11,28]. Notably, reducing adipocyte iron through adipocyte-specific transferrin receptor 1 deficiency protects mice substantially from high-fat-diet (HFD)-induced metabolic disorders [29]. Considering the common biological milieu and interconnectivity between obesity and diabetes, in this study, the role of Lindqvist-type POVs (V6-C14) in the maintenance of systemic metabolism is investigated. Administration of V6-C14 lowers body weight and fat mass in HFD mice through a substantial reduction in visceral fat mass while improving insulin resistance and reducing adipose tissue inflammation, resulting in amelioration of metabolic disorders in mice.

We have previously investigated the insulin-sensitizing activity of POVs in an STZ-induced diabetic mouse model [23]. Visceral obesity is highly relevant with type 2 diabetes (T2D) with its signature evident in mesenteric adipose tissues. Besides, visceral obesity impairs glycaemic control and causes glucose intolerance that precedes overt T2D. To eliminate the potential driving factors that connect visceral adipose tissue accumulation to prediabetes, two POVs ($Na_2[V_6O_{13}\{(OCH_2)_3CCH_2OH\}_2]$, V6-OH, molecular weight 825.87 g/mol; $Na_2[V_6O_{13}\{(OCH_2)_3CCH_2OOC(CH_2)_{12}CH_3\}_2]$, V6-C14, molecular weight 1246.57 g/mol) were orally administrated 50 μg per day to the mouse model to reduce diet-induced obesity (18.50 μg V per mouse per day for V6-OH, 12.26 μg V per mouse per day for V6-C14). V6-OH and V6-C14 were synthesized according to the literature with minor modifications. The detailed structural confirmation of V6-C14 by ESI-MS, UV, and IR has been characterized (Fig. 1a, Figs. S1 and S2 in Supporting information). Due to the two-terminal hydrophobic chains, V6-C14 self-assembled in aqueous solutions into ~180 nm bilayer vesicles, which is similar with our previous work [30]. While the scattering intensity of V6-OH solution was as low as pure water, indicating no self-assembled nanostructures were formed in V6-OH solution. The formation of vesicles was demonstrated by CONTIN analysis based on dynamic light scattering (DLS) measurements and Static light scattering (SLS) analysis (Fig. 1b and Fig. S4 in Supporting information). TEM image of V6-C14 in aqueous solutions confirmed the vesicular structures (Fig. 1c).

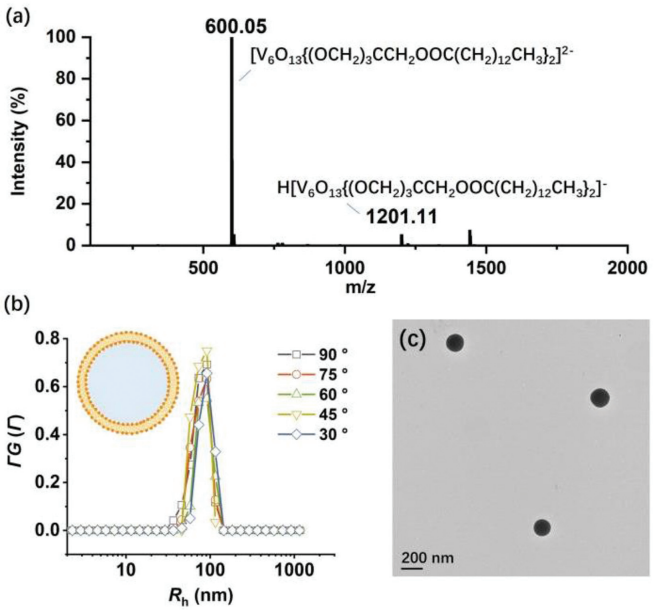


**Fig. 1.** (a) ESI-MS spectrum of V6-C14 in the negative mode showing the anions formed. (b) CONTIN analysis of the DLS data, showing that the $R_h$ of the vesicles formed by V6-C14 is about 91 nm with a narrow size distribution detected from 30° to 90°. (c) TEM images of vesicular structures self-assembled by V6-C14. Scale bar: 200 nm.

To determine whether POVs reduce diet-induced obesity, male C57BL/6 J mice of 4∼5 weeks old were fed with an HFD (60% kcal) for 12 weeks to induce obesity and orally received POVs daily during the next 8 weeks. The animal study protocol was approved by the Institutional Animal Care and Use Committee at South China University of Technology (SYXK2017-0178). POV administration gradually reduced whole body weight while keeping the HFD-feed (Figs. 2a-c). Although the POV-treated mice still looked larger than normal chow diet (NCD)-fed mice (Fig. 2d), the average body weight was 9% (V6-OH) or 15% (V6-C14) less than that 8 weeks before the POV treatment. That is 32.71 g *versus* 35.79 g in V6-OH-treated group, about 3.08 g in weight loss, and 30.56 g *versus* 36.10 g in V6-C14-treated group, about 5.54 g in weight loss. In addition, the fat mass of each POV-treated mouse was measured by nuclear magnetic resonance (NMR) and compared with NCD-fed mice. Mice fed with HFD presented with adipocyte hyperplasia and hypertrophy. The average mass loss of fat is 2.74 g and 4.69 g in V6-OH-treated group and V6-C14-treated group, respectively (Fig. 2c). In the POV-treated group, the mean fat mass decreased by approximately 31% in the V6-OH-treated group and 52% in the V6-C14-treated group. Reduction of fat mass accounts for more than 80% of the mass remarkably contributes to the mean weight loss. In the POV-treated mice, subcutaneous adipose tissues decreased 11% in the V6-OH-treated group and 29% in the V6-C14-treated group, and the visceral adipose tissues decreased 53% in the V6-OH-treated group and 73% in the V6-C14-treated group, which suggests the systemic fat reduction (Fig. S5 in Supporting information). These data indicate that POV treatment mainly reduces visceral fat. Furthermore, the average cell sizes of adipocytes were also decreased in the POV-treated groups (Figs. 2e and f, Fig. S6 in Supporting information), indicating that POV treatment could limit adipocyte hypertrophy in HFD-fed mice. Besides the reduction in body fat, no significant difference in appearance, behaviours, physical activity, or food consumption was observed in mice treated with POVs compared to the NCD-fed mice (Fig. 2d, Figs. S7 and S8 in Supporting information). These results prove that the decrease in body weight upon POV treatment is a result of a substantial

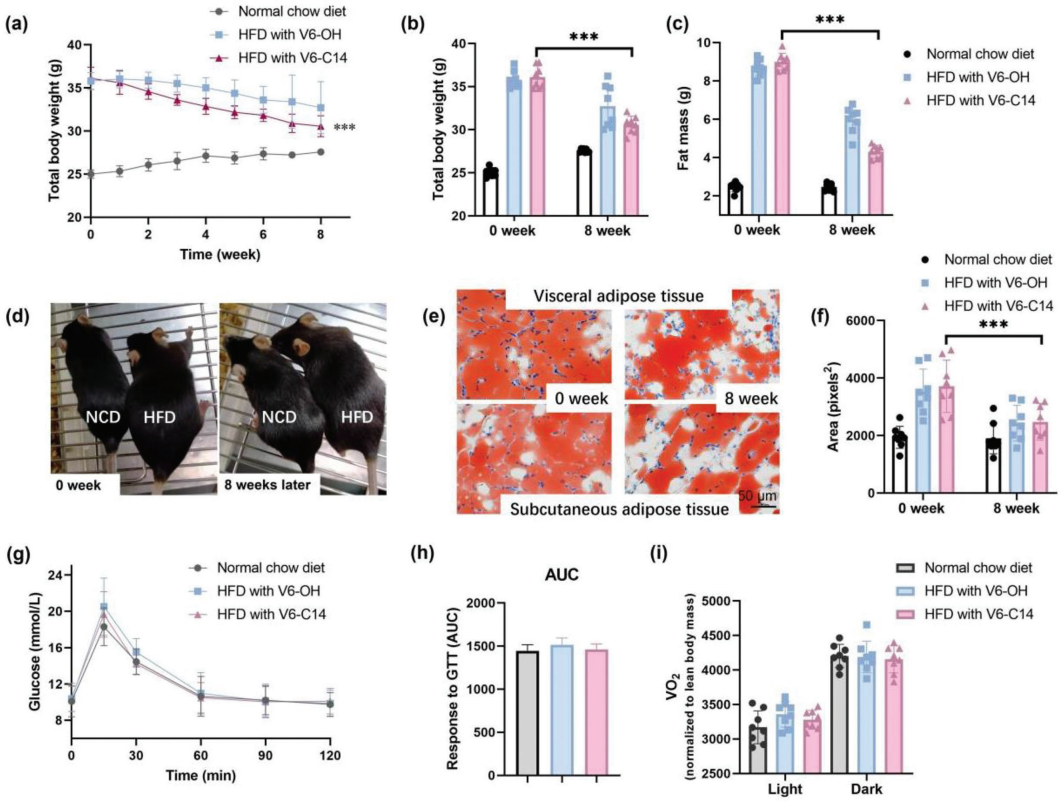


**Fig. 2.** (a) Total body weight variation of male C57BL/6J mice fed with high fat diet (HFD) or normal chow diet (NCD) monitored for 8 weeks. HFD-fed mice were daily administrated with 50 μg POVs (V6-OH and V6-C14) per mouse since the 13th week and lasted for 8 weeks. Histogram of total body weight (b) and fat mass (c) of HFD-fed mice administrated with POVs. (d) Photos of 17-week old mice (before V6-C14 treatment) and 25-week old mice (after V6-C14 treatment). NCD-fed mice were referred as control groups. (e) Images of oil red-stained inguinal white adipose tissues and subcutaneous adipose tissues of HFD-fed mice after administrated with V6-C14 for 8 weeks or before the treatment. Scale bar: 50 μm. (f) Statistical size of adipocytes of HFD-fed mice administrated with POVs or before treatment. (g) Fasting glucose tolerance test (GTT) after treating the HFD-fed mice with POVs for 8 weeks. (h) Area under curve (AUC) of GTT test. (i) $VO_2$ of mice recorded by caging them in the metabolic cages after administrated with POVs. Compared with the NCD-fed mice, no statistical significance among the three groups. Unless otherwise notified, $n = 8$ per group. Data shown of body weight and fat mean values ± s.d. Data of body weight changes are shown as individual replicates with means connected. Data were analysed using two-tailed Student's *t*-test or two-way ANOVA with Bonferroni *post hoc* test. $^{*}P < 0.05$; $^{**}P < 0.01$; $^{***}P < 0.001$; ns, not statistically significant.

reduction in body fat rate rather than the negative side impact of POVs.

Numerous studies have demonstrated a strong association between obesity and insulin resistance. To ensure the effectiveness of POVs in improving insulin resistance, HFD-fed mice underwent both glucose and insulin challenge. Obesity is a major risk factor for impaired glycaemic control. Mice exhibited prediabetic symptoms after being fed with HFD for more than 20 weeks, such as insulin resistance, glucose intolerance, elevated fasting, or postprandial blood glucose (Figs. 2g and h, Figs. S9 and S10 in Supporting information). In the fasting glucose tolerance test (GTT), the blood glucose of the tested mice peaked 15 min after intraperitoneal injection of 20 mg D-glucose and decreased in the period of latter two hours (Figs. 2g and h). While the blood glucose hit the bottom 30 min after intraperitoneal injection of 0.015 units of insulin and gradually climbed to the normal level in the following 2 h (Fig. S9 and S10). Compared with the NCD-fed group, similar insulin sensitivity and subsequent same glucose levels were detected in the POV-treated mice. These data, in agreement with previous studies [23], demonstrate that POV treatment reduces the fluctuation of blood glucose, promotes glucose homeostasis, and improves insulin resistance.

To further examine the effect of POVs on whole-body metabolic function, open-circuit indirect calorimetry, a non-invasive method for studying energy expenditure, was performed to measure oxygen consumption ($VO_2$) and correspondingly assess the overall metabolic rates of these mice. POV-treated mice showed little difference in $VO_2$ consumption and a slight decrease in respiratory exchange ratio in the V6-OH group compared to the NCD-fed mice (Fig. 2i and Fig. S11 in Supporting information). 8 weeks of treatment with POVs reduced the mice fat mass; however, it seems that POVs have no obvious effect directly on improving carbohydrate metabolism in mice. Despite a slight decrease in respiratory exchange ratio in the V6-OH group, its level is still within the normal range for these obese mice. Taken together, POV treatment reduces body weight and fat mass of HFD-fed mice by improving insulin resistance and promoting glucose homeostasis, but currently has no obvious effect on body metabolic function in C57BL/6J mice during the 8-week POV-treatment.

Non-resolving inflammation is a character of obesity associated adverse profile. Several inflammatory markers, including interleukin 6 (IL-6) and interferon-$\alpha$ (IFN$\alpha$), usually increased in obese people. To estimate the activity of POVs in reducing adipose tissue inflammation, an enzyme-linked immunosorbent assay (ELISA) was carried out to examine the level of inflammatory factors in mouse subcutaneous adipose tissues and epididymal adipose tissues. Analytical results of subcutaneous and epididymal adipose tissues revealed an elevated level of inflammatory factors in HFD-mice and a decrease of anti-inflammatory factors and immunoregulatory factors (Figs. 3a-h). In contrast, a substantial reduction of key inflammatory factors (IL-6 and IFN$\alpha$) in both subcutaneous and epididymal adipose tissues was observed (Figs. 3a-d), whereas interleukin-10 (IL-10), the key anti-inflammatory cytokine, were elevated when V6-C14 were admin-

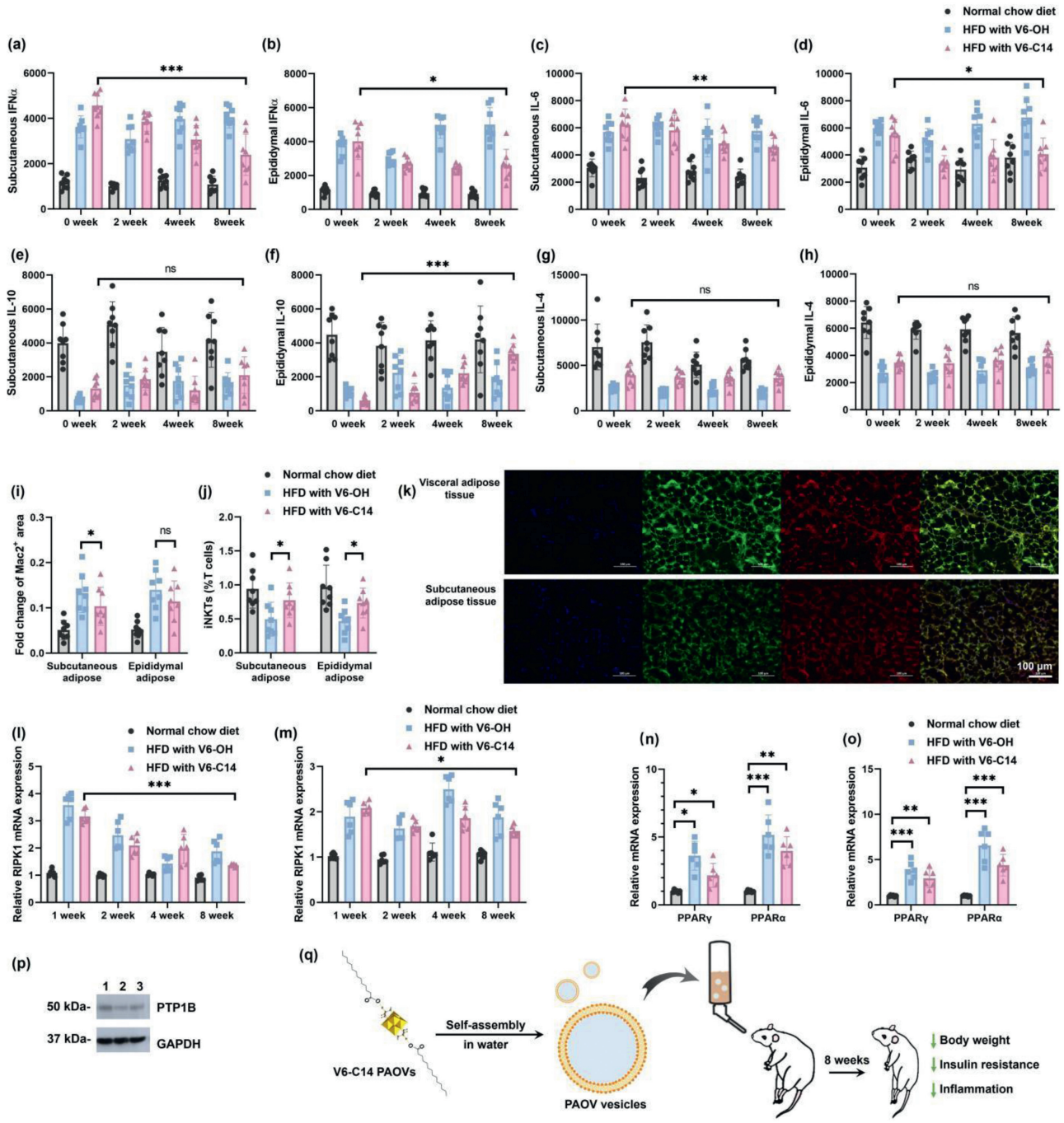


**Fig. 3.** mRNA expression of inflammatory factors in subcutaneous adipose tissues and epididymal adipose tissues: (a, b) IFN$\alpha$, (c, d) IL-6, (e, f) IL-10, and (g, h) IL-4, in NCD-fed mice after 8 weeks of POV treatment. (i) Quantification of $Mac2^+$ area on average of three sections per mouse. (j) iNKT percentage of T cells from adipose tissue of HFD-induced obese mice after administration of POVs. NCD-fed mice were referred to as control groups. (k) Images of double immunofluorescence-stained subcutaneous and epididymal adipose tissues of HFD-fed mice administrated with V6-C14 (iNKT makers: Cd1d and NK1.1). *RIPK1* mRNA expression in (l) subcutaneous adipose tissues and (m) epididymal adipose tissues from HFD-induced obese mice after 8-week POV-treatment ($n = 6$). Expression level of mRNA genes of PPAR$\alpha$ and PPAR$\gamma$ in (n) subcutaneous adipose tissues and (o) epididymal adipose tissues from HFD-induced obese mice after 8-week POV-treatment ($n = 6$). (p) PTP1B inhibition activity of POVs determined by *in vivo* assays. Glyceraldehyde phosphate dehydrogenase (GAPDH) gene as the loading control. (q) Schematic representation of the protective activity of polyalkoxyvanadate POV clusters for reducing obesity in mice. Unless otherwise notified, $n = 8$ per group. Data shown are the mean values ± s.d. Each data was based on three measurements from one individual mouse with 3 mice per experiment. Data were analysed using two-tailed Student's *t*-test or two-way ANOVA with Bonferroni *post hoc* test. $^*P < 0.05$; $^{**}P < 0.01$; $^{***}P < 0.001$; ns, not statistically significant.

istrated to the HFD-mice (Figs. 3e and f). Interleukin 4 (IL-4) is an STAT-6 signaling-dependent glycoprotein. It is a multifunctional cytokine that is active in the suppression or blockage of the monocyte-derived cytokines, including IL-6 and IFN-$\alpha$. IL-4 in HFD-mice was significantly lower than NCD-mice, and the administration of POVs showed no noticeable activities to restore IL-4 levels (Figs. 3g and h). Meanwhile, in HFD-mice, treatment of V6-OH further not only showed negligible effect on the other three inflammatory markers, but also aggravated the IL-4 deficiency. Taken together, V6-C14 treatment demonstrated a certain competency in reducing subcutaneous and epididymal adipose tissue inflammation, suggesting that the decrease in adipose tissue inflammation by V6-C14 treatment is not site-selective but a systemic impact.

Accumulation of lymphocytes in adipocyte tissue is the key to maintaining tissue immune homeostasis. Lipid staining by oil red O staining in epididymal adipose tissues and subcutaneous adipose tissues demonstrated that both adipocytes dwindled in size (Fig. 2e and Fig. S6), which was accompanied by a reduction in macrophage accumulation in V6-C14-treated mice (Fig. 3i). In addition, the administration of V6-C14 augments invariant natural killer T (iNKT) cells in HFD-induced obese mice (Figs. 3j and k, Fig. S12 in Supporting information). Adipose tissue iNKT cells are tissue-resident T cells that induce an anti-inflammatory phenotype in macrophages and control the number, proliferation, and suppressor function of regulatory T cells (Treg cells) in adipose tissues. Hence, iNKT cells are unique regulators of immunological homeostasis in adipose tissues [31]. By using the iNKT cell marker CD1d and NK1.1 stained by immunofluorescence, iNKT cells were determined by the immunofluorescence method. Compared to V6-OH, an increase in adipose tissue iNKT cells after V6-C14 treatment was observed. Coupled with that iNKT cells have been reported to induce IL-10 production by other cells or to produce IL-10 themselves [32], these results indicate that V6-C14 helps maintain the anti-inflammatory population of iNKT cells and the production of IL-10. Anti-inflammatory adipose-resident lymphocytes are often depleted in obese adipose tissues. To maintain an anti-inflammatory state, resident iNKT cells in adipose tissues recognize lipid antigens presented by CD1d to promote IL-10 and IL-4 production [33]. Conversely, fat-resident macrophages mediate systemic inflammation and insulin resistance in obese mice in a diet-regulated manner [34,35]. An alleviation of adipose tissue inflammation was reinforced by the reduction in macrophage accumulation and the augment of anti-inflammatory iNKT cells in adipose tissues of V6-C14-treated mice. At the same time, the effect of V6-OH treatments is not obvious, even negative to the adipose tissue inflammation in some cases (Fig. 3 and Fig. S12). Together, one of the possible reasons that the administration of V6-C14 reduces diet-induced obesity is by alleviating systemic adipose tissue inflammation in HFD-fed mice.

RIPK1 plays a central role in driving inflammation by regulating inflammatory cell function and is genetically associated with obesity in mice [4]. To find whether POVs could inhibit the activity of RIPK1, *in vitro* cell-based viability assays were implemented to evaluate the effect of POVs on RIPK1 inhibition. Meanwhile, expression of RIPK1 in subcutaneous and epididymal adipose tissues of mice was also measured by reverse transcription qPCR. After 8-week treatment, the relative expression of RIPK1 mRNA in both adipose tissues of HFD-mice was decreased significantly by V6-C14 (Figs. 3l and m). V6-OH also lowered the RIPK1 expression in subcutaneous adipose tissues; however, no detectable impact was observed in epididymal adipose tissues. Even worse, RIPK1 expression during the last four weeks was higher than that in the first four weeks in V6-OH-treated group, which agrees with the results of ELISA assays. It could be reasonable that RIPK1 is a class of metalloenzymes that is not one of the reported targets of vanadium-containing compounds. The long-chain aliphatic acid modification onto the POV skeleton endows POVs with the unexpected capacity to modulate immune homeostasis.

An attractive target for the treatment of both diabetes and obesity is a protein kinase, tyrosine-phosphate protein (PTPase) PTP1B, a sister phosphatase of RIPK1 that has an active site with a key cysteine residue. PTP1B has been demonstrated a target of vanadium. Vanadium compounds inhibit PTPases by the oxidization of this cysteine residue and the formation of free radicals [11–13]. In our previous report, the insulin-sensitizing activities of POVs were confirmed, and the role of POVs in enhancing cells' response to insulin was tried to interpret by *in vitro* assays [23]. The antidiabetic activity of vanadium possibly comes from the similarity between vanadate and phosphate. Although vanadate is slightly larger than phosphate, from a geometrical point of view, they are indistinguishable, making vanadate a formidable competitor for phosphate in the active site of a phosphate-dependent enzyme, such as PTPase PTP1B. The inhibition of PTP1B is also a possible anti-inflammatory therapy in obesity by enhancing the anti-inflammatory response through changing the JAK-STAT signaling and thereby altering the IL-10 transcriptional program [36]. Perhaps because of that, this anti-inflammatory response will be converted into a proinflammatory response if the inhibition is too efficient or prolonged [37]. Encouragingly, all the POVs presented a moderate inhibition effect on PTP1B (Fig. 3p), which is coincident with literature reports. These data illustrate that POVs are capable of alleviating the relative strengths of the inflammatory responses by modulating PTP1B activities.

Another group of nuclear hormone receptors, known as peroxisome proliferator-activated receptors (PPARs), have attracted escalating research interest in treating obesity. PPARs are expressed in many tissues, including adipocytes, hepatocytes, muscles, and endothelial cells [38]. PPARs, in particular those of PPAR$\alpha$ and PPAR$\gamma$, inhibit the activation of inflammatory gene expression and can negatively interfere with proinflammatory transcription factor signaling pathways in inflammatory cells [39]. Vanadium compounds are promising agents that can modulate PPAR$\gamma$ activity primarily by increasing PPAR$\gamma$ protein levels in mouse insulinoma NIT-1 cells [40]. Vanadyl acetylacetonate, $VO(acac)_2$, upregulates PPAR$\gamma$ and adiponectin expression in differentiated rat adipocytes [41]. Activation of PPAR$\gamma$ mediates protection from experimental inflammatory bowel disease. Different from simple vanadium complexes, POVs are a class of sub-nanosized clusters (~0.8 nm in diameter) with distinct physiological characteristics. To investigate the role of POVs in interaction with PPARs, the expression level of PPARs was determined by qPCR. Of note, gene expression of PPAR$\alpha$ and PPAR$\gamma$ was increased in adipose tissues of the POV-treated mice [31], especially in the V6-OH-treated mice (Figs. 3n and o), but no noticeable changes are observed in liver tissue. It has been reported that vanadyl complexes have the capability of causing significant elevation of PPAR$\gamma$ and a slight increase of PPAR$\alpha$ that is analysed by western blot [42]. In comparison, the changes of PPAR$\gamma$ expression in adipose tissues caused by POVs are less distinct than that by vanadyl complexes [31]. This may be attributed to the sized effect of sub-nanosized POV clusters and their nanosized assemblies (Fig. 1) that changes their distribution and pharmacokinetics in mice [23]. Together, these data indicate that long-chain aliphatic acid-modified POVs adjust the adipose tissue inflammatory by decreasing the activation of multiple inflammatory pathways in the adipose tissues of obese mice (Fig. 3q) [31], and clearly, additional mechanisms of action that can match the performance of POVs would be expected to be explored in future research.

In conclusion, administration of long-chain aliphatic acid-modified POVs for 8 weeks significantly reduces body weight and especially reduces adipose tissue accumulation and inflammation, both of which are known to contribute to obesity and its complicating disease. In this respect, we have made a preliminary exploration of the potential role of POVs that functionalizes as anti-obesity agents. However, we did not identify a distinct molecular mechanism that directly explains the POV-adopted paths, and therefore the deep mechanism and long-term clinical trials are needed to be explored in further research. Obesity is characterized by pathophysiologic adipose tissue expansion and systemic inflammation. The inflammation occurring particularly in the visceral adipose depots increases the risk of developing many obesity-associated comorbidities. Treatment of long-chain aliphatic acid-modified POVs improves local inflammatory by dampening multiple inflammatory paths in adipose tissues, which may be utilized in the remission of obesity-associated

complications and the regulation of other metabolic dysfunction diseases.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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## Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.cclet.2022.06.061.

## References

[1] A. Afshin, M.H. Forouzanfar, et al., G.B.D.O. Collaborators, N. Engl. J. Med. 377 (2017) 13–27.
[2] M. Blüher, Nat. Rev. Endocrinol. 15 (2019) 288–298.
[3] Q.X. Zeng, W. Wei, T.Y. Fan, et al., CCS Chem. 3 (2021) 1954–1963.
[4] D. Karunakaran, A.W. Turner, A.C. Duchez, et al., Nat. Metab. 2 (2020) 1113–1125.
[5] A. Simonnet, M. Chetboun, J. Poissy, et al., Obesity 28 (2020) 1195–1199.
[6] S.B. Heymsfield, T.A. Wadden, New Engl. J. Med. 376 (2017) 254–266.
[7] M. Blüher, Endocr. Rev. 41 (2020) bnaa004.
[8] W.M. Artis, J.A. Fountain, H.K. Delcher, H.E. Jones, Diabetes 31 (1982) 1109–1114.
[9] E. Vergari, J.G. Knudsen, R. Ramracheya, et al., Nat. Commun. 10 (2019) 139.
[10] B.C. Kieboom, S. Ligthart, A. Dehghan, et al., Diabetologia 60 (2017) 843–853.
[11] J.C. Pessoa, S. Etcheverry, D. Gambino, Coord. Chem. Rev. 301 (2015) 24–48.
[12] M. Aureliano, N.I. Gumerova, G. Sciortino, et al., Coord. Chem. Rev. 447 (2021) 214143.
[13] S. Treviño, A. Díaz, E. Sánchez-Lara, et al., Biol. Trace Elem. Res. 188 (2019) 68–98.
[14] E. Irving, A.W. Stoker, Molecules 22 (2017) 2269.
[15] H. Cui, M. López, K. Rahmouni, Nat. Rev. Endocrinol. 13 (2017) 338–351.
[16] T.D. Müller, M. Blüher, M.H. Tschöp, R.D. DiMarchi, Nat. Rev. Drug. Discov. 21 (2022) 201–223.
[17] T.D. Müller, C. Clemmensen, B. Finan, R.D. DiMarchi, M.H. Tschöp, Pharmacol. Rev. 70 (2018) 712–746.
[18] D. Rubino, N. Abrahamsson, M. Davies, et al., J. A. M. A. 325 (2021) 1414–1425.
[19] M. Aureliano, C.A. Ohlin, J. Inorg. Biochem. 137 (2014) 123–130.
[20] A. Bijelic, M. Aureliano, A. Rompel, Angew. Chem. Int. Ed. 58 (2019) 2980–2999.
[21] M.T. Pope, Y. Jeannin, M. Fournier, Heteropoly and Isopoly Oxometalates, Springer-Verlag, Berlin, 1983.
[22] A.V. Anyushin, T.N.Parac-Vogt A.Kondinski, Chem. Soc. Rev. 49 (2020) 382–432.
[23] K. Chen, H. Jia, Y. Liu, P. Yin, Y. Wei, Adv. Biosys. 4 (2020) 1900281.
[24] J.K. Li, J. Dong, C.P. Wei, et al., Inorg. Chem. 56 (2017) 5748–5756.
[25] P. Yin, A. Bayaguud, P. Cheng, et al., Chem. Eur. J. 20 (2014) 9589–9595.
[26] J. Zhang, Y. Huang, G. Li, Y. Wei, Coord. Chem. Rev. 378 (2019) 395–414.
[27] M. Zhao, X.Y. Zhu, Y.Z. Li, et al., Tungsten 4 (2022) 121–129.
[28] A. Gorzsás, I. Andersson, L. Pettersson, Eur. J. Inorg. Chem. 2006 (2006) 3559–3565.
[29] Z. Zhang, J.B. Funcke, Z. Zi, et al., Cell Metab. 33 (2021) 1624–1639.
[30] K. Chen, A. Bayaguud, H. Li, et al., Nano Res. 11 (2018) 1313–1321.
[31] L. Lynch, X. Michelet, S. Zhang, et al., Nat. Immunol. 16 (2015) 85–95.
[32] D. Sag, P. Krause, C.C. Hedrick, M. Kronenberg, G. Wingender, J. Clin. Invest. 124 (2014) 3725–3740.
[33] L. Lynch, Immunology 142 (2014) 337–346.
[34] N. Cox, L. Crozet, I.R. Holtman, et al., Science 373 (2021) eabe9383.
[35] Y. Song, Y. Huang, F. Zhou, J. Ding, W. Zhou, Chin. Chem. Lett. 33 (2022) 597–612.
[36] L. Grant, K.D. Shearer, A. Czopek, et al., Diabetes 63 (2014) 456–470.
[37] K.A. Pike, A.P. Hutchins, V. Vinette, et al., Sci. Signal. 7 (2014) ra43.
[38] B. Grygiel-Górniak, Nutr. J. 13 (2014) 17.
[39] L.A. Moraes, L. Piqueras, D. Bishop-Bailey, Pharmacol. Ther. 110 (2006) 371–385.
[40] P. Zhao, X. Yang, Metallomics 5 (2013) 836–843.
[41] Y. Wu, M. Huang, P. Zhao, X. Yang, J. Biol. Inorg. Chem. 18 (2013) 623–631.
[42] J. Bassaganya-Riera, K. Reynolds, S. Martino-Catt, et al., Gastroenterology 127 (2004) 777–791.