JOTCSA
Journal of the Turkish Chemical Society
Section: A
Chemistry

TURKISH
CHEMICAL SOCIETY

Ameliorative Effects of Vanadyl Sulfate on Some Biochemical Parameters of Experimental Diabetic Rat Kidneys

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Abstract: Diabetes mellitus (DM), closely related to diabetic nephropathy, is one of the major public health problems worldwide. Today, with the increasing understanding of the underlying pathophysiology of DM, new oral anti-diabetic treatment strategies are being developed. Vanadium is a transition element that is widely distributed in nature, and its oral administration has been reported to improve DM in humans and a variety of diabetic animal models. The purpose of the research is to explore the effect of vanadyl sulfate (VS) administration on the different enzyme activities associated with kidney injury in streptozotocin-(STZ) induced diabetic rats. Male rats were assigned into groups as follows: untreated control, control animals given VS (100 mg/kg), diabetic (a single dose of intraperitoneal STZ, 65 mg/kg), and diabetic + VS (same dose) group. VS was administered orally for 60 days after the induction of diabetes. On the 60th day of experiment, kidney samples were taken for analysis. According to the data obtained from the biochemical analysis, the activities of transaminases, alkaline phosphatase, carbonic anhydrase, and γ-glutamyl transpeptidase decreased, whereas superoxide dismutase activity elevated in the kidney tissue of VS treated hyperglycemic animals. The results suggested that VS improved the diabetic renal injury, probably by VS insulin-mimic and antioxidant behavior through decreased oxidative stress and increased antioxidant capacity. Therefore, vanadyl sulfate might be used as a potential oral anti-diabetic compound in the treatment of the diabetic nephropathy, and as an important control for elevated blood glucose levels in the diabetic state.

Keywords: Diabetes mellitus, vanadyl sulfate, kidney tissue, oxidative stress.

Submitted: February 11, 2021. **Accepted:** April 11, 2022.

Cite this: Orhan N, Tunali S, Yanardag R. Ameliorative Effects of Vanadyl Sulfate on Some Biochemical Parameters of Experimental Diabetic Rat Kidneys. JOTCSA. 2022;9(3):721–8.

DOI: https://doi.org/10.18596/jotcsa.1071151.

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INTRODUCTION

Diabetes mellitus (DM) is a metabolic disease defined by unusual insulin secretion disorder, insulin deficiency, and hyperglycemia. Dysfunction in various tissues such as the kidney and liver can be counted among the secondary complications caused by DM (1). Renal failure, the important long-term complications of DM worldwide, is the result of kidney disease caused by hyperglycemia. Most of patients with both type 1 and 2 DM develop chronic kidney disease characterized by clinically damaged renal functions or increased albumin excretion with urine (2).

Oxidative stress plays a pivotal role in the pathogenesis and progression of diabetes (3). Increased oxidative stress, inflammation, and abnormal growth factors all qualify as mediators of tissue damage. High intracellular glucose levels are closely associated with the formation of advanced glycation end products (AGEs), which cause dysfunction and stimulation of expression of some transcription factors that are the major contributors to the development of diabetic kidney disease (2,4).

In the last three decades, streptozotocin (STZ) has been widely applied to many animal species in the

inducement of experimental diabetic models and, accordingly, in the screening and development of various anti-diabetic compounds. STZ causes necrosis of pancreatic beta cells, reducing insulin secretion and inducing clinical features of diabetes similar to those in humans. For this reason, STZ-induced diabetic models are used both to examine the mechanisms of various anti-diabetic agents and to understand their effects on hyperglycemia (5).

Since 1980s, vanadium and its different compounds have been evaluated as potential anti-diabetic compounds in type 1 and type 2 DM (6). Some compounds of vanadium have demonstrated interesting effects in lowering blood glucose levels and improving many biochemical parameters in various diabetic tissues (7-10).

Vanadium, either in its vanadate $[VO_4]^{3-}$ or vanadyl $[VO]^{2+}$ forms, has received great interest because of its possible therapeutic value as an insulin-mimic agent, as insulin is not orally active against diabetes (11). It is known that different vanadyl compounds or their synthesized new complexes exhibit insulin-mimic properties, which means they are involved in the regulation of glucose homeostasis (12).

Previous studies of our research team have demonstrated that both VS and its new synthesized oxovanadyl complex have potential effects on the treatment of DM and recovery in the different tissues on the biochemical and histopathological levels (7,8,13-15). On the other hand, the fact that we obtained remarkable data in kidney tissue in our previous research forced us to examine the effect of VS on different biochemical parameters of the same tissue (16).

EXPERIMENTAL SECTION

Animals, Induction of Diabetes, and Administration of Vanadyl Sulfate

All care and handling of animals were performed with the approval of Animal Care and Use Institute's Committee of Istanbul University. Male, 6-6.5-month-old, Swiss albino rats weighing between 230 g and 250 g were used. The animals were completely healthy and fed with commercial standard pellets. The rats were randomly divided as follows: Group I: untreated control (n=13); group II: control animals given VS (100 mg/kg; n=5); group III: STZ-diabetic (a single dose of intraperitoneal STZ, 65 mg/kg; n=8); group IV: (STZ)-diabetic animals given VS (same dose; n=9). Diabetes was induced in the two diabetic groups with only one dose of 65 mg STZ in citric acid buffer (pH=4.5; 0.01 M) solution per 1 kg of body mass (17). At 24 hours subsequent to the injections, the weight and level of glucose were measured and the animals with glucose levels above 200 mg/dL were accepted as diabetic and used for the study. Briefly, after assessment of 1^{st} day fasting blood glucose, the rats were administered with VS in a dose of 100 mg/kg/day *via* intragastric gavage for 60 days. Throughout the experimental period, body weights and blood glucose levels were monitored at 0^{th}, 1^{st}, 30^{th}, and 60^{th} days (13). In all samples, blood was collected through the tail vein of the rats, and the 18-h-fasting blood glucose levels were determined by o-toluidine method (18). At the end of experiment day, animals were sacrificed and kidney tissues were directly inserted into plastic tubes containing ice-cold physiological saline and kept frozen at −80 °C until the time of analysis.

Biochemical Assays of Kidney Tissue

Cold saline solution (0.9%) was used for preparation of 10% (w/v) kidney homogenates, which were centrifuged before determination of the activities of kidney enzymes and protein analysis.

Transaminase activities (AST and ALT) were determined by Reitman-Frankel method (19). For the clear kidney homogenates, AST and ALT activities were performed using buffered solutions. The quantities of formed oxaloacetate and pyruvate were measured spectrophotometrically at 490 nm.

Alkaline phosphatase (ALP) activity was estimated by Walter and Schüt's two-points method (20). The dense yellow color obtained under alkaline conditions was measured at 405 nm.

Kidney γ-glutamyl transpeptidase (GGT) activity was determined by Szasz (21). The absorbance of formed nitroaniline as a result of the reaction was measured at 405 nm.

Carbonic anhydrase (CA) activity was assayed according to the method described by Verpoorte et al (22). The absorbance changes obtained of 3 min period at 25 °C were monitored at 348 nm.

The activity of superoxide dismutase (SOD) was estimated according to Mylroie et al., and measurements of kidney total protein levels were performed according to the method of Lowry (23,24).

Statistical Analysis

Results were evaluated using an unpaired t test and analysis of variance (ANOVA) using the NCSS statistical computer package. The values were expressed as mean ± SD. $p < 0.05$ was considered as significant.

RESULTS

This part of the results regarding body weight and fasting blood glucose levels in the current animal study has already been published previously (13,16). The loss seen in the body weight of the diabetic animals was prevented by VS administration in the days of 1^{st}, 30^{th} and 60^{th} days (P_{ANOVA} = 0.011, P_{ANOVA} = 0.0001, P_{ANOVA} = 0.0001, respectively) (Table 1). Blood glucose levels that

were increased by STZ administration were diminished by VS treatment. Accordingly, significance was also observed between groups in the blood glucose levels for 1st, 30th, and 60th days (P_{ANOVA}=0.0001, P_{ANOVA}=0.0001, P_{ANOVA}=0.0001, respectively) (Table 2) (13).

Table 1: Mean levels of weight parameters (g) for all groups (13).

Groups	0 Day*	1 Day*	30 Day*	60 Day*	$P_{t\text{-test}}$
Control	246.64±44.43	243.35±39.50	275.51±34.40	283.48±30.35	0.016
Control + VS	224.14±16.13	221.03±12.58	253.14±14.06	251.91±20.41	0.007
Diabetic	231.67±37.71	197.02±37.47	175.74±38.48	171.70±34.67	0.002
Diabetic + VS	229.65±32.14	203.93±30.57	197.46±34.40	199.16±36.2	0.101

*Mean± SD
SD: standard deviation; P_{ANOVA}:analysis of variance; $P_{t\text{-test}}$: unpaired t test; VS: vanadyl sulfate.

Table 2: Mean levels of blood glucose for all groups (mg%) (13).

Groups	0 Day*	1 Day*	30 Day*	60 Day*	$P_{t\text{-test}}$
Control	74.52±14.69	78.19±12.74	80.92±13.31	69.05±9.15	0.107
Control + VS	72.92±9.40	85.05±19.30	76.06±16.19	86.40±11.03	0.401
Diabetic	65.52±5.76	211.75±43.12	216.71±36.61	323.39±131.29	0.0001
Diabetic + VS	71.88±13.78	253.93±38.62	135.76±46.16	131.68±72.30	0.0001
P_{ANOVA}	0.324	0.0001	0.0001	0.0001	

*Mean± SD
SD: standard deviation; P_{ANOVA}:analysis of variance; $P_{t\text{-test}}$: unpaired t test; VS: vanadyl sulfate.

Significant increases in kidney tissue transaminase (AST and ALT) activities were observed in STZ-diabetic rats as compared to control animals (p<0.005). VS application caused a remarkable decrease in the activities of both transaminases (p<0.005) in comparison to diabetic rats (Table 3). Similar results were observed in the ALP activities. There was a significant increment in the diabetic group ALP activity as compared to non treated healthy animals (p<0.005). In fact, VS administration significantly reversed this increase compared to kidney tissue of hyperglycemic animals (p<0.005) (Table 3).

Table 3: Effect of VS on the kidney tissue AST, ALT and ALP activities in control and experimental groups.

Groups	AST(mU/mg protein)*	ALT(mU/mg protein)*	ALP(mU/mg protein)*
Control	15.68 ± 1.75	18.24 ± 4.19	122.43 ± 32.70
Control + VS	12.00 ± 5.20	14.30 ± 1.92	100.76 ± 28.45
Diabetic	22.91± 4.49[a]	28.28 ± 13.33[a]	237.82 ± 56.47[a]
Diabetic + VS	12.50 ± 5.20[b]	15.83 ± 5.47[b]	118.09 ± 46.46[b]
P_{ANOVA}	0.002	0.0001	0.001

*Mean ± SD
[a]p<0.005 versus to control group
[b]p<0.005 versus to diabetic group
SD: standard deviation; P_{ANOVA}:analysis of variance; VS: vanadyl sulfate; AST: aspartate aminotransferase; ALT: alanine aminotransferase; ALP: alkaline phosphatase.

Table 4 presents the GGT, CA, and SOD activities for all groups. The activity of GGT, the marker enzyme of enhanced oxidative stress, was significantly elevated in STZ diabetic renal tissue as compared to untreated control group (p<0.05). VS application lowered this activity in a significant manner in comparison to diabetic rats (p<0.0001). Consistent with these data, elevated CA activity in the diabetic kidneys when compared to controls (p<0.005) was also seen. In addition, vanadium significantly reduced the kidney CA activities in the diabetic animals in comparison to non treated hyperglycemic animals (p<0.0001). On the contrary, it was observed that the activity of SOD was decreased meaningfully in the renal tissue of hyperglycemic animals (p<0.05) whereas this value was insignificantly increased in the hyperglycemic group treated with VS (Table 4).

Table 4: Effect of VS on the kidney GGT, CA and SOD activities in control and experimental groups.

Groups	GGT(mU/mg protein)*	CA(U/mg protein) *	SOD(U/mg protein) *
Control	48.63±11.67	6.63±0.32	24.26±3.91
Control + VS	52.66±28.09	4.96±0.44	16.53±2.63
Diabetic	76.90±10.73[a]	10.23±1.30[c]	15.87±1.57[a]
Diabetic + VS	40.60±6.23[b]	5.94±0.80[b]	18.29±1.87
P_{ANOVA}	0.020	0.0001	0.021

*Mean ± SD
[a]p<0.05 versus to control group
[b]p<0.0001 versus to diabetic group
[c]p<0.005 versus to control group
SD: standard deviation; P_{ANOVA}:analysis of variance; VS: vanadyl sulfate; GGT: γ-glutamyl transpeptidase; CA: carbonic anhydrase; SOD: superoxide dismutase.

DISCUSSION

Kidney diseases, one of the most notable problems in DM, are also the main cause of renal failure (2). Loss of function in the kidneys, changes the body's homeostasis excessively, which can result in death from kidney failure (25). Although the liver is the main organ where gluconeogenesis takes place, the studies demonstrated that the production of glucose under diabetic conditions in the renal tissue is ranged about 25% and increased to 50% during prolonged starvation or DM (26). This suggests that renal gluconeogenesis is of physiological importance for maintaining blood glucose concentration at a certain level (27).

Vanadium is involved in many mechanisms with its insulin-enhancing activity on diabetes, and the most widely accepted of them is the inhibition of tyrosine phosphatase, an enzyme acting on insulin receptors (28). According to the studies, the anti-diabetic effect of vanadium is verified by the diversity of vanadyl compounds and its different oxidation states (29,30). Kiertszan et al. reported that vanadium inhibits gluconeogenesis more strongly in kidney tissue than in the liver (27). In the same work, it was demonstrated that vanadyl acetylacetonate - an organically chelated vanadyl compound - reduced gluconeogenesis in renal cortex tubules by inhibition of pyruvate carboxylase (PC), phosphoenol-pyruvate carboxykinase (PEPCK), and also decreased the activity of fructose-1,6-bisphosphatase (FBP) (27). The first reason for the differences in the effects of the same compound on glucose synthesis metabolism in the liver and kidney, may be caused by the differences between isosymes of regulatory enzymes in the gluconeogenic pathway, such as FBP, a main enzyme in this process, which is unaffected by ribose-1,5-bisphosphate in rabbit liver but is inhibited in rat kidney cortex (31, 32). The second point of inhibition of FBP activity in isolated hepatocytes could also be clarified by the vanadyl-induced elevated level of fructose-2,6-bisphosphate (33). In general, the reason why vanadium is more effective on the kidney gluconeogenesis than the hepatic one is may be due to the high accumulation of vanadium in the kidney cortex in comparison to hepatic tissue (27).

In our previous research, we observed that hyperglycemia caused loss of renal function in diabetic rats, which was closely related to the decreased GSH level, the formation of non enzymatic glycolization (NEG), and increased serum creatinine and urea concentrations. Treatment with VS resulted in an increase in body weight, a decrease in blood glucose concentration, and both biochemical and histological improvement in diabetic damaged kidney tissue (16). These effects may be associated with insulin-mimic behavior of vanadyl compounds. Obtaining remarkable data in this sense, made us wonder about the influence of VS on other biochemical parameters such as transaminases, ALP, GGT, CA, and SOD in diabetic kidney tissue.

AST and ALT are the transferases that are involved in the transport of amino groups from one specific amino acid to another alpha keto acid (34). Instead of AST and ALT being the markers of hepatic injury, both transaminases are also mainly expressed in a variety of tissues, including kidney, skeletal and cardiac muscles (8,10,35). Feilleux-Duche et al. demonstrated in their research that AST is expressed too much in the renal cortex, and is regulated by glucocorticoids in an extremely cell-specific manner (36). Under stress conditions (both somatic and psychological), the glucocorticoid hormone synthesis is increased significantly in the adrenal cortex. According to the same research, the reason for the high AST activity in the kidneys is an indication of the high physiological stress exposure of the animals. This suggests that the renal AST levels might serve as a sensitive marker for evaluating the induced stress (35). In our previous research, based on the effect of VS on the liver tissue, we observed increased serum AST and ALT

activities as well as degenerative changes in diabetic liver detected by light and electron microscopes (10). In support of this findings, in the current research, we also observed the elevation of both transaminases activities that significantly increased in diabetic rats in comparison to non treated animals kidney tissues. Administration of VS lowered the activities of AST and ALT meaningfully in comparison to the diabetic animals.

ALP is a membrane-bound glycoprotein hydrolase capable of transferring phosphate groups from molecules such as nucleotides and proteins. Most effectively operating in an alkaline environment, ALP stimulates mineralization mainly by balancing the levels of inorganic phosphate and inorganic pyrophosphate. In patients with chronic kidney disease, ALP is a well-recognized biomarker of renal osteodystrophy and a risk factor for increased mortality (37). Therefore, ALPs are important for bone mineralization, but increment of their levels can also be deleterious for other processes, such as vascular calcification. In our research administration with vanadyl, the evident decrement of ALP activity in diabetic rats' renal tissue in comparison to non treated diabetic animals was observed. Another enzyme widely found in tissues with secretory activity, such as the proximal tubular cells in kidneys is GGT (38). This enzyme plays the essential role in the glutathione metabolism (GSH) by catalyzing its degradation into glutamyl and glutamate amino acids (39). It has been previously reported that the highest GGT activity in kidneys is detected on the outer surface of the microvillus membrane in the renal proximal tubule (40). The activation of GGT in the proximal tubule may enhance oxidative stress, leading to kidney damage (38). In this study, we examined the higher GGT activity in diabetic kidney tissue in comparison to non treated animals' renal tissue. In our previous research, we detected a decreased GSH level in the renal tissue of non treated diabetic animals (16). Since GGT is an enzyme responsible for the breakdown of GSH after glomerular infiltration, an increment in its activity in the kidney tissue of diabetic animals is expected (41). Application of oral vanadyl decreased the level of kidney's GGT activity in the hyperglycemic rats via vanadyls' antioxidant behavior during the oxidant and pro-oxidant diabetic conditions in the kidney tissue.

CA is a cytosolic enzyme that is responsible for the inter-conversion of CO_2 to HCO_3^- in many tissues of higher vertebrates. It is related to some processes such as gas swapping, ion carriage, and pH control (42). In metabolic diseases like DM and hypertension, the activity of CA is variable (43). It was reported that changed activity in erythrocyte CA can count as early evidence of altered DM metabolism (43). Similarly, in another study, it was noted that CA activity elevated twofold in the hyperglycemic liver due to its important function in providing substrate for hepatic gluconeogenesis and ureagenesis (44). Consistent with previous research on different tissues, we also found a higher activity in diabetic kidney CA (9,10,15). The oral administration of vanadyl supplement reduced the activity of the enzyme in diabetic animals.

SOD is one of the most essential endogenous enzymes in the living organisms' antioxidant system, which scavenges the superoxide radicals by converting them into H_2O_2 and molecular oxygen. Overproduction of free radicals in damaged tissues may be a response to decreased or inhibited SOD activity (45). According to our results shown in Table 4, the hyperglycemic animals' kidney SOD activities demonstrated a significant decrease as compared to non treated rats. The treatment with VS enhanced the activity of SOD and that may assist in controlling diabetic rats' free radical levels (45).

Looking at the literature in general, the effect of vanadyl compounds on the kidney is a contentious issue. Some vanadyl compounds are nephrotoxic, even in therapeutic doses, but some articles support that some vanadyl compounds may improve diabetic kidney function because of its hypoglycemic potential (46-50). In our current and previous studies, we observed death in normal rats administered only VS. On the contrary, there was no such loss in diabetic animals given VS, and also, a healing effect on diabetic kidney tissue was observed. These findings show that VS may be a suitable oral anti-diabetic for the improvement of hyperglycemia if it is used in appropriate doses only in diabetic rats.

CONCLUSION

The present study showed that VS exerted insulin-mimic behavior and antioxidant properties that prevent kidney damage caused by diabetes. It has been observed previously that orally given vanadyl (IV) supplemention dramatically reduced STZ-induced blood glucose, improved AGEs formation, lipid peroxidation levels, some renal biomarkers, and renal histopathological damage. In the current research, we demonstrate that vanadyl treatment also alleviated activities of transaminases and ALP in diabetic rats' kidney tissue. Also, VS reduced the activities of GGT and CA, and increased antioxidant capability by inducing the activity of SOD in diabetic rats. Therefore, based on previous and current studies, we can say that the applicability of VS as a new anti-diabetic agent in the treatment of renal tissue damage with diabetic nephropathy would be appropriate. Further research into the functions of vanadyl and its different complexes will aid in the development of new substances to improve the treatment of diabetic nephropathy.

CONFLICT OF INTEREST

Authors declared no conflict of interest.

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