Possible Therapeutic Role of Novel Vanadium Complexes in Diabetes Mellitus Animal Models

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Abstract

Diabetic mellitus is a group of metabolic disorders in which there are high blood sugar levels over a prolonged period, diabetes can causes many complications. The trace element vanadium has unclear biological functions. Vanadate, an oxidized form of vanadium, appears to have an insulin-like action, the effect of vanadate on blood glucose was assessed in male Wistar rats after they were made diabetic with Streptozotocin (STZ). The animals were fasted overnight and a single intraperitoneal injection of a freshly prepared solution of STZ (55 mg/Kg b.wt) in 0.1 M cold citrate buffer (PH 4.5) was given to induce diabetes. The animals were allowed to access to 5 per cent glucose solution overnight, to prevent total hypoglycemia, induced by STZ by massive pancreatic insulin release. The animals were considered as diabetic, if their blood glucose values were above 250 mg/dL on the third day (72 hours) after STZ injection.The treatment was started on the fourth day after STZ injection and the day was considered as first day of treatment. The treatment was continued for 15 days**.** Diabetes causes disturbance in liver and kidney functions and causes hyperlipidemia also decreased the antioxidant activity; after the treatment with the two novel vanadium complexes , all functions of liver (Alanine transferase, Aspartate transferase and total protein) and kidney functions (Creatinine and urea) were improved.

Also, lipid profile (total cholesterol and Triglycerides) level decreased and the activity of antioxidant enzymes (Superoxidedismutase , Glutathione peroxidase, Glutathione reductase and Malonodialdhyde) improved.

{**Citation**: M.A. Diab, A.F. Shoir, B. Hassan, H.A. El-mezayen. Possible therapeutic role of novel vanadium complexes in diabetes mellitus animal models. American Journal of Research Communication, 2018, Vol 6(4): 10-32} www.usa-journals.com, ISSN: 2325-4076.

1. Introduction

Diabetes mellitus (DM), a lifestyle-related disease and one of the most widespread diseases of our times, is important because DM develops many severe secondary complications, including atherosclerosis , renal (kidney) dysfunction and failure, cardiac (heart) abnormalities, diabetic retinopathy (functional defect of the retina, which relates to the whole body disorder), and ocular disorders (eye disorders that often induce blindness). Diabetes mellitus treated by daily injections of insulin or several types of synthetic therapeutic substances, respectively.Unfortunately, these methods of treatment have some defects: the injections of insulin several times a day are painful and elevate the levels of patient stress, especially in young people, and synthetic therapeutic substances often have some side effects. For these reasons, the creation and development of new therapeutic substances to replace insulin injections and synthetic drugs during the 21st century are extremely desirable. Before Banting and Best's discovery of insulin in 1921 and its clinical trial for treating DM, an interesting result was reported in 1899 in which orally administered sodium vanadate (NaVO3) was found to be effective in improving the conditions of patients with DM. Because of the finding in 1899 (Lyonnet et al., 1899) and an increased interest in the nutritive values of trace elements in the latter. half of this past century, the correlation between DM and trace elements has been studied with a focus on the micronutrient status of patients with DM and the therapeutic effects of trace elements. Many studies have revealed changes in the status of trace elements in patients with DM. Deficiencies in certain trace elements have been found to correlate with the development of DM as well as the presence of diabetic complications. The effective chemical forms of metal ions causes antidiabetic activities in all expermintal design.In this study we aimed to prepare some new Oxovanadium complexes toward developing Vanadium-based drugs for diabetes, which act as the insulin-mimetic action and the therapeutic agents for treatment of streptozotocin (STZ)-induced diabetic rats and show the important role of these complexes.

2. Materials and Methods

2.1. Vanadium complexes

Vanadium complexes used for this expriment have been synthesized characterized by (A.Z.El-Sonbati et al., 2016) from the faculty of Science of Demitta university, from 4-{(8-hydroxyquinoline-7-yl)-methyleneamino}-1,2-dihydro-1,5-dimethyl-2-phenylpyrazol-3-one (I) and 8-hydroxy-7-formylquinoline (II) which used as two ligands, two complexes were synthesized by reacted the two ligand with the vanadium (IV).

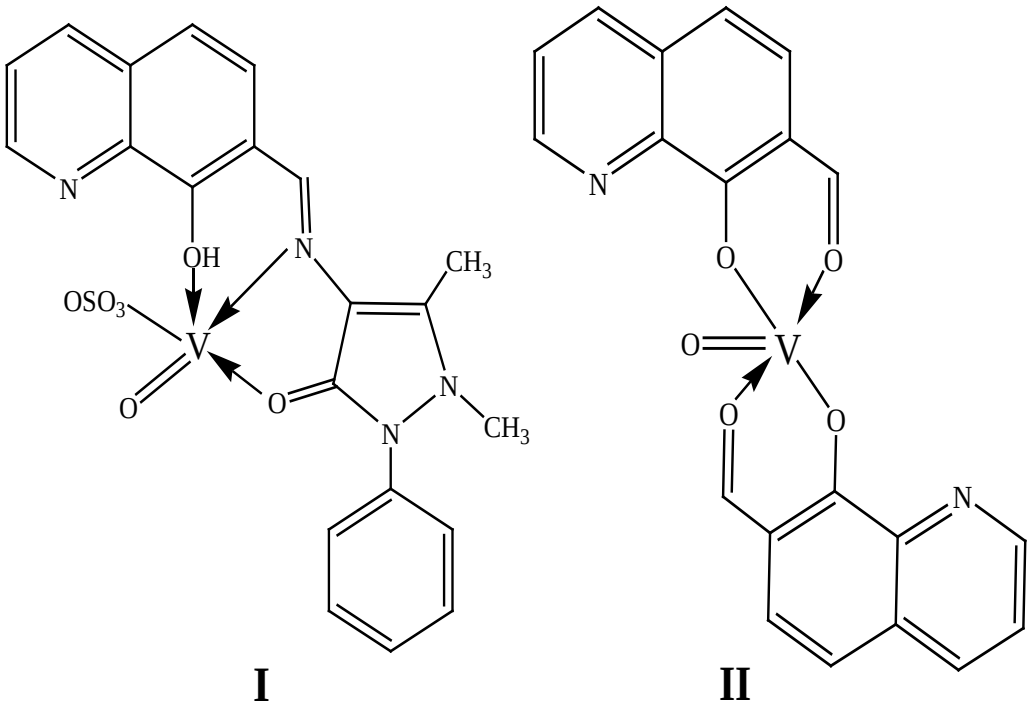

Figure (1)

(I): 4-{(8-hydroxyquinoline-7-yl)-methyleneamino}-1,2-dihydro-1,5-dimethyl-2-phenylpyrazol-3-one.

(II): 8-hydroxy-7-formylquinoline.

2.2. Experimental animals

Male albino Wister rats, weighting about 160–180 grams were obtained from laboratory Animals, They were randomly divided into seven groups, each consisiting of six animals.Animals were identified by marking different parts of the body. The animals were maintained on standard rat feed. All animals were housed in cages with 12/12 hours light/dark cycle.The animals were acclimatized for one week prior to the start of the experiment.

2.3. Experimental design

This study was a repeated measures parallel design animal experiment with the following groups: Group I served as normal control. Group II served as control of Dimethyle Sulfoxide (DMSO) solvent to the vanadium complexes. Group III served as Diabetic control un treated. Groups IV and V were Streptozotocin induced diabetic rats treated with vanadium complexes (1) and (2) at the dose rate of 5 mg/kg b.wt/ml/day orally. Groups VI and VII were normal control treated with vanadium complexes (1) and (2) at the dose rate 5 mg/kg/b.wt/ml/day orally for 15 days.

2.4. Induction of diabetes mellitus

The animals were fasted overnight and a single intraperitoneal injection of a freshly prepared solution of STZ (55 mg/Kg b.wt) in 0.1 M cold citrate buffer (PH 4.5) was given to induce diabetes.The animals were allowed to access to 5 per cent glucose solution overnight, to prevent total hypoglycemia, induced by STZ by massive pancreatic insulin release. The animals were considered as diabetic, if their blood glucose values were above 250 mg/dL on the third day (72 hours) after STZ injection.The treatment was started on the fourth day after STZ injection and the day was considered as first day of treatment. The treatment was continued for 15 days (Williamson et al., 1996).

3. Methods

Biochemical Analysis

At the end of the treatment, the blood was collected and the serum was seperated at 3.000 rpm for 15 min.Biochemical parameters in serum, including fasting blood glucose (FBS) (Kaplan, 1984) , Haemoglobin (Hb) (Titez, 1976) , Glycosylated Haemoglobin (HbA1C) Creatinine (Murray, 1984), Urea (Chaney, 1962 and Vassault, 1986), Total cholesterol (TCHO) (Tietz, 1976 and Watson, 1960) , Triglycerides (TG) (Fossati and Principe, 1982), Alanine amino transferase (ALT) , Aspartate amino transferase (AST) , Total protein .Superoxide dismutase (Nishikimi et al., 1972), Glutathione reductase (GSH reductase) (Goldberg and Spooner, 1983), Glutathione peroxidase (GSH peroxidase) (D.E. Pagila and W.N. Valentive, 1967) and Malonodialdhyde (MDA) (Satoh, 1978 and Ohkawa et al., 1979).

4. Statistical analysis

The results in this study were expressed as the means and standard deviations (M ± SD). The Statistical analyses were carried out using Instate software computer program, Version 2.03 (Graph pad, USA) and IBM PC compatibles computer.

5. Results

As shown in table (1), during the whole experimental period, the body weights of the control rats were gradually and significantly elevated.

Table (1): Effect of vanadium complexes on the body weight

	First weight	After 14 days	After 21 days
Group 1 (N)	**160 ± 19.94**	**192 ± 20.0[a]**	**194 ± 23.73***
Group 2(DMSO)	**147.95 ± 17.53**	**168.66± 17.18[a]**	**162.66 ± 26.53[*]**
Group 3 (D)	**171 ± 43.7**	**156± 43.1[b]**	**140.2 ± 42.6[*]**
Group 4 (DC1)	**187.5 ± 30.8**	**167.05 ± 25.13[a]**	**132.5 ± 23.51[a]**
Group 5 (DC2)	**195 ± 11.99**	**185.8 ± 12.98[a]**	**157.2± 24.34[b]**
Group 6 (NC1)	**107 ± 8.83**	**139.8 ± 13.84[b]**	**133.5 ± 10.82[*]**
Group7 (NC2)	**140.8 ± 7.98**	**166.5 ± 11.25[a]**	**127 ± 18.17[c]**

a:significant ($p < 0.05$), b: very significant ($p < 0.01$), c:extremely significant ($p < 0.001$), *: non significant

However, the body weights of STZ-induced diabetes rats were significantly lower than those controls and also vanadium causes loss of the weight in all groups treated with vanadium complexes.

As shown in table (2), we studied the effect of vanadium complexes.

Blood glucose

There was an extremly significant ($p < 0.001$) increased in the blood glucose level in the diabetic group and very significant ($p < 0.01$) increased in both diabetic treated groups compared to the normal control, also there was significant decrease ($p < 0.05$) in blood glucose level in diabetic treated group with complex (1) and also an extremely significant decrease ($p < 0.001$) in glucose level in diabetic group treated with complex (2) compared with the diabetic group.

Haemoglobin

There was non significant change in Haemoglobin in all groups but only significant decrease (p <0.05) in Diabetic untreated group compared to control group, in addition to there was significant increase (p <0.05) in Haemoglobin level in diabetic treated group with complex(2) and significant increase (p < 0.05) in the diabetic models treated with complex (1) compared with the positive control group.

Table (2): Effect of vanadium complexes in Blood glucose, Hemoglobin and HbA1c in all groups

Groups	Blood Glucose	Hemoglobin	HbA1C
Normal (Control)	89 ± 10.4	14.3 ± 1.126	3.9 ± 0.42
DMSO solvent of complexes	95.6 ± 8.64*	15.2 ± 1.19*	3.8 ± 0.21*
Diabetic Untreated	366.8 ± 24.4^{c}	12.78 ± 0.567^{a}	4.2 ± 0.364*
Diabetic treated complex 1	205.7 ± 74.8 ^{bd}	13.6 ± 2.47^{*s}	3.2 ± 0.31$^{*\$}$
Diabetic treated complex 2	135.5 ± 14.8 ^{bf}	15.8 ± 1.17^{*d}	3.3 ± 0.316^{*d}
Normal treated complex 1	89.8 ± 9.19*	15.9 ± 14.8*	3.8 ± 0.48*
Normal treated complex 2	83.6 ± 7.96*	14.8 ± 0.81*	3.6 ±0.49*

a:*significant* (p < 0.05), b: *very significant* (p <0.01), c:*extremely significant* (p <0.001*), *: non significant compared to the normal group.*
d:*significant* (p < 0.05), e: *very significant* (p <0.01), f :*extremely significant* (p <0.001*), $: non significant compared to the diabetic group*

Glycosylated Haemoglobin

The glycosylated Haemoglobin was non significantly changes in all groups compared with the control group, but there was significant decrease (p <0.05) in diabetic groups treated with complex (1) and complex(2) compared with diabetic untreated.

Alanine amino transferase (ALT)

When we compared the activity of ALT in all groups with the normal group we found; there was non significant increased in the animals treated with DMSO solvent , diabetic untreated and the normal animals treated with complex (2). In addition to; there was significant increased (p <0.05) in the normal animal which treated with complex (1) and very significant increased (p <0.01) in diabetic animals treated with complex (1).When we compared the diabetic untreated animals with the two diabetic groups which treated with the two novel complexes (1) and (2), there was non significant changes.

Aspartate amino transferase (AST)

AST activity was non significant increased in all animals when compared with the normal animals except; the normal group treated with complex (2) was very significant increased (p <0.01); there was non significant decreased in both diabetic group treated with the complex (1) and complex (2) when compared with the diabetic untreated group.

Total protein

Highly significant increased (p<0.01) in the total protein level was observed in DMSO and two diabetic group treated with the complex (1)and complex (2) and non significant increased in all other groups when compared it with the normal group . According to the comparison between the diabetic group and the two treated diabetic groups with the two complexes ;there were significant increased (p<0.05).

Table (3): Effect of vanadium complexes in Alanine transferase (ALT), Aspartate transferase (AST) and total protein in all groups

Groups	Alanine transferase	Aspartate transferase	Total protein
Normal (Control)	58.6 ± 13.14	125.5 ± 24.8	5.2 ± 0.204
DMSO solvent of complexes	68.3 ± 22.1*	145 ± 22.5*	5.7 ± 0.3^{b}
Diabetic Untreated	74.0 ± 18.13*	177 ± 29.6*	5.3 ± 0.22*
Diabetic treated complex 1	91.2 ± 14.8 ^{bs}	103.6 ± 20.1$^{*\$}$	6.3 ± 0.26 ^{cd}
Diabetic treated complex 2	84.2 ± 8.09 ^{bs}	139.5 ± 45.4$^{*\$}$	6.4 ± 0.34 ^{cd}
Normal treated complex 1	84.6 ± 6.18^{a}	160.5 ± 36.2*	5.2 ± 0.318*
Normal treated complex 2	75.6 ± 7.4*	184.5 ± 29.28^{b}	5.3 ±0.32*

a:significant ($p < 0.05$), b: very significant ($p < 0.01$), c:extremely significant ($p < 0.001$), *: non significant compared to the normal group.
d:significant ($p < 0.05$), e: very significant ($p < 0.01$), f :extremely significant ($p < 0.001$), $: non significant compared to the diabetic group

Creatinine

we noticed when compared the normal animals with the other animals ; there was non significant increased in the DMSO, the two diabetic groups treated with the complexes and the normal group treated with the complex (1); there was significant increased ($p < 0.05$) in the diabetic untreated group and very significant ($p < 0.01$) increased in diabetic treated with complex (2).When we compared the diabetic untreated animal with the treated animals ; there was significant decreased ($p < 0.05$) in the animals treated with vanadium complexes.

Urea

There was not significant increase in the DMSO, two treated diabetic groups and the normal group treated with the complex (1). In contrast ; there was an extremely significant (p <0.001) increased urea level in the diabetic untreated animals and significant increased (p<0.05) in the normal group treated with the complex (2), that when we compared them with the normal group but When we compared the diabetic groups treated with the vanadium complexes and the diabetic untreated group ; there was non significant decreased in the urea level.

Table (4): Effect of vanadium complexes in creatinine, urea, Cholesterol and Triglycerides level in all groups studied

Groups	Creatinine	Urea	Cholesterol	Triglycerides
Normal (Control)	0.96 ± 0.136	42.1 ± 8.28	120 ± 13.14	90.1 ± 10.8
DMSO solvent of complexes	1.0 ± 0.14*	46.5 ± 7.5*	109 ± 9.89*	91.5 ± 9.85*
Diabetic Untreated	1.46 ± 0.17c	65.7 ±10.6c	146.6 ± 8.35a	140 ± 53.29a
Diabetic treated complex 1	0.97 ±0.17*d	59.0 ±7.3*$	96.2 ± 8.7 af	47.2 ± 8.3 a$
Diabetic treated complex 2	0.85 ±0.12*d	56.2 ±9.1*$	104.7 ±4.7*f	52.5 ± 9.0 a$
Normal treated complex 1	1.2 ± 0.19*	43.6 ± 7.0*	115 ± 14.6*	55.5 ± 14.2a
Normal treated complex 2	1.3 ± 0.18b	45.6 ±6.43a	116 ± 5.42*	76.5 ±17.2*

a:significant (p < 0.05), b: very significant (p <0.01), c:extremely significant (p <0.001), *: non significant compared to the normal group
d:significant (p < 0.05), e: very significant (p <0.01), f :extremely significant (p <0.001), $: non significant compared to the diabetic group

Cholesterol

There was significant increased (p <0.05) in the diabetic untreated animals and the diabetic animals treated with complex (1) also, there was non significant decreased in the normal groups treated with the complexes and DMSO group when we compared it with the control group. There was an extremely significant (p <0.001) decreased in the cholesterol level in the two groups treated with the complex (1) and the complex (2) compared with the diabetic untreated animals..

Triglycerides

when we compared the all groups with the normal control group ,there was non significant increased in animals treated with DMSO solvent and non significant decreased in the normal animals treated with the complex (2).In addition to that ; the level of triglycerides increased significally (p <0.05) in the diabetic untreated group and significant deceased (p <0.05) in both groups treated with vanadium complexes and the normal group treated with the complex (1) .

when we compared the diabetic animals which treated with the two vanadium complexes and the diabetic untreated animals, there was non significant decreased.

Effect of vanadium complexes in antioxidant profile

Superoxide dismutase (SOD)

As shown in the table (5) ; there was non significant increased in the DMSO group and significant decreased (p <0.05) in the diabetic animals groups treated with the vanadium complexes and the normal animals treated with the vanadium complexes, also there was very significant decreased (p <0.01) in the SOD activity in the diabetic untreated group compared with the normal group; in addition to; there was non significant increased in the two groups which treated with the vanadium complexes when compared them with the diabetic untreated group.

Table (5): Antioxidant profile ; Superoxide dismutase (SOD), Glutathione peroxidase (Gpx), Glutathione reductase and Malonodialdhyde (MDA)

Groups	Superoxide dismutase	Glutathionr eductase	Glutathion peroxidase	Malonodialdhyde
Normal (Control)	285 ± 43.3	729 ± 250	589.5± 235.1	3.28 ± 2.9
DMSO solvent of complexes	300 ± 30.6*	544 ± 142*	141 ± 51.6 ^{b}	3.0 ± 1.3*
Diabetic Untreated	155 ± 41.7^{b}	240 ± 27.2^{a}	112.9 ±69 ^{b}	4.9 ± 3.18*
Diabetic treated complex 1	211.8± 47$^{*\$}$	531 ±254^{*d}	235 ± 72 ^{ad}	5.4 ± 1.95^{*d}
Diabetic treated complex 2	235 ± 47.8$^{*\$}$	682 ±205^{*d}	375 ±189^{*d}	12.8 ± 4.5 ^{bd}
Normal treated complex 1	244 ± 34*	465 ± 51.6^{a}	256 ± 88.3 ^{b}	5.01 ± 0.6*
Normal treated complex 2	320 ± 19.2*	637 ± 30.6*	486 ± 131*	5.0 ±0.63*

a:significant ($p < 0.05$), b: very significant ($p < 0.01$), c:extremely significant ($p < 0.001$), *: non significant compared to the normal group.
d:significant ($p < 0.05$), e: very significant ($p < 0.01$), f :extremely significant ($p < 0.001$), $: non significant compared to the diabetic group

Glutathione reductase

There was non significant decreased in DMSO group, diabetic group treated with complex (1) and diabetic group treated with complex (2) and normal animals treated with complex (2), Also there is significant decreased ($p < 0.05$) in diabetic untreated and the normal animals treated with the complex (1).when we compared the two diabetic treated groups with the diabetic untreated group ; there was significant ($p < 0.05$) increased in the GSH reductase activity.

GSH peroxidase (Gpx)

There was very significant (p <0.01) decreased in the DMSO group, diabetic untreated group and normal animals treated with complex (1) , in addition to the significant decreased (p <0.05) in the diabetic animals treated with complex (1) and also, non significant decreased in the diabetic animals treated with complex (2) and the normal group treated with complex (2).

The significant increase (p <0.05) in the diabetic animals treated with the complex (1) and the diabetic group treated with complex (2) compared with the diabetic untreated animals.

Malonodialdhyde

There was non significant decreased in the DMSO group and non significant increased in the diabetic group treated with the complex (1) and normal group treated with complex (1) and complex (2). we also noticed there was very significant (p <0.01) increased in the diabetic group treated with complex (2).In addition to there was significant increased (p <0.05) in the diabetic animals treated with vanadium complexes compared with the diabetic untreated group.

6. Discussion

Diabetes mellitus, commonly refered to as diabetes, is a group of metabolic diseases in which there are high blood sugar levels over a prolonged period (WHO, 2004). Symptoms of high blood sugar include frequent urination, increased thirst, and increased hunger. if left untreated, diabetes can cause many complications. Acute complications can include diabeteic ketoacidosis, non ketotic hyper osmolar, coma or death (Kitabchi et al., 2009). Serious long-term complications include heart disease, stroke, chronic kidney failure, foot ulcers, and damage of the eyes.

As of 2015, an estemiated 415 million people had diabetes world wide with type 2 DM making up about 90% of the cases (Shi et al., 2014). This represents 8.3 % of the adult population, with equal rate in both women and men and this number might double by 2025.

DM is classified as either insulin dependent type 1 DM (caused by destruction of pancreatic β cells) or non insulin- dependent type 2 DM (causing by age, obesity and other enviromental factors. Hyper glycemia and free fatty acid intake are among the cause of oxidative stress conditions (Evans et al., 2002). Hence, it may not be surprising that diabetic subjects tend to have more oxidative cell and organism enviroments than healthy subjects i.e an increase in ROS generation (Guzik et al., 2002). Morever, diabetic patients present a decrease in antioxidant defense. The antoxidant enzymes level are affected by diabetes, which further increase oxidative stress (Ranis and Jain, 2011). Oxidative stress has been proposed as a major participant in the pathophysiology of diabetic complications (Brownlee, 2005). Nevertheless, regarding diabetes onset and development, oxidative stress has also shown to affect the two major mechanisms failing during diabetes: insulin resistance and insulin secretion.

DM which are treated by daily injections of insulin or several types of synthetic therapeutic substances, respectively , unfortunately, these methods of treatment have some defects, the injections of insulin several times a day are painful and elevate the levels of patients stress. For these reasons, the creation and development of new therapeutic substances to replace insulin injections and synthetic drugs during the 21 st century are extremely desirable. Before Banting and Best's discovery of insulin in 1921 and its clinical trial for treating DM, an interesting result was reported in 1899 in which orally administrated sodium vanadate ($NaVO_3$) was found to be effective in improving the conditions of patients with DM. Because of the finding in 1899 (Lyonnet et al., 1899) and increased interest in the nutritive values of trace elements in the latter, half of this past century, the correlation between DM and trace elements has been studied with a focus on the micronutrient status of patient with DM and the therapeutic effects of trace elements. Many studies have revealed changes in the status of trace elements in patients with DM. The effective chemical forms of metal ions causes antidiabetic activities in all experimental design. To better elucidate the mechanism for the pathogenesis of some complications in diabetes and the role of vanadium complexes to prevent them, Streptozotocin is a widely used chemical agents to induce type 1 diabetes, causing the selective destruction of pancreatic β cells (Bennet and Pegg, 1981). STZ-induced diabetes rats presented poly phagia, poly dipsia, hyperglycemia and loss of body weight, which consistent with the previous reports (Yuen et al., 1999 and Tan et al., 2005). In previous study, the changes of body weight in control group, diabetes group and all the vanadium treated groups. During the whole experimental period, the

body weight of the control rats were gradually and significantly elevated. However, the body weights of the STZ-induced rats were significantly lower than those of the controls. Moreover, there were no significant difference in body weight among diabetic rats. In STZ-induced diabetic rats, insulin deficiency was reported to cause weight loss, probably due to poor utilization of nutrients and muscle protein degeneration (Wei et al., 2007) .

In our study, there were a highly significant decrease in body weight of diabetic group than the normal rats, in addition, there were highly significant decreased in normal treated groups than normal control which could be a result of the ability vanadium complexes to reduce food intake.

The insulin-mimetic effect of vanadium (V) compounds have been extensively studied both in vivo and vitro (Reul et al., 1999 and Kawabe et al., 2006). Inorganic vanadium salts with different chemical valances significally lowered the blood glucose of diabetic rats have been reported since, the early 1980s by (Heyliger et al., 1985). Several vanadyl complexes have been reported to exhibit effective and long-term insulin-mimetic activities in experimental diabetic rats by daily oral administration (Yuen et al., 1993 and Sakurai et al., 1995)

One of the important biological roles of insulin during absorptive state (after meals) is stimulation of glycogen disposal in the peripheral tissues. This effect of insulin mediated by both enhancing glucose uptake and stimulation of glycogen synthesis (Hei, 1998).

The metabolic effect of insulin are initiated by activation of its receptors on the surface of the cell leading to activation two main signaling cascades to as phosphotidyl inositol-3-kinase (PI3-K) pathway and mitogenactivated protein kinase (MAPK) pathway. Because vanadium mimics/enhances the metabolic rather than the mitogenic effect of insulin. As with insulin, vanadium stimulates both glucose uptake and glycogen synthesis , therefore, several insulin receptor and post receptors sites have been suggested as potential sites for vanadium action.

In our study, the treatment with vanadium lowered the blood glucose level by both newly synthesized complexs from 4-{(8-hydroxy quinoline-7-yl)-methyleneamino}1,2-dihydro-1,5-dimethyl-2-phenyl pyrazol-3-one (1) and 8-hydroxy-7-formyl quinoline (2) which used as two ligands. We found the diabetic group treated with the complex (2) has extremely significant decreased in the blood glucose level compared to the complex (1) and glycosylated haemoglobin decreased significantly in the diabetic groups treated with vanadium . It has been previously

reported that hyperglycemia was associated with liver dysfunction in type 1 diabetes. Typical serum biochemical parameters, such as ALT, AST and total protein often tested to evaluate whether the liver was damaged or diseased, when the liver was not functioning properly, the levels of ALT and AST will be elevated (Arkkila et al., 2001 and Nannipieri et al., 2005). After treatment of vanadium complexes, the activities of both AST and ALT were significantly decreased. the results suggest that vanadium complexes may be capable of ameliorating the impaired liver function in STZ-vanadyl sulfate (Koyuturk et al., 2005).

The major complications of all types of diabetes was dyslipidemia (Biesenbach 1989 and Gylling et al., 2004) the largest class of diabetes altered gene expression returned to normal levels by vanadyl sulfate treatment involved gene from major lipid biosynthetic parhways in gene expression studies using DNA microarrays. (Willsky et al., 2006)

As expected both serum TCHO and TG concentration were elevated in the diabetic groups compared to the normal group and after the treatment with the vanadium complexes, there was significant decreased of the elevated TCHO and TG. In our study, the levels of TCHO and TG elevated in the diabetic group and the treatment with the two novel vanadium complexes extremely significantly decreased the levels of TCHO and TG. So, the adminstration of vanadium and anti-hyperlipidemia effect.

Oxidative stress plays a foremost role in etiology of several diabetic complications (D.Giugliano et al., 1996).Oxidative stress in type 2 diabetes may be the result of both antioxidant system failure and increased production of oxidative stress .Laboratory markers of oxidative stress and measurment of total antioxidant activity of plasma are a useful tool for the qualitative and quantative determination of free radical events. These parameters help to control the treatment of chronic diseases, including type 2 diabetes (D.Gossai and CA Lau-cam, 2009).

In other study, suggested the effect of vanadium complexes in the antioxiadant enzymes, which improve the antioxidant defense. Superoxide dismutase (SOD) scavenges the superoxide radical by converting it into H_2O_2 and molecular oxygen. It is known that the SOD activity is low in diabetic mellitus (Damasceno et al., 2004 and Rajasekaran et al., 2005), adminstration of vanadium complexes increased the activity of SOD that may help to control free radicals in diabetic rats. This may be in part due to normalizing the blood glucose value. This finding are

similar to (Ramachandran et al., 2004 and Yanardag et al., 2009) who also reported an increased tissue SOD activity in vanadium treated diabetic rates.This is in agreement with our study, that there was very significant decreased in the SOD activity in the diabetic group and when treated with vanadium complexes, there was improvment in the SOD activity.

Glutathione peroxidase (GPx) activity decreased significally in diabetic rats. The values were reversed to almost normal in vandium complex, the adminstration of vanadium increased the content of reduced GSH in tissues of diabetic rats, which in turn would have increased the GPx activity. The observation are similar to the findings of (Ramachandren et al., 2004 and Yanardag et al., 2009) who had reported that reduced GPx activity in the tissues of diabetic rats, increased after the adminstration of vanadium.

In our study, there was very significant decreased in the diabetic rats, and after the treatment with the two vanadium complexes, there was significant increased in the Gpx activity .Reduced glutathione level was significantly decreased in the diabetic rats as compared to normal control. Adminstration of vanadium complex significantly increased the GSH level similar findings have been reported by (Koyutruk et al., 2005) in STZ-induced diabetic rats. Adminstration of vanadium complexes increased the activity of glucose-6-phosphate dehydrogenase in diabetic rats which in turn enhances NADPH levels (Nanda et al., 1995). In our study, Aggrement with the past studied , there was significant decreased in the diabetic rats, the oral adminstration of the vanadium complexes, there was significant increased in the GSH reductase activity.

Lipid peroxidation (Malonodialdyde) increased significantly in diabetic rats compared to normal control. Increased level of LPO observed in the present study in the diabetic control may be due to hyperglycemia followed by oxidative stress as suggested by (Koyutruk et al., 2005 , Wolff and Dean, 1987 and Dos et al., 2000).Vanadyl ion may act as a scavenger of oxy radicals , the adminstration of malonate complexes of oxovandium (IV) to STZ-induced diabetic rats increased the antioxidant status and lowered the LPO level in the liver of vanadium treated diabetic rats. Decreased LPO level found in the present study in vanadium treated diabetic rats showed the protective effect of vanadium in diabetic groups by scavenging the oxy radical produced due to oxidative stress. In our study, our result contrast with the other studied, there was very significant increased in the diabetic group compared to the normal rats, but when we treated the diabetic groups with the two vanadium complexes , the LPO level increased.

7. **Conclusion**

STZ-induced diabetic caused hyperglycemia which causes elevated liver functions tests (ALT, AST and Total protein) and kidney functions (Creatinine and Urea) and hyperlipidemia (TCHO, TG) also increased oxidative stress , the two novel complexes of vanadium treated the diabetic animals and suggested the antidiabetic effect of the vanadium (mimetic-insulin action) , also improved the liver and kidney functions that there wasnot any side effect of the vanadium to the kidney and liver , deceased TCHO and TG level and increased the antioxidant enzymes activity which act as the scavenges of the free radicals and decreased the diabetic complications.

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