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" Effect of Trace Elements Vanadium and Nickel on Experimentally Diabetic Rats"

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ABSTRACT

The purpose of this study to investigate the protective and therapeutic effect of vanadylsulphate($Voso_4$) and nickel chloride ($Nicl_2$) against hyperglycemia and oxidative stress induced by STZ in albino rats.
Vanadylsulphate was administrated in adose 0.5 mg/ml and 1.0 mg/ml in drinking water before and after the induction of hyperglycemia, Nickel chloride was administrated similarlyin adose 100µg/kg body weigth by stomach tube.
The gained results revealed a significant increase in plasma glucose, total cholesterol, tri acylglycerol, LDL-cholesterol, urea and creatinine,and asignificant decreas in insulin and HDL-choleasterol,GSH concentration and SOD activity, while ALT& AST ,GSH px activities and MDA concentration, were non significantly affected by STZ injection in rats.
Administration of vanadylsulphate and nickel chloride may improve some of the adverse effects induced by STZ in rats. Vanadylsulphate is more effective in lowering blood glucose level than nickel chloride , moreover administration of nickel chloride for long time lead to increase in urea&creatinine concentration.

Keywords:hyperglycemia, vanadylsulphate, nickel chloride, streptozotocin.

Introduction

Diabetes mellitus is worlds most severe endocrine disease involving metabolic disorders characterized by hyperglycemia and inducing alterations in carbohydrate, fat ,and protein metabolisms, diabetes is recognized as one of the leading causes of morbidity and mortality in the world (Kannel and McGree ,1979), currently there are over 150 million diabetics worldwide and this is likely to be increased to 300 million or more by the year of 2025(King et al.,1998). Research at present is directed not only towards to finding ways of controlling hyperglycemia but also in trying to find means of preventing, slowing or reversing the development of diabetic complication, Therefore, it is indeed necessary to search for new drugs to manage this common health problem.

Vanadium is an essential trace element believed to be important for normal cell function and development in mammals (Meyerovitch etal.,1987 and Cusi,et al.,2001). It has been reported that administration of vanadium in drinking water to diabetic rats normalized high blood glucose concentration, suggesting that vanadate has an insulinlike effect on glucose metabolism in vivo(Heyliger et al.,1985 and Srivastava ,2000) .the insulin mimetic effect of vanadate is well established, and vanadate has been shown to improve insulin sensitivity in diabetic rats and human(Barbagallo et al.,2001).

Nickel chloride has been reported to prevent STZ and alloxan induced diabetes in rats. The protective effects of nickel chloride are reported to be linked to increase in activity of copper-zinc superoxide dismutase, in addition nickel chloride stimulates insulin release in rats(Novelli et al.,1988).

Therefore the aim of the present study was doneto evaluate the protected and therapeutic effect of vanadylsulphate and nickel chloride against some adverse effect induced by STZ in rats.

Material And Methods

Atotal number of 120 males albino rats weigthing (180-250 g) were divided into 6 groups each group (20 rats) the 1st group was servied as normal control , the remaining 100 rats were subjected to hyper glycemic regim by I.P injection of 50 mg/kg body weigth of STZ,the hyper glycemic rats were divided to 5 groups the 2nd groups servied as control diabetic, the 3rd groups recived 0.5mg/ml vanadylsulphate in drinking water daily for one week befor the induction of hyperglycemia after that recived 1.0 mg/ml daily for 9 weeks, the 4th the hyper glycemic group recived 0.5 mg/ml vanadylsulphate daily in drinking water for one week then 1.0 mg/ml for 9 weeks, similary the 5th and 6th groups were recived 100 µg/kg B.w nickel chloride dissolved in saline by stomach tube.blood samples were collected after two weeks of administration of vanadyl sulfate and nickel chloride then after one and two months.

At the end of experiment the animals were scarified ,liver and pancrease samples were taken for biochemical and histopathological examination, blood samples were used for estimation of plasma glucose(Tinder,1969)

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.serum insulin(Frier et al., 1981), serum total cholesterol(Richmond,1973;Allain et al.,1974) ,serum triacylglycerol(Fossati and Prencipe,1982), LDL -chlosterol(Friedwalid et al.,1972),HDL-cholesterol (Burstein et al.,1970),creatinine(Larsen,1972),urea(Batton and Crouch,1977), and serum ALT&AST activity(Reitman and Frankel 1957). liver samples were used for determination of total protein (Bradford,1976), MDA concentration(Mitsuru andMidori,1978), GSH concentration(Ellman,1959), GSH-px activity(Lawrence and burk1976), SOD activity(Marklund and marklund,1974).

HISTOPATHOLOGY

Samples from liver and pancreas were kept in 10% formalin for histopathological examination (Bancroft et al., 1994).

STATISTICAL ANALYSIS

Analysis of variance (ANOVA) or (F) test was performed (Snedecor and Cochran,1980).

Results

Table (1) showed that STZ injection inrats causedsignificant increase the glucose level with a significant dcrease in insulin concentration .Serum total cholecsterol, triacylglycerol, LDL – cholesterol was significantly increased while HDL – cholesterol was significantly decreased.

Administration of vanadylsulphate significantly lowered the plasma glucose level from 2nd week till the end of experiment with concomitant increase of insulin concentration.vanadylsulphate is more effective when used for protection than treatment.on the other hand administration of nickel chloride significantly lower the plasma glucose level specially after 2 weeks and one month with significant increase in serum insulin level. Concerning the effect of vanadylsulphate and nickel chloride on lipid profile the concentration of total cholesterol,triacylglycerol and LDL- cholesterol was significantly decrese specially after 2 month on the other hand HDL-cholesterol was significantly increased.

Table (2)showed anon significant change in ALT&AST activities in STZ injected rats while ,urea &creatinine concentration were significantly increased specially after one and two month of STZ injection.

Administration of vandylsulphate significantly lower urea&creatinineconcentration after 1st month and 2nd months when used for protection on the contrary administration of nickel chloride resulted in a significantly increase in urea &creatinine concentration in both protectedand treated groups in 1st month and 2nd month , on the other hand ALT& AST activity not affected by administration of both vanadylsulphate and nickel chloride.

Table (1): effect of vanadylsulphate or nickel chloride on,Glucose,Insulin,Triacylglycerol,Cholesterol,LDL and HDL in all groups of rats:

Time	Treatments	Glucose (mg/dl)	Insulin (m U/ L)	Triacylglycerol (mg/dl)	Cholesterol (mg/dl)	LDL (mg/dl)	HDL (mg/dl)
2 Week	Normal control	116.50 g ±3.19	12.58 a ±0.75	48.67 i ±0.50	80.67 f ±2.96	21.33 h ±2.72	49.83 a ± 1.58
	Positive control	389.67 bc ±5.36	4.90 c ±0.95	77.33 fg ±7.11	96.33 c ±2.27	54.67 cd ±3.11	26.50 i ± 1.48
	Vanadyl protected	224.33 e ±23.69	9.32 b ±0.86	110.00 c ±4.52	70.17 g ±1.87	5.50 I ±1.52	43.83 bc ± 1.35
	Vanadyl treated	300.33 d ±5.24	8.73 b ±1.09	116.67 c ±3.99	81.17 f ±3.73	18.83 h ±3.27	39.83 de ± 1.51
	Nickel protected	138.00 fg±7.71	10.80 ab±0.87	97.00 d±2.36	70.17 g±1.24	19.17 h±1.16	31.83 f ± 0.95
	Nickel treated	351.17 cd ±10.86	10.40 ab ±1.07	72.00 gh ±2.77	73.67 fg ±4.47	31.67 g ±3.93	27.67 hi ± 1.26
1 Month	Normal control	117.50 g ±4.00	12.58 a ±0.75	81.17 f ±4.55	108.50 d ±3.48	43.00 ef ±2.44	49.67 a ± 1.63
	Positive control	369.67 c ±10.76	4.78 c ±0.92	116.83 c ±2.37	155.33 b ±3.31	102.33 b ±3.94	30.00 fgh ± 1.73
	Vanadyl protected	111.33 g ±3.06	9.73 b ±1.15	63.17 h±1.10	156.17 b ±4.07	98.67 b ±4.18	45.00 b ± 1.37
	Vanadyl treated	186.17 ef ±2.04	9.52 b ±0.89	82.33 ef ±4.29	148.67 bc ±3.05	95.67 b ±1.83	36.83 e ± 1.19
	Nickel protected	228.67 e±23.52	10.08 b±1.15	94.00 d±4.62	144.17 c±3.57	94.17 b±3.37	31.33 fg ± 0.71
	Nickel treated	310.67 d ±14.47	9.69 b ±0.64	69.67 gh ±1.39	157.83 b ±3.62	115.67 a ±3.60	28.67 h ± 1.43
2 Month	Normal control	91.33 g ±2.52	12.62a ±0.71	143.33 b ±5.04	143.33 c ±5.04	62.83 c ±3.61	52.17 a ± 2.65
	Positive control	495.67 a ±21.00	4.53 c ±0.97	181.00 a ±2.75	181.00 a ±2.75	116.50 a ±1.46	28.33 ghi ± 2.40
	Vanadyl protected	114.00 g ±1.74	9.57 b ±1.16	70.17 gh ±2.55	72.67 fg ±1.97	14.00 hi ±1.61	45.50 b ± 2.11
	Vanadyl treated	143.50 fg±1.59	9.38 b±0.85	91.50 d±2.41	94.50 e±1.35	35.17 fg±2.24	41.33 cd ± 1.58
	Nickel protected	434.17 b ±44.07	9.15 b ±0.63	91.00 de ±2.01	96.83 e ±1.27	47.50 de ±1.24	31.50 fg ± 0.62
	Nickel treated	499.17 a ±18.15	9.42 b ±0.85	76.67 fg ±1.20	77.00 fg ±1.14	33.50 g ±1.67	28.83 h ± 1.54
LSD value at 0.05		54.17	2.44	8.87	10.02	9.44	3.46

Data shown are mean ± standard error of number of observations within each treatment.
Data followed by the same letter are not significantly different at $P \leq 0.05$.

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Table (2): effect of vanadylsulphate or nickel chloride on Serum ALT,AST,Creatinine,Urea for all groups:

Time	Treatments	ALT (IU/ml)	AST (IU/ml)	Creatnine(mg/dl)	Urea(mg/dl)
2 Week	Normal control	5.33 c ±0.69	7.50 b±0.41	0.80 efg±0.05	25.33 ij±1.28
	Positive control	6.67bc ±1.09	8.50ab ±0.84	0.87ef ±0.07	36.83 ef±1.02
	Vanadyl protected	7.33abc ±1.00	9.00ab ±0.52	0.67 gh±0.05	21.50 j±0.35
	Vanadyl treated	6.67bc ±1.09	8.50ab ±0.84	0.80 efg±0.05	36.33 ef±1.15
	Nickel protected	5.33 c±0.69	8.50ab ±0.55	0.77 fgh±0.03	35.50 fg±0.55
	Nickel treated	5.33 c±0.69	7.50 b±0.41	0.95 dc±0.05	41.33 e±1.22
1 Month	Normal control	7.00bc ±1.01	8.00 ab±0.42	0.62 h±0.03	29.83 hi±0.57
	Positive control	10.00 a ±0.60	8.67ab ±0.54	1.05 cd±0.06	52.17 d±3.43
	Vanadyl protected	8.00abc ±1.12	9.50 a ±0.51	0.83efg ±0.07	30.83 gh±0.95
	Vanadyl treated	6.33bc ±0.78	9.83 a±0.77	1.20 bc±0.05	54.50 cd±3.59
	Nickel protected	7.00bc ±1.01	8.67 ab±0.40	1.40 a±0.05	55.50 bcd±1.64
	Nickel treated	8.67ab ±0.91	9.33 ab±0.58	1.37 ab±0.06	53.83 d±1.95
2 Month	Normal control	8.33 ab±0.98	9.50 a ±0.62	0.70 fgh±0.05	41.67 e±1.09
	Positive control	8.67 ab±0.91	9.83 a±0.93	1.20 bc±0.05	56.50 bcd±1.57
	Vanadyl protected	6.67bc ±1.17	8.67 ab±0.40	0.82 efg±0.06	41.33 e±1.33
	Vanadyl treated	8.00abc ±0.94	9.83 a ±0.68	1.33 ab±0.05	59.50 bc±1.82
	Nickel protected	6.67bc ±0.81	8.50ab ±0.35	1.48 a±0.04	60.00 ab±1.79
	Nickel treated	9.00ab ±0.70	9.83 a ±0.44	1.42 a±0.05	65.00a ±2.97
LSD value at 0.05		2.85	1.89	0.17	5.44

Data shown are mean ± standard error of number of observations within each treatment.Data followed by the same letter are not significantly different at $P \leq 0.05$.

Table (3) demonstrated that STZ injection in rats revealed a non significantchange in liver MDA concentration while GSH concentration, SOD and GSH px activities were significantly decreased

Administration of vanadylsulphate resulted in a significant increasein liver GSH concentration and liver SOD activity in both protected and treated group.witha significant decrease in MDA concentration in porotective , on the other hand GSH peroxidase activity was non significantly affected by vanadylsulphate.

Administration of nickel chloridesignificantly lowered liver MDA and GSH concentration in treated group with a significant increase in SOD activity in both protected and treated groups with a non significantchange in GSH px in both groups.

Table (3): effect of vanadylsulphate or nickel chloride on liver parameters:

Treatments	GSH(µMol/g)	GSH peroxidase(EU/mg protein)	MDA(nMol/g)	SOD (U/mg protein)
Normal control	34.48 b ± 0.63	0.025 a ± 0.001	7.33 a ± 0.67	27.832 a±0.418
Positive control	24.73 c ± 0.86	0.014 a ± 0.002	7.12 a ± 0.46	13.010 d±0.325
Vanadyl protected	42.77 a ± 1.40	0.027 a ± 0.002	5.32 bc ± 0.39	25.532 b±0.629
Vanadyl treated	41.97 a ± 1.18	0.028 a ± 0.003	7.33 a ± 0.36	22.365 c±0.306
Nickel protected	26.63 c ± 1.83	0.015 a ± 0.001	6.32 ab ± 0.11	26.587 b±0.363
Nickel treated	20.73 d ± 1.49	0.030 a ± 0.014	4.73 c ± 0.45	21.653 c±0.390
LSD value at 0.05	3.62	0.017	1.14	1.16

Data shown are mean ± standard error of number of observations within each treatment.
Data followed by the same letter are not significantly different at $P \leq 0.05$.

Histopathological results:

Liver sections from control normal(group1) showed that apparently healthy hepatic paranchyma (figure1-A), liver sections from control diabetic(group2) showed that dilatation of hepatic sinusoids and focal area of hepatic cell necrosis infiltrated with mononuclear cell infiltration (figure1-B),liver sections from vanadyl protected rats(group3) showed that vacuolation of hepatocytes together with congestion of blood sinusoids(figure1-C),liver sections from vanadyl treated rats(group4) showed that severly dilated blood sinusoids leading to disorganized hepatic cords(figure1-D),liver sections from nickel protected &treated rats (group5&6) showed that severly congested hepatoportal vessels and vaculated hepatocytes (figure1- E,F).

Pancreas sections from control normal (group1)showed that apparently healthy pancreatic acini,(figure2-G), pancreas sections

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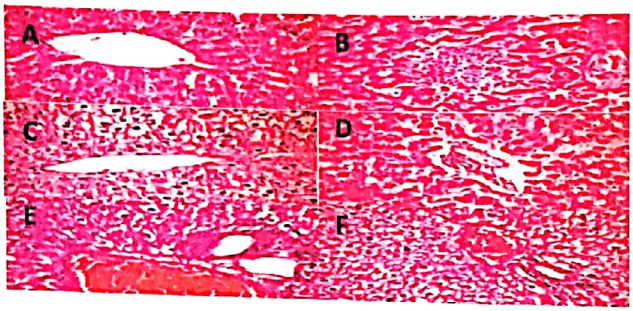
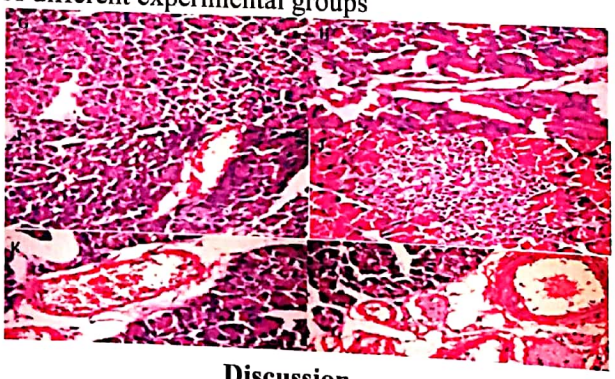
from control diabetic(group2) showed that degenerated pancreatic acini and dilated blood vessel(figure 2-H),pancreas sections from vanadyl protected rats(group3)showed that dilated and congested blood vessel (figure 2-I). pancreas sections from vanadyl treated rats (group4) showed thatvacuolation of pancreatic islets (figure 2-J),pancreas sections from nickel protected rats(group5) showed that severlydiltated blood vessels (figure 2-K),pancreas sections from nickel chloride treated rats(group6) showed that interlobular edema with severly dilated blood vessels(figure 2-L).

Light Microscopic Results

Fig(1): Photomicrograph in the liver of rats of different experimental groups



Fig(2): Photomicrograph in the pancreas of rats of different experimental groups



Discussion

The study has shown that oral administration ofvanadylsulphate in STZ treated rats significantly lowered blood glucose level in both protected and treated groups on the contrary oral administration of nickel chloride significantly lowered blood glucose level in protected group with a non significant effect in treated one. The decrease in blood glucose level was accompanied with a significant increase in serum insulin levels ,it is possible that the hypoglycemic effect of vanadium observed in the present study may be explained by various mechanisms, the study Glod fine et al.,1995 recorded a decrease in insulin requirement in vanadium treated subjected with type 1 diabetes suggesting that vanadium has insulin sensitizyingaction , also Cam , et al.,2000 reported that vanadium exerts a protective effect on pancreatic B- cells and enhance the effect of residual insulin. The stimulatory effect of vanadium on glucose transport has been demonstrated in rat adipocytes(Paquet et al.,1992), vanadium exposure of STZ diabetic rats can restore the expression and or cell surface translocation of insulin sensitive glucose transporter protein CLUT-4 in skeletal muscle (Mohamed et al., 2002). Another physiological response modulated by vanadium is its action on glycogen synthesis , the studies of Cohen(1995) reveled that 3 weeks VS therapy (100 mg(day) in type 2 diabetes patient has been associated with an increase in insulin – stimulated glycogen synthesis in addition vanadium can suppress gluconeogenesis in isolated hepatocytes and kidney cortex tubules from control and diabetic rabbits (Kiersztan et al., 2002), also (Marzban, et al., 2002) reported that vanadium treatment decresed the expression of the gluconeogenic enzyme PFPCK and glucose 6- phosphatase.

The protectiveeffect of Nickel chlorid against STZ induced hyperglycemia is in accordance with the previous study of (Bthel, et al.; 1988)

Concerning the hypoglycemic effect of nickel chloride(Ribas , B.O;etal.,1981) observed an increase a serum insulin secretion after nickel chloride ingetion and may attributed these increment to the hypothesis of(Sanchez Reus et al.,1981) who found that exogenous nickel chloride administration induced accumulation of calcium and zinc in rat pancreas and thus favors the synthesis and secretion of insulin , a processes which depend on zinc and calcium , respectively .

The study has shown that oral administration of vanadylsulphateand nickel chloride significantly lowered serumtotal cholesterol ,triacylglycerol and LDL- cholesterol concentration (table 1).

The hypolipidimic effect of vanadium observed in present study may be explained by various mechanisms , (MenonAS,et al., 1980 &AzarnoffDL.,and Curran DL.,1957)recorded a vanadate has reduced total cholesterol in normal subjects which may be due to inhibition of the steps involved in cholesterol biosynthesis , (Mehdi, H and Mohsen, A, 2003) showed that administration of vanadylsulphate probably cause a decrease in plasma triglyceride due to increase transcription of certain insulin sensitivity gene,

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and promotes the expression of genes encoding lipoprotein lipase (LPL).

Rodriguez-Mercado JJ,et al.,2003 recorded that BFOV administration (0.02,0.06 and 0.2 mmol/kg body weight) on a rat model of type 2 diabetes also caused a reduction in the release of free fatty acids (FFA) from adipocytes and their uptake by the liver, which may be resulted in adecrease in the synthesis of lipoproteins of very low density (VLDL) and pools of circulating triglycerides.

The hypolipidimic effect of nickel chloride observed in the present study disagree with that reported by(Kusal et al ,2006) showed that the nickel-induced rise of serum LDL-cholesterol, total cholesterol, and triglycerides and fall of serum HDL-cholesterol .

The study has shown that oral administration of vanaylsulphate in stztreated rats significantly lower urea&creatinine concentration after 1st month and 2nd months when used for protection.The decresed in creatinine concentration by vanadium may be attributed todecrese in lean body mass as reported (Benedicte et al., 1999).

On the contrary oral administration of nickel chloride significantly increase in urea &creatinine concentration in both protected and treated groups the effect of nickel may be explained by Phillip et al., 1998 suggested that non protein nitrogenous compound were elevated in normal rats by administration nickel chloride , it is also possible that this was also secondary to reduce GFR and dehydration . in addition , nickel chloride probably increase tissue catabolism as well.

The non significant change in ALT and AST activities observed in the present study by administration of vanadylsulphateor nickel chloride disagree with that reported by(Pari L., and Prasath A.,(2008).

The oxidative stress induced by STZ injection in rats manifested by a significant decrease in GSH concentration and GSHpx and SOD activities was ameliorated by administration of vanadylsulphate in both treated and protected group, on the contrary nickel chloride increase the activity of SOD only in both protected and treated groups. The effect of vanadylsulphate are in accordance with that reported by (MarwaM.A.Khalaf, et al.,2012)they observed that vanadylsulphate significantly elevate GSH and SOD activities in comparison with diabetic control , also(Koyuturk.M., Tunall. et al.,2005) reported that vanadylsulphate increase the content of GSH in the liver of diabetic rats. The significant increase in SOD activity by administration of nickel chloride may be explained by the fact that nickel chloride may increase plasma ceruloplasmin and thus the copper content in the pancreas which is important for SOD activity (Ethel L.B , et al.,1988).

Conclusion

Vanadylsulphate is more effective in lowering blood glucose level than nickel chloride , moreover administration of nickel chloride for long time lead to increase in urea&creatinine concentration.

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الملخص العربي

تاثير الفانديم والنيكل علي الجرذان المصابه بمرض السكري التجريبي

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اجريت هذه الدراسه لمعرفه التاثير الواقي والعلاجي لكلا من سلفات الفانديم وكلوريد النيكل ضد ارتفاع السكر والاجهاد التاكسدي الناتج من حقن الاستربتوزوتوسين في الجرذان، تم اعطاء سلفات الفانديم بجرعه ٠.٥ و واحد مليجرام لكل ملي في ماء الشرب قبل وبعد احداث مرض السكري كما تم اعطاء كلوريد النيكل بجرعه ١٠٠ ميكروجرام لكل كيلو من وزن الجسم باستخدام الانبوبه المعديه كما سبق في سلفات الفانديم ، اظهرت النتائج زياده معنويه في تركيز الجلوكوز والكوليسترول الكلي والدهون الثلاثيه والكوليسترول منخفض الكثافه والبوليبا والكرياتينين بينما حدث انخفاض معنوي في مستوي الانسولين والكوليسترول عالي الكثافه والجلوتاثيون المختزل ونشاط انزيم السوبر اكسيد الديسميوتيز بينما لم تظهر فروق معنويه في نشاطات الانزيمات الناقله لمجموعه الامين والجلوتاثيون بيراوكسيديز وتركيز المالندايالدهيد نتيجه لحقن ماده الاستربتوزوتوسين، وعند اعطاء سلفات الفانديم وكلوريد النيكل حدث تحسن في مع معظم القياسات المحدثه بحقن الاستربتوزوتوسين.