Results
5.1 Vanadium

5.1.1 Effect of chronic treatment with vanadium complexes in type I (IDDM) diabetic rats

5.1.1.1 Body Weight, Food Intake and Water Intake

Intravenous injection of 40mg/kg STZ in adult rats produced cardinal signs of type I diabetes i.e. loss of body weight (Fig. 1), polyphagia (Fig. 2A) and polydipsia (Fig. 2B). Glucosuria (>2%) and polyuria observed in these animals persisted throughout the period of six weeks. Chronic treatment with either BMOV or VUR1 did not prevent the loss of body weight in STZ-diabetic rats. Treatment also did not alter the normal gain in body weight of control rats (Fig. 1). However, treatment with BMOV and VUR1 significantly reduced the elevated food and water intakes of diabetic rats. There was no significant effect on the food and water intakes of control rats (Fig. 2).

The average vanadium intake of the groups receiving vanadium treatment was calculated according to the following formula.

\[
\text{vanadium intake (mM)} = \frac{\text{concentration (mM/ml) } \times \text{ fluid intake (ml)}}{\text{rat weight (g)}}
\]

The average vanadium intake in non-diabetic rats treated with BMOV and VUR1 was found to be 0.39 ± 0.16 and 0.45 ± 0.08 mM/day respectively. In case of IDDM rats treated with BMOV and VUR1, the vanadium intake was found to be 0.46 ± 0.10 and 0.45 ± 0.08 mM/day respectively.

5.1.1.2 Serum glucose and insulin

STZ-diabetic rats were found to exhibit significant hyperglycemia (Fig. 3A) with a corresponding hypoinsulinaemia (Fig. 3B) as compared to control rats. Treatment with BMOV and VUR1 produced a significant decrease in the elevated serum glucose levels (Fig. 3A) without any significant change in serum insulin levels of diabetic rats (Fig. 3B). However, the levels of serum glucose in diabetic treated rats were still significantly higher than that of control rats. Treatment did not produce
Fig. 1: Effect of treatment with BMOV and VUR1 on body weight of IDDM diabetic rats. C = control; CT-BMOV = control-treated with BMOV; CT-VUR1 = control-treated with VUR1; IDDM = IDDM control; DT-BMOV = diabetic-treated with BMOV; DT-VUR1 = diabetic-treated with VUR1. n=7 in each group. Values are mean ± SEM. * significantly different from control group (p<0.05, F = 33.72).
Fig. 2: Effect of treatment with BMOV and VUR1 on food (A) and water (B) intake of IDDM diabetic rats. C = control; CT-BMOV = control-treated with BMOV; CT-VUR1 = control-treated with VUR1; IDDM = IDDM control; DT-BMOV = diabetic-treated with BMOV; DT-VUR1 = diabetic-treated with VUR1. n=7 in each group. Values are mean ± SEM. * significantly different from control group; # significantly different from diabetic control group (p<0.05, F(a) = 17.74, F(b) = 7.93).
Fig. 3: Effect of treatment with BMOV and VUR1 on serum glucose (A) and insulin (B) levels of IDDM diabetic rats. C = control; CT-BMOV = control-treated with BMOV; CT-VUR1 = control-treated with VUR1; IDDM = IDDM control; DT-BMOV = diabetic-treated with BMOV; DT-VUR1 = diabetic-treated with VUR1. n=7 in each group. Values are mean ± SEM. * significantly different from control group; # significantly different from diabetic control group (p<0.05, F(a) = 70.15, F(b) = 12.8).
any significant effect on the serum glucose and insulin levels of control rats (Fig. 3).

5.1.1.3 Oral Glucose Tolerance Test (OGTT)

At time 0 i.e. prior to glucose challenge, fasting serum glucose levels of diabetic control rats were significantly higher compared to control rats. Diabetic rats treated with BMOV and VUR1 exhibited significantly lower serum glucose levels compared to diabetic controls (Fig. 4A). Fasting serum glucose levels of control rats treated with BMOV and VUR1 were not significantly different from those of control rats. Administration of glucose (1.5 g/kg, p.o.) did not produce any significant change in the serum glucose levels of all three control group animals throughout 120 min (Fig. 4A). Following oral glucose administration, serum glucose in all the three diabetic groups increased with a peak rise at 60 min. Serum glucose levels of diabetic controls remained high and there was no decline in the glucose levels even upto 120 min. However, the elevated glucose levels in diabetic rats treated with BMOV and VUR1 declined markedly after 60 min of glucose challenge. Moreover, the serum glucose levels in diabetic treated rats were significantly lower at all sample points as compared to diabetic rats (Fig. 4A).

The basal insulin levels of diabetic control and diabetic rats treated with BMOV and VUR1 were significantly lower compared to control rats (Fig. 4B). Fasting serum insulin levels of control and control rats treated with BMOV and VUR1 were not significantly different from each other. Further, there was no significant difference between the serum insulin levels of diabetic control and diabetic rats treated with BMOV and VUR1. Administration of glucose in control group produced an increase in serum insulin levels with a peak rise at 30 min, followed by a decline towards near normal levels over next 90 min (Fig. 4B). Control rats treated with BMOV and VUR1 demonstrated a response pattern that was similar and insignificantly different from that of control group (Fig. 4B). In diabetic group, a slight increase in insulin levels with a peak value at 60 min was observed after oral glucose challenge. The response pattern of diabetic rats treated with BMOV and VUR1 was not significantly
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Fig. 3: Effect of treatment with BMOV and VUR1 on serum glucose (A) and insulin (B) levels of IDDM diabetic rats. C = control; CT-BMOV = control-treated with BMOV; CT-VUR1 = control-treated with VUR1; IDDM = IDDM control; DT-BMOV = diabetic-treated with BMOV; DT-VUR1 = diabetic-treated with VUR1. n=7 in each group. Values are mean ± SEM. * significantly different from control group; # significantly different from diabetic control group (p<0.05, F(a) = 70.15, F(b) = 12.8).
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different from that of diabetic control throughout 120 min after oral
glucose challenge (Fig. 4B).

Integrated areas under the glucose curves over 120 min (AUCglucose) of control rats treated with BMOV and VUR1 were not
significantly different from that of control group (Fig. 5A). AUCglucose of
diabetic control group was significantly higher compared to that of
control. Treatment with BMOV and VUR1 produced a significant
decrease in AUCglucose of diabetic rats compared to that of diabetic
control (Fig. 5A).

AUCinsulin of diabetic control was significantly lower compared to
that of control group (Fig. 5B). Chronic treatment with BMOV and VUR1
did not produce any significant change in AUCinsulin of diabetic rats
compared to that of diabetic control. AUCinsulin of control and control
rats treated with BMOV and VUR1 were not significantly different from
each other (Fig. 5B).

5.1.1.4 Insulin Tolerance Test

Injection of insulin (0.2U/100g) produced time dependent decrease
in glucose levels over a period of one hour. Insulin sensitivity measured
as glucose disposal rate (Krrr) was significantly lower in diabetic control
group as compared to that of control rats (Fig. 6). Chronic treatment
with BMOV and VUR1 significantly increased the Krrr values of diabetic
rats as compared to that of diabetic controls (Fig. 6). Krrr values of control
rats treated with BMOV and VUR1 were not significantly different from
that of control rats (Fig. 6).

5.1.1.5 Serum cholesterol and triglyceride

STZ-diabetic rats exhibited significantly higher cholesterol (Fig. 7A)
and triglyceride (Fig. 7B) levels as compared to those of control rats.
Chronic treatment with BMOV and VUR1 significantly decreased elevated
cholesterol and triglyceride levels in diabetic rats. Treatment, however,
did not produce any change in serum cholesterol and triglyceride levels of
control rats (Fig. 7).
Fig. 5: Effect of treatment with BMOV and VUR1 on integrated areas under glucose (A) and insulin (B) curves of IDDM diabetic rats during oral glucose tolerance test. C = control; CT-BMOV = control-treated with BMOV; CT-VUR1 = control-treated with VUR1; IDDM = IDDM control; DT-BMOV = diabetic-treated with BMOV; DT-VUR1 = diabetic-treated with VUR1. n=7 in each group. Values are mean ± SEM. * significantly different from control group; # significantly different from diabetic control group. (p<0.05, F(A) = 59.25, F(B) = 16.58).
Fig. 6: Effect of treatment with BMOV and VUR1 on insulin sensitivity index ($K_{IR}$) values of IDDM diabetic rats. C = control; CT-BMOV = control-treated with BMOV; CT-VUR1 = control-treated with VUR1; IDDM = IDDM control; DT-BMOV = diabetic-treated with BMOV; DT-VUR1 = diabetic-treated with VUR1. n=7 in each group. Values are mean ± SEM. * significantly different from control group; # significantly different from diabetic control group (p<0.05, F = 5.63).
Fig. 7: Effect of treatment with BMOV and VUR1 on serum cholesterol (A) and triglyceride (B) levels of IDDM diabetic rats. C = control; CT-BMOV = control-treated with BMOV; CT-VUR1 = control-treated with VUR1; IDDM = IDDM control; DT-BMOV = diabetic-treated with BMOV; DT-VUR1 = diabetic-treated with VUR1. n=7 in each group. Values are mean ± SEM. * significantly different from control group; # significantly different from diabetic control group (p<0.05, F(a) = 38.12, F(b) = 9.26).
5.1.1.6 Serum creatinine and urea

STZ-diabetic rats exhibited significantly higher serum creatinine (Fig. 8A) and urea (Fig. 8B) levels as compared to those of control rats. Chronic treatment with BMOV and VUR1 significantly decreased elevated serum creatinine and urea levels of diabetic rats, however, did not produce any significant effect on serum creatinine and urea levels of control rats (Fig. 8).

5.1.1.7 Serum GPT and GOT

STZ-diabetic rats exhibited significantly higher serum GPT (Fig. 9A) and GOT (Fig. 9B) levels of control rats. Chronic BMOV and VUR1 treatment significantly decreased elevated GPT and GOT levels of diabetic rats, however, did not produce any significant effect on serum GPT and GOT levels of control rats (Fig. 9).

5.1.2 Effect of chronic treatment with vanadium complexes in type II (NIDDM) diabetic rats

5.1.2.1 Body Weight, Food Intake and Water Intake

Intraperitoneal injection of 90mg/kg STZ in two day old Wistar neonates lead to development of type II diabetes in the adult state. Body weight in the diabetic group was not significantly different from that of control group (Fig. 10). Chronic treatment with BMOV and VUR1 did not produce any significant effect on the body weights of control as well as diabetic rats (Fig. 10).

There was no significant difference between food intake (Fig. 11A) and water intake (Fig. 11B) of type II diabetic rats as compared to that of controls. Chronic BMOV and VUR1 treatment did not produce any significant effect on the food and water intake of diabetic as well as control rats (Fig. 11).

The average vanadium intake in each group of rats was calculated according to the average fluid intake and body weight. The average vanadium intake in non-diabetic rats treated with BMOV and VUR1 was found to be 0.398 ± 0.079 and 0.40 ± 0.11 mM/day respectively.
Fig. 8: Effect of treatment with BMOV and VUR1 on serum creatinine (A) and urea (B) levels of IDDM diabetic rats. C = control; CT-BMOV = control-treated with BMOV; CT-VUR1 = control-treated with VUR1; IDDM = IDDM control; DT-BMOV = diabetic-treated with BMOV; DT-VUR1 = diabetic-treated with VUR1. n=7 in each group. Values are mean ± SEM.

* significantly different from control group; # significantly different from diabetic control group (p<0.05, F(α) = 3.63, F(β) = 19.4).
Fig. 9: Effect of treatment with BMOV and VUR1 on serum GPT (A) and GOT (B) levels of IDDM diabetic rats. C = control; CT-BMOV = control-treated with BMOV; CT-VUR1 = control-treated with VUR1; IDDM = IDDM control; DT-BMOV = diabetic-treated with BMOV; DT-VUR1 = diabetic-treated with VUR1. n=7 in each group. Values are mean ± SEM. * significantly different from control group; # significantly different from diabetic control group (p<0.05, F(A) = 98.06, F(b) = 19.27).
Results

Fig. 10: Effect of treatment with BMOV and VUR1 on body weight of NIDDM diabetic rats. C = control (n=8); CT-BMOV = control-treated with BMOV (n=7); CT-VUR1 = control-treated with VUR1 (n=7); NIDDM = NIDDM control (n=7); DT-BMOV = diabetic-treated with BMOV (n=8); DT-VUR1 = diabetic-treated with VUR1 (n=8). Values are mean ± SEM. (p = 0.963, F = 0.19).
Fig. 11: Effect of treatment with BMOV and VUR1 on food (A) and water (B) intake of IDDM diabetic rats. C = control (n=8); CT-BMOV = control-treated with BMOV (n=7); CT-VUR1 = control-treated with VUR1 (n=7); NIDDM = NIDDM control (n=7); DT-BMOV = diabetic-treated with BMOV (n=8); DT-VUR1 = diabetic-treated with VUR1 (n=8). Values are mean ± SEM. (p = 0.802, F(9) = 0.46; p = 0.975, F(9) = 0.15).
Vanadium intake in NIDDM rats treated with BMOV and VUR1 was found to be 0.49 ± 0.14 and 0.46 ± 0.08 mM/day respectively.

5.1.2.2 Serum glucose and insulin

Neonatal STZ-diabetic rats exhibited significant hyperglycemia (>140 mg/dl) as compared to control rats (Fig. 12A). However, serum insulin levels of diabetic rats were not significantly different from that of control rats (Fig. 12B). Chronic treatment with BMOV and VUR1 significantly decreased serum glucose levels without any significant change in serum insulin levels of diabetic rats (Fig. 12). Chronic BMOV and VUR1 treatment did not produce any significant effect on serum glucose and insulin levels of control rats (Fig. 12).

5.1.2.3 Oral Glucose Tolerance Test (OGTT)

At time 0 i.e. immediately prior to glucose challenge, fasting serum glucose levels of diabetic rats were significantly higher compared to control rats, whereas, those of control rats treated with BMOV and VUR1 were not significantly different from those of control rats (Fig. 13A). Administration of glucose (1.5 g/kg, p.o.) did not produce any significant change in the serum glucose levels of all three control group animals throughout 120 min (Fig. 13A). Fasting serum glucose levels of diabetic control rats were significantly higher compared to control rats. Diabetic rats treated with BMOV and VUR1 exhibited significantly lower serum glucose levels compared to diabetic controls (Fig. 13A). Following oral glucose administration, serum glucose levels in the diabetic control group increased continuously with a peak value at 120 min. The serum glucose levels in diabetic treated rats were significantly lower at all sample points as compared to diabetic rats. Moreover, the elevated glucose levels in diabetic rats treated with BMOV and VUR1 declined markedly after 60 min of glucose challenge (Fig. 13A).

The basal insulin levels in control and control rats treated with BMOV and VUR1 were not significantly different from each other (Fig. 13B). Oral administration of glucose in control group produced an increase in serum insulin levels with a peak rise at 30 min, followed by a
Fig. 12: Effect of treatment with BMOV and VUR1 on serum glucose (A) and insulin (B) levels of IDDM diabetic rats. C = control (n=8); CT-BMOV = control-treated with BMOV (n=7); CT-VUR1 = control-treated with VUR1 (n=7); NIDDM = NIDDM control (n=7); DT-BMOV = diabetic-treated with BMOV (n=8); DT-VUR1 = diabetic-treated with VUR1 (n=8). Values are mean ± SEM. * significantly different from control group; # significantly different from diabetic control group. (p<0.05, F(a) = 33.2; p = 0.835, F(b) = 0.42).
Fig. 13: Effect of treatment with BMOV and VUR1 on glucose (A) and insulin (B) responses of NIDDM diabetic rats during oral glucose tolerance test. (○) = control (n=8); (□) = control-treated with BMOV (n=7); (○) = control-treated with VUR1 (n=7); (♦) = NIDDM control (n=7); (■) = diabetic-treated with BMOV (n=8); (●) = diabetic-treated with VUR1 (n=8). Values are mean ± SEM. * significantly different from control group; # significantly different from diabetic control group (p<0.05).
decline towards near normal levels over next 90 min. Control rats treated with BMOV and VUR1 demonstrated a response pattern that was similar and insignificantly different from that of control group (Fig. 13B). Basal serum insulin levels of diabetic control rats were not significantly different from those of control rats. Further, there was no significant difference between the serum insulin levels of diabetic control and diabetic rats treated with BMOV and VUR1 (Fig. 13B). In diabetic group, a slight increase in insulin levels with a peak value at 60 min was observed after oral glucose challenge. The response pattern of diabetic rats treated with BMOV and VUR1 was not significantly different from that of diabetic control throughout 120 min after oral glucose challenge (Fig. 13B).

AUCglucose of diabetic control group was significantly higher compared to that of control (Fig. 14A). Treatment with BMOV and VUR1 produced a significant decrease in AUCglucose of diabetic rats compared to that of diabetic control (Fig. 14A). AUCglucose of control and control rats treated with BMOV and VUR1 were not significantly different from each other. AUCinsulin of diabetic control was not significantly different from that of control group (Fig. 14B). Chronic treatment with BMOV and VUR1 did not produce any significant change in AUCinsulin of diabetic rats compared to that of control and diabetic control rats (Fig. 14B).

5.1.2.4 Insulin Tolerance Test

Insulin sensitivity index i.e. \( K_{\text{ITT}} \) (as explained in 5.1.1.4) of neonatal STZ-diabetic rats was significantly lower compared to that of control rats (Fig. 15). Chronic treatment with BMOV and VUR1 significantly increased \( K_{\text{ITT}} \) values of diabetic rats treated with BMOV and VUR1, however, did not produce any significant change in \( K_{\text{ITT}} \) values of control rats treated with BMOV and VUR1 (Fig. 15).
Fig. 14: Effect of treatment with BMOV and VUR1 on integrated areas under glucose (A) and insulin (B) curves of NIDDM diabetic rats during oral glucose tolerance test. C = control (n=8); CT-BMOV = control-treated with BMOV (n=7); CT-VUR1 = control-treated with VUR1 (n=7); NIDDM = NIDDM control (n=7); DT-BMOV = diabetic-treated with BMOV (n=8); DT-VUR1 = diabetic-treated with VUR1 (n=8). Values are mean ± SEM. * significantly different from control group; # significantly different from diabetic control group (p<0.05, F(a) = 42.11; p=0.176, F(b) = 1.63).
Fig. 15: Effect of treatment with BMOV and VUR1 on insulin sensitivity index (Kitt) values of NIDDM diabetic rats. C = control (n=8); CT-BMOV = control-treated with BMOV (n=7); CT-VUR1 = control-treated with VUR1 (n=7); NIDDM = NIDDM control (n=7); DT-BMOV = diabetic-treated with BMOV (n=8); DT-VUR1 = diabetic-treated with VUR1 (n=8). Values are mean ± SEM. * significantly different from control group; # significantly different from diabetic control group (p<0.05, F = 7.6).
5.1.2.5 Serum cholesterol and triglyceride

Neonatal STZ-diabetic rats exhibited significantly higher cholesterol levels compared to those of control (Fig. 16A), however, serum triglyceride levels of the two groups were not significantly different from each other (Fig. 16B). Chronic treatment with BMOV and VUR1 produced a significant decrease in elevated cholesterol levels of diabetic rats (Fig. 16A). Chronic BMOV and VUR1 treatment did not produce any significant change in serum triglyceride levels of control as well as diabetic rats (Fig. 16).

5.1.2.6 Serum creatinine and urea

STZ-diabetic rats exhibited significantly higher serum creatinine (Fig. 17A) and urea (Fig. 17B) levels compared to those of control rats. Chronic treatment with BMOV and VUR1 significantly decreased elevated serum creatinine and urea levels of diabetic rats, however, did not produce any significant effect on serum creatinine and urea levels of control rats (Fig 17).

5.1.2.7 Serum GPT and GOT

STZ-diabetic rats exhibited significantly higher serum GPT (Fig. 18A) and GOT (Fig. 18B) levels of control rats. Chronic BMOV and VUR1 treatment significantly decreased elevated GPT and GOT levels of diabetic rats. The treatment, however, did not produce any significant effect on serum GPT and GOT levels of control rats (Fig. 18).

5.1.3 Effect of BMOV and VUR1 on triglyceride synthesis in 3T3-L1 adipocytes

After days incubation of 3T3-L1 preadipocytes with BMOV and VUR1 (0-10 μM) and insulin (1 μg/ml), cellular triglyceride accumulation normalized by protein levels was measured as an index of the differentiated adipocyte phenotype. Incubation of cells with BMOV (Fig. 19A) and VUR1 (Fig. 19B) alone significantly increased the intracellular triglyceride accumulation above that observed in the control cultures (no drug well) at 10 μM with EC50 value of 3.16 μM.
Fig. 16: Effect of treatment with BMOV and VUR1 on serum cholesterol (A) and insulin (B) levels of NIDDM diabetic rats. C = control (n=8); CT-BMOV = control-treated with BMOV (n=7); CT-VUR1 = control-treated with VUR1 (n=7); NIDDM = NIDDM control (n=7); DT-BMOV = diabetic-treated with BMOV (n=8); DT-VUR1 = diabetic-treated with VUR1 (n=8). Values are mean ± SEM. * significantly different from control group; # significantly different from diabetic control group. (p<0.05, F(a) = 9.27; p = 0.032, F(b) = 2.74).
Effect of treatment with BMOV and VUR1 on serum creatinine (A) and urea (B) levels of NIDDM diabetic rats. C = control (n=8); CT-BMOV = control-treated with BMOV (n=7); CT-VUR1 = control-treated with VUR1 (n=7); NIDDM = NIDDM control (n=7); DT-BMOV = diabetic-treated with BMOV (n=8); DT-VUR1 = diabetic-treated with VUR1 (n=8). Values are mean ± SEM. * significantly different from control group; # significantly different from diabetic control group (p<0.05, F(A) = 4.98, F(B) = 9.34).
Fig. 18: Effect of treatment with BMOV and VUR1 on serum GPT (A) and GOT (B) levels of NIDDM diabetic rats. C = control (n=8); CT-BMOV = control-treated with BMOV (n=7); CT-VUR1 = control-treated with VUR1 (n=7); NIDDM = NIDDM control (n=7); DT-BMOV = diabetic-treated with BMOV (n=8); DT-VUR1 = diabetic-treated with VUR1 (n=8). Values are mean ± SEM. * significantly different from control group; # significantly different from diabetic control group (p<0.05, F(a) = 12.35, F(b) = 6.48).
Fig. 19: Effect of treatment with BMOV and VUR1 on 3T3-L1 cell differentiation. The cells were cultured in medium containing fetal bovine serum (5%), dexamethasone (1 μM) and IBMX (0.5 mM) for 2 days. The cells were then incubated with BMOV (A) and VUR1 (B) (0-10 μM) in the presence and absence of insulin (1 μg/ml) for 4 days. The cellular triglyceride levels were then measured. * Significantly different from no drug well (p<0.05).
Simultaneous incubation of cells with vanadium compounds and insulin significantly increased triglyceride synthesis, however, the effect was not significantly different from that with vanadium compounds alone (Fig. 19).

5.1.4 Effect of BMOV and VUR1 on glucose uptake in C2C12 myoblasts

From the preliminary results and the earlier reports by Hajduch et al. (1999), it was found that the maximum uptake of glucose by insulin occurs at a concentration of 6pM/ml at 30 min. BMOV and VUR1 alone as well as in the presence of insulin significantly increased uptake of radiolabeled glucose into C2C12 myoblasts compared to basal glucose uptake, however the difference between the effect of the complexes in the absence and presence of insulin was not significantly different from each other (Fig. 20).

5.1.5 Histopathological alterations and effect of BMOV and VUR1 in STZ-induced type-I and type-I diabetic rats.

5.1.5.1 Kidney

No remarkable abnormalities were observed on the gross examination of the kidneys of rats in all groups. Microscopically none of the control rats showed pathological changes in the kidneys (Fig. 21-26). Except for the multifocal areas of cortical tubular regeneration characterized by the presence of basophilic tubules with mononuclear cell infiltration (Fig. 44), the kidney sections of control rats treated with vanadium compounds (Fig. 39-43) were comparable to those of untreated control rats.

Histological examination of the sections of kidneys from STZ-induced type I diabetic rats showed marked microscopic changes like multifocal areas of moderate cortical tubular vacuolations (Fig. 27, 31) and interstitial mononuclear cell infiltration (Fig. 28, 32). Dilatation of cortical tubules especially at the corticomedullary junction was also observed (Fig. 31). However, the classical signs of diabetic nephropathy such as nodular lesions of glomerulus were evident. STZ-induced type I
Fig. 20: Effect of treatment with BMOV and VUR1 on glucose transport by muscle cells. C2C12 myoblasts were incubated with BMOV and VUR1 along with 2-(1,2-H)deoxy-D-glucose for 30 min and radiolabeled glucose in the cells was measured as explained in the materials and methods section, n = 3. Values are the mean ± SEM. * significantly different from basal; # significantly different from insulin (p<0.05).
diabetic rats treated with BMOV and VUR1 had similar pathological changes in kidney. However, the incidence of the changes was lower (Fig. 52, 55). The intensity of cortical tubular vacuolations (Fig. 51) and cellular infiltration (Fig. 52, 56) in the diabetic rats treated with vanadium compounds was much milder as compared to those of type I diabetic control rats.

Histological examination of kidney sections of STZ-induced type II diabetic rats showed multiple areas of tubular vacuolations with tubular epithelial hypertrophy (Fig. 34, 38). Multifocal tubules also revealed degeneration of epithelium characterized by eosinophilic appearance with pyknosis of nuclei (Fig. 37). However, these changes of epithelial hypertrophy and degeneration were not evident in the kidney sections of type II diabetic rats treated with vanadium complexes (Fig. 57, 61, 58). Further, one animal showed focal areas of moderate fibrosis with dilatation of cortical tubules (Fig. 62). The incidence and intensity of pathological changes in case of either control or type I and type II diabetic rats treated with BMOV and VUR1 were not different from each other.

5.1.5.2 Liver

Livers of all groups except STZ-induced type II diabetic control group appeared normal, both grossly and microscopically. Histopathological examination of liver section of control animals showed normal hepatic lobules (Fig. 75, 76). The central venoule with radiating columns of liver cells of normal shape and size were seen. There were no signs of congestion, inflammation, cellular necrosis or cholestasis in control liver sections (Fig. 75, 76). Liver sections of type I diabetic rats (Fig. 81, 82) showed no appreciable histological changes compared to controls. However those of type II diabetic rats showed multifocal areas of hepatocellular vacuolations and hypertrophy (Fig. 87, 88). Focal areas of chronic inflammation with eosinophil infiltration were also seen (Fig. 87, 88). Type II diabetic rats treated with vanadium complexes also showed similar pathological changes (Fig. 89, 90). Liver sections of both type I (Fig. 83, 84) as well as control rats (Fig. 77, 78) treated with BMOV and VUR1 did not show appreciable histological changes and were comparable to those of control rats.
Plate 1: Control rats
Plate 2: STZ-induced type I diabetic control rats
Plate 3: STZ-induced type II diabetic control rats
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Plate 4: Control rats treated with vanadium complexes
Plate 5: Control rats treated with chromium compounds
Plate 6: Type I diabetic rats treated with vanadium complexes
Plate 7: Type II diabetic rats treated with vanadium complexes
Plate 8: Type I diabetic rats treated with chromium compounds
Plate 9: Type II diabetic rats treated with chromium compounds
Plate 10

Fig. 75. Normal hepatocytes of control rats (X400)

Fig. 76. Normal hepatocytes of control rats (X400)

Fig. 77. Normal hepatocytes of control rats treated with vanadium complexes (X400)

Fig. 78. Normal hepatocytes of control rats treated with vanadium complexes (X400)

Fig. 79. Normal hepatocytes of control rats treated with chromium compounds (X400)

Fig. 80. Normal hepatocytes of control rats treated with chromium compounds (X400)
Fig. 81. Normal hepatocytes of type I diabetic control rats (X400)

Fig. 82. Normal hepatocytes of type I diabetic control rats (X400)

Fig. 83. Normal hepatocytes of type I diabetic rats treated with vanadium complexes (X400)

Fig. 84. Normal hepatocytes of type I diabetic rats treated with vanadium complexes (X400)

Fig. 85. Normal hepatocytes of type I diabetic rats treated with vanadium complexes (X400)

Fig. 86. Normal hepatocytes of type I diabetic rats treated with vanadium complexes (X400)

Plate 11
Results

Fig. 87. Focal hepatocellular vacuolation & hypertrophy (arrow) (X400)

Fig. 88. Focal hepatocellular vacuolation & hypertrophy (arrow) (X400)

Fig. 89. Focal hepatocellular vacuolation & hypertrophy of type II diabetic rats treated with vanadium complexes (arrow) (X400)

Fig. 90. Focal hepatocellular vacuolation & hypertrophy of type II diabetic rats treated with vanadium complexes (arrow) (X400)

Fig. 91. Focal hepatocellular vacuolation & hypertrophy of type II diabetic rats treated with chromium compounds (arrow) (X400)

Fig. 92. Focal hepatocellular vacuolation & hypertrophy of type II diabetic rats treated with chromium compounds (arrow) (X400)

Plate 12
5.2 Chromium

5.2.1 Effect of chronic treatment with chromium compounds in type I (IDDM) diabetic rats

5.2.1.1 Body Weight, Food Intake and Water Intake

As mentioned in 5.1.1.1, a single tail vein injection of 40 mg/kg resulted in development of type I diabetes characterized by loss of body weight (Fig. 93), polyphagia (Fig. 94A), polydipsia (Fig. 94B), glucosuria (>2%) and polyuria. Chronic treatment with chromium chloride and chromium picolinate did not prevent loss of body weight in diabetic rats treated with chromium chloride and chromium picolinate (Fig. 93). Treatment did not produce any effect of the body weights of control rats either (Fig. 93).

Chronic treatment with chromium chloride and chromium picolinate did not prevent STZ-induced polyphagia and polydipsia in diabetic animals (Fig. 94). Treatment also did not produce any effect on the food and water intakes of control animals (Fig. 94).

The average chromium intake in each group of rats was calculated according to the average fluid intake and body weight. The average chromium intake in non-diabetic rats treated with chromium chloride and chromium picolinate was found to be 8.91 ± 0.097 and 4.59 ± 0.31 µM/day respectively. In case of NIDDM rats treated with chromium chloride and chromium picolinate, the chromium intake was found to be 7.38 ± 0.09 and 3.63 ± 0.21 µM/day respectively.

5.2.1.2 Serum glucose and insulin

STZ-diabetic rats were found to exhibit significant hyperglycemia (Fig. 95A) with a corresponding hypoinsulinaemia (Fig. 95B) as compared to control rats. Chronic treatment with chromium chloride and chromium picolinate did not produce any significant change in serum glucose and insulin levels of diabetic rats as well as control rats (Fig. 95).
Fig. 93: Effect of treatment with chromium chloride and chromium picolinate on body weight of IDDM diabetic rats. C = control (n=8); CT-CC = control-treated with chromium chloride (n=8); CT-CP = control-treated with chromium picolinate (n=8); IDDM = IDDM control (n=7); DT-CC = diabetic-treated with chromium chloride (n=8); DT-CP = diabetic-treated with chromium picolinate (n=8). Values are mean ± SEM. * significantly different from control group (p<0.05, F = 11.66).
Fig. 94: Effect of treatment with chromium chloride and chromium picolinate on food (A) and water (B) intake of IDDM diabetic rats. C = control (n=8); CT-CC = control-treated with chromium chloride (n=8); CT-CP = control-treated with chromium picolinate (n=8); IDDM = IDDM control (n=7); DT-CC = diabetic-treated with chromium chloride (n=8); DT-CP = diabetic-treated with chromium picolinate (n=8). Values are mean ± SEM. * significantly different from control group (p<0.05, F(a) = 4.32, F(B) = 4.38).
Fig. 95: Effect of treatment with chromium chloride and chromium picolinate on serum glucose (A) and insulin (B) levels of IDDM diabetic rats. C = control (n=8); CT-CC = control-treated with chromium chloride (n=8); CT-CP = control-treated with chromium picolinate (n=8); IDDM = IDDM control (n=7); DT-CC = diabetic-treated with chromium chloride (n=8); DT-CP = diabetic-treated with chromium picolinate (n=8). Values are mean ± SEM. * significantly different from control group. (p<0.05, F(α) = 123.29, F(β) = 10.2).
5.2.1.3 Oral Glucose Tolerance Test (OGTT)

At time 0 i.e. immediately prior to glucose challenge, fasting serum glucose levels of diabetic rats were significantly higher compared to those of control rats (Fig. 96A). Fasting serum glucose levels of control rats treated with chromium chloride and chromium picolinate were not different from those of control rats. Following oral glucose administration (1.5 g/kg), serum glucose levels in control rats increased slightly with a peak value at 30 min and declined thereafter to normal levels by 120 min. Serum glucose levels in control rats treated with chromium chloride and chromium picolinate followed a pattern similar and insignificantly different from that of control rats (Fig. 96A). Serum glucose levels in diabetic rats increased throughout 120 min with no decline in serum glucose levels even at 120 min after oral glucose load (Fig. 96A). Serum glucose levels in diabetic rats treated with chromium chloride and chromium picolinate were significantly lower at 15 and 120 min and at 15, 30 and 120 min respectively, compared to those of diabetic rats with a marked decline in serum glucose levels at 120 min in both the treated groups (Fig. 96A).

Prior to glucose challenge, serum insulin levels in control rats treated with chromium chloride and chromium picolinate were not significantly different from those of control rats, however, those of diabetic control rats were significantly lower as compared to control rats (Fig. 96B). Basal serum insulin levels of diabetic rats treated with chromium chloride and chromium picolinate were not significantly different from those of diabetic control rats (Fig. 96B). After oral glucose load, serum insulin levels in control rats increased slightly with a peak value at 30 min and declined thereafter to original levels by 120 min. There was no significant difference in the insulin response of control rats treated with chromium chloride and chromium picolinate over 120 min after oral glucose load compared to that of control rats (Fig. 96B). Serum insulin levels in diabetic rats did not change significantly over 120 min after oral glucose load. Insulin response to oral glucose load of diabetic
Fig. 96: Effect of treatment with chromium chloride and chromium picolinate on glucose (A) and insulin (B) responses of IDDM diabetic rats during oral glucose tolerance test. (O) = control (n=8); (□) = control-treated with chromium chloride (n=8); (O) = control-treated with chromium picolinate (n=8); (♦) = IDDM control (n=7); (■) = diabetic-treated with chromium chloride (n=8); (●) = diabetic-treated with chromium picolinate (n=8). Values are mean ± SEM. * significantly different from control group; # significantly different from diabetic control group (p<0.05).
rats treated with chromium chloride and chromium picolinate was not significantly different from that of diabetic control rats (Fig. 96B).

AUCglucose of diabetic control rats was significantly higher as compared to that of control rats. AUCglucose of diabetic rats treated with chromium chloride and chromium picolinate were significantly lower compared to that of diabetic control rats (Fig. 97A). AUCglucose of control rats treated with chromium chloride and chromium picolinate were not significantly different from that of control rats (Fig. 97A). AUCinsulin of diabetic rats was significantly lower as compared to control rats. Treatment with chromium chloride and chromium picolinate did not produce any significant effect on AUCinsulin of diabetic rats as compared to diabetic control rats (Fig. 97B). AUCinsulin of control rats treated with chromium chloride and chromium picolinate were not significantly different from that of control rats (Fig. 97B).

5.2.1.4 Insulin Tolerance Test

Insulin sensitivity index ($K_{irr}$) of STZ-diabetic rats was significantly lower as compared to that of control rats (Fig. 98). Chronic treatment with chromium chloride and chromium picolinate produced slight but significant increase in the $K_{irr}$ values of diabetic rats. Treatment with chromium chloride and chromium picolinate also increased the $K_{irr}$ values of control rats, however, the effect was significant only in case of chromium picolinate (Fig. 98).

5.2.1.5 Serum cholesterol and triglyceride

STZ-diabetic rats exhibited significantly higher serum cholesterol (Fig. 99A) and triglyceride (Fig. 99B) levels compared to those of control rats. Chronic treatment with chromium chloride and chromium picolinate produced significant decrease in serum cholesterol and triglyceride levels of diabetic rats as compared to diabetic rats. The treatment, however, did not produce any significant change in serum cholesterol and triglyceride levels of control rats (Fig. 99).
Fig. 97: Effect of treatment with chromium chloride and chromium picolinate on integrated areas under glucose (A) and insulin (B) curves of IDDM diabetic rats. C = control (n=8); CT-CC = control-treated with chromium chloride (n=8); CT-CP = control-treated with chromium picolinate (n=8); IDDM = IDDM control (n=7); DT-CC = diabetic-treated with chromium chloride (n=8); DT-CP = diabetic-treated with chromium picolinate (n=8).

Values are mean ± SEM. * significantly different from control group; # significantly different from diabetic control group.

(p<0.05, F(α) = 354.65, F(β) = 12.88).
Fig. 98: Effect of treatment with chromium chloride and chromium picolinate on insulin sensitivity index (K\textit{mtr}) values of IDDM diabetic rats. C = control (n=8); CT-CC = control-treated with chromium chloride (n=8); CT-CP = control-treated with chromium picolinate (n=8); IDDM = IDDM control (n=7); DT-CC = diabetic-treated with chromium chloride (n=8); DT-CP = diabetic-treated with chromium picolinate (n=8). Values are mean ± SEM. * significantly different from control group; # significantly different from diabetic control group (p<0.05, F = 22.8).
Fig. 99: Effect of treatment with chromium chloride and chromium picolinate on serum cholesterol (A) and triglyceride (B) levels of IDDM diabetic rats. C = control (n=8); CT-CC = control-treated with chromium chloride (n=8); CT-CP = control-treated with chromium picolinate (n=8); IDDM = IDDM control (n=7); DT-CC = diabetic-treated with chromium chloride (n=8); DT-CP = diabetic-treated with chromium picolinate (n=8).

Values are mean ± SEM. * significantly different from control group; # significantly different from diabetic control group.

(p<0.05, F(1,4) = 7.51, F(1,8) = 33.62).
5.2.1.6 Serum creatinine and urea

STZ-diabetic rats exhibited significantly higher serum creatinine (Fig. 100A) and urea (Fig. 100B) levels compared to those of control rats. Chronic treatment with chromium chloride and chromium picolinate significantly decreased elevated serum creatinine and urea levels of diabetic rats, however, did not produce any significant effect on serum creatinine and urea levels of control rats (Fig 100).

5.2.1.7 Serum GPT and GOT

STZ-diabetic rats exhibited significantly higher serum GPT (Fig. 101A) and GOT (Fig. 101B) levels compared to those of control rats. Chronic treatment with chromium chloride and chromium picolinate significantly reduced elevated serum GPT and GOT levels of diabetic rats as compared to diabetic control rats. The treatment, however, did not produce any significant effect on serum GPT and GOT levels of control rats (Fig. 101).

5.2.2 Effect of chronic treatment with chromium compounds in type II (NIDDM) diabetic rats

5.2.2.1 Body Weight, Food Intake and Water Intake

As mentioned in 5.2.2.1, a single intraperitoneal injection of 90 mg/kg STZ in two day old Wistar neonates lead to the development of type II diabetes in the adult state. Body weight in diabetic control group was not significantly different from that of control group (Fig. 102). Chronic treatment with chromium chloride and chromium picolinate did not produce any significant effect on the body weights of control as well as diabetic rats (Fig. 102).

Food (Fig. 103A) and water (Fig. 103B) intakes of diabetic rats were also not significantly different from that of control rats. Chronic treatment with chromium compounds did not produce any significant change in food and water intakes of control as well as diabetic rats (Fig. 103).
Fig. 100: Effect of treatment with chromium chloride and chromium picolinate on serum creatinine (A) and urea (B) levels of IDDM diabetic rats. C = control (n=8); CT-CC = control-treated with chromium chloride (n=8); CT-CP = control-treated with chromium picolinate (n=8); IDDM = IDDM control (n=7); DT-CC = diabetic-treated with chromium chloride (n=8); DT-CP = diabetic-treated with chromium picolinate (n=8). Values are mean ± SEM. * significantly different from control group; # significantly different from diabetic control group (p<0.05, F(5,12) = 5.2, F(3,8) = 11.97).
Fig. 101: Effect of treatment with chromium chloride and chromium picolinate on serum GPT (A) and GOT (B) levels of IDDM diabetic rats. C = control (n=8); CT-CC = control-treated with chromium chloride (n=8); CT-CP = control-treated with chromium picolinate (n=8); IDDM = IDDM control (n=7); DT-CC = diabetic-treated with chromium chloride (n=8); DT-CP = diabetic-treated with chromium picolinate (n=8). Values are mean ± SEM.

* significantly different from control group; # significantly different from diabetic control group (p<0.05, F(4) = 29.72, F(b) = 3.47).
Fig. 102: Effect of treatment with chromium chloride and chromium picolinate on body weight of NIDDM diabetic rats. C = control (n=8); CT-CC = control-treated with chromium chloride (n=8); CT-CP = control-treated with chromium picolinate (n=8); NIDDM = NIDDM control (n=9); DT-CC = diabetic-treated with chromium chloride (n=9); DT-CP = diabetic-treated with chromium picolinate (n=9). Values are mean ± SEM. (p = 0.459, F = 0.95).
Fig. 103: Effect of treatment with chromium chloride and chromium picolinate on food (A) and water (B) intake of NIDDM diabetic rats. C = control (n=8); CT-CC = control-treated with chromium chloride (n=8); CT-CP = control-treated with chromium picolinate (n=8); NIDDM = NIDDM control (n=9); DT-CC = diabetic-treated with chromium chloride (n=9); DT-CP = diabetic-treated with chromium picolinate (n=9). Values are mean ± SEM. ($p = 0.977$, $F(a) = 0.95$; $p = 0.891$, $F(b) = 0.33$).
The average chromium intake in each group of rats was calculated according to the average fluid intake and body weight. The average chromium intake in non-diabetic rats treated with chromium chloride and chromium picolinate was found to be $8.34 \pm 0.64$ and $4.59 \pm 0.49$ μM/day respectively. In case of NIDDM rats treated with chromium chloride and chromium picolinate, the chromium intake was found to be $8.41 \pm 0.54$ and $3.63 \pm 0.78$ μM/day respectively.

### 5.2.2.2 Serum glucose and insulin

Neonatal STZ-diabetic rats exhibited significant hyperglycemia (>140 mg/dl) compared to control rats (Fig. 104A). However, serum insulin levels of diabetic rats were not significantly different from those of control rats (Fig. 104B). Chronic treatment with chromium chloride and chromium picolinate significantly decreased serum glucose levels in diabetic rats without any significant change in serum insulin levels (Fig. 104). Treatment with chromium chloride and chromium picolinate also reduced serum glucose levels of control rats, however, the decrease was statistically significant only with chromium picolinate treatment. Treatment did not produce any significant effect on serum insulin levels of control rats (Fig. 104B).

### 5.2.2.3 Oral Glucose Tolerance Test (OGTT)

At time 0 i.e. immediately prior to glucose challenge, fasting serum glucose levels control rats treated with chromium chloride were not significantly different from those of control rats, however, serum glucose levels of control rats treated with chromium picolinate were significantly lower as compared to control rats (Fig. 105A). Following an oral glucose load, the serum glucose levels of control rats increased with a peak value at 30 min after glucose challenge. Serum glucose levels in control rats treated with chromium chloride and chromium picolinate were lower as compared to those in control rats, however, the decrease was significant at 30 min only in case of chromium picolinate (Fig. 105A).

Serum glucose levels of diabetic rats were significantly higher throughout 120 min after oral glucose challenge as compared to control...
Fig. 104: Effect of treatment with chromium chloride and chromium picolinate on serum glucose (A) and insulin (B) levels of NIDDM diabetic rats. C = control (n=8); CT-CC = control-treated with chromium chloride (n=8); CT-CP = control-treated with chromium picolinate (n=8); NIDDM = NIDDM control (n=9); DT-CC = diabetic-treated with chromium chloride (n=9); DT-CP = diabetic-treated with chromium picolinate (n=9). Values are mean ± SEM.

* significantly different from control group;  # significantly different from diabetic control group (p <0.05, F(a) = 103.87; p = 0.997, F(b) = 0.07).
Fig. 105: Effect of treatment with chromium chloride and chromium picolinate on glucose (A) and insulin (B) responses of NIDDM diabetic rats during oral glucose tolerance test. (◊) = control (n=8); (□) = control-treated with chromium chloride (n=8); (○) = control-treated with chromium picolinate (n=8); (♦) = NIDDM control (n=9); (■) = diabetic-treated with chromium chloride (n=9); (●) = diabetic-treated with chromium picolinate (n=9). Values are mean ± SEM. * significantly different from control group; # significantly different from diabetic control group (p<0.05).
rats. Following an oral glucose load, serum glucose levels in the diabetic rats treated with chromium chloride and chromium picolinate were significantly lower at all the sample points as compared to diabetic control group (Fig. 105A).

Fasting serum insulin levels in control rats treated with chromium chloride and chromium picolinate were not significantly different from those of control rats (Fig. 105B). After oral glucose challenge, serum insulin levels in control group increased reaching a peak value at 30 min, declining thereafter to original value by 120 min. Insulin response to oral glucose load in control rats treated with chromium chloride and chromium picolinate was not significantly different from that of control rats (Fig. 105B).

AUCglucose of control rats treated with chromium chloride and chromium picolinate was lower compared to that of control rats, however, the difference was not statistically significant (Fig. 106A). AUCglucose of diabetic rats was significantly higher compared to that of control rats (Fig. 106A). AUCglucose of diabetic rats treated with chromium chloride and chromium picolinate were significantly lower compared to that of diabetic control rats (Fig. 106A). AUCinsulin of control rats treated with chromium chloride and chromium picolinate were not significantly different from that of control rats. AUCinsulin of diabetic control rats was also not significantly different from that of control rats (Fig. 106B). Treatment with chromium chloride and chromium picolinate did not produce any significant change in AUCinsulin of diabetic rats as compared to diabetic control rats (Fig. 106B).

5.2.2.4 Insulin Tolerance Test

Insulin sensitivity index (K_i) of diabetic rats was significantly lower compared to that of control (Fig. 107). Chronic treatment with chromium chloride and chromium picolinate significantly increased the K_i values of diabetic rats. Treatment also increased K_i values of control rats, however, the effect was not statistically (Fig. 107).
Fig. 106: Effect of treatment with chromium chloride and chromium picolinate on integrated areas under glucose (A) and insulin (B) curves of NIDDM diabetic rats. C = control (n=8); CT-CC = control-treated with chromium chloride (n=8); CT-CP = control-treated with chromium picolinate (n=8); NIDDM = NIDDM control (n=9); DT-CC = diabetic-treated with chromium chloride (n=9); DT-CP = diabetic-treated with chromium picolinate (n=9). Values are mean ± SEM. * significantly different from control group; # significantly different from diabetic control group. (p<0.05, \( F(A) = 57.18; \) p = 0.634, \( F(B) = 0.69 \)).
Fig. 107: Effect of treatment with chromium chloride and chromium picolinate on insulin sensitivity index (KITT) values of NIDDM diabetic rats. C = control (n=8); CT-CC = control-treated with chromium chloride (n=8); CT-CP = control-treated with chromium picolinate (n=8); NIDDM = NIDDM control (n=9); DT-CC = diabetic-treated with chromium chloride (n=9); DT-CP = diabetic-treated with chromium picolinate (n=9). Values are mean ± SEM. (p <0.05, F = 7.78).
5.2.2.5 Serum cholesterol and triglyceride

Neonatal STZ-diabetic rats exhibited significantly higher cholesterol levels compared to those of control (Fig. 108A), however, serum triglyceride levels of the two groups were not significantly different from each other (Fig. 108B). Chronic treatment with chromium chloride and chromium picolinate produced a significant decrease in elevated cholesterol levels of diabetic rats. Treatment with chromium chloride and chromium picolinate also significantly decreased serum triglyceride levels of control as well as diabetic rats (Fig. 108B). There was slight decrease in the serum cholesterol levels of control rats by chronic treatment with chromium chloride and chromium picolinate, however, the effect was not statistically significant (Fig. 108A).

5.2.2.6 Serum creatinine and urea

Neonatal STZ-diabetic rats exhibited significantly higher serum creatinine (Fig. 109A) and urea (Fig. 109B) levels compared to those of control rats. Chronic treatment with chromium chloride and chromium picolinate significantly decreased elevated serum creatinine and urea levels of diabetic rats, however, did not produce any significant effect on serum creatinine and urea levels of control rats (Fig. 109).

5.2.2.7 Serum GPT and GOT

Neonatal STZ-diabetic rats exhibited significantly higher serum GPT (Fig. 110A) and GOT (Fig. 110B) levels as compared to control rats. Chronic chromium chloride and chromium picolinate treatment significantly decreased elevated GPT and GOT levels of diabetic rats, however, did not produce any significant effect on serum GPT and GOT levels of control rats (Fig. 110).
Fig. 108: Effect of treatment with chromium chloride and chromium picolinate on serum cholesterol (A) and triglyceride (B) levels of NIDDM diabetic rats. C = control (n=8); CT-CC = control-treated with chromium chloride (n=8); CT-CP = control-treated with chromium picolinate (n=8); NIDDM = NIDDM control (n=9); DT-CC = diabetic-treated with chromium chloride (n=9); DT-CP = diabetic-treated with chromium picolinate (n=9).

Values are mean ± SEM. * significantly different from control group; # significantly different from diabetic control group.

(p <0.05, $F_{(a)} = 21.83, F_{(b)} = 7.89$).
Fig. 109: Effect of treatment with chromium chloride and chromium picolinate on serum creatinine (A) and urea (B) levels of NIDDM diabetic rats. C = control (n=8); CT-CC = control-treated with chromium chloride (n=8); CT-CP = control-treated with chromium picolinate (n=8); NIDDM = NIDDM control (n=9); DT-CC = diabetic-treated with chromium chloride (n=9); DT-CP = diabetic-treated with chromium picolinate (n=9). Values are mean ± SEM. * significantly different from control group; # significantly different from diabetic control group (p <0.05, $F_{(a)} = 4.29$, $F_{(b)} = 4.25$).
Fig. 110: Effect of treatment with chromium chloride and chromium picolinate on serum GPT (A) and GOT (B) levels of NIDDM diabetic rats. C = control (n=8); CT-CC = control-treated with chromium chloride (n=8); CT-CP = control-treated with chromium picolinate (n=8); NIDDM = NIDDM control (n=9); DT-CC = diabetic-treated with chromium chloride (n=9); DT-CP = diabetic-treated with chromium picolinate (n=9). Values are mean ± SEM. * significantly different from control group; # significantly different from diabetic control group (p < 0.05, $F(\alpha) = 14.37$, $F(9) = 13.24$).
5.2.3 Effect of chromium chloride and chromium picolinate on triglyceride synthesis in 3T3-L1 adipocytes

After days incubation of 3T3-L1 preadipocytes with BMOV and VUR1 (0-10 μM) and insulin (1 μg/ml), cellular triglyceride accumulation normalized by protein levels was measured as an index of the differentiated adipocyte phenotype. Incubation of cells with chromium chloride (Fig. 111A) and chromium picolinate (Fig. 111B) alone failed to elevate triglyceride accumulation above that observed in the control cultures (no drug well) at 10 μM with EC50 value of 3.16 μM. However, simultaneous incubation of cells with chromium compounds and insulin resulted in a dose-dependent increase in the accumulation of intracellular triglycerides. The increase was significant at 1 and 10 μM of chromium chloride and 300 nM and 1 and 10 μM of chromium picolinate with EC50 values of 367.7 nM and 386.9 nM respectively (Fig. 111).

5.2.4 Effect of chromium chloride and chromium picolinate on glucose uptake in C2C12 myoblasts

From the preliminary results, it was found that the maximum uptake of glucose by insulin occurs at a concentration of 6pM/ml at 30 min. Chromium compounds alone did not significantly affect the basal glucose uptake into C2C12 myoblasts, however, when co-incubated with insulin produced a significant increase in the uptake of radiolabeled glucose into the myoblasts (Fig. 112).

5.2.5 Histopathological alterations and effect of chromium chloride and chromium picolinate in STZ-induced type-I and type II diabetic rats.

5.2.5.1 Kidney

Histopathological examination of sections of kidney from control rats showed no pathological changes (Fig. 21-26). Control rats treated with chromium chloride and chromium picolinate showed no pathological changes (Fig. 45-50) and were comparable to those of control rats.
Fig. 111: Effect of treatment with chromium chloride and chromium picolinate on 3T3-L1 cell differentiation. The cells were cultured in medium containing fetal bovine serum (5%), dexamethasone (1 μM) and IBMX (0.5 mM) for 2 days. The cells were then incubated with chromium chloride (A) and chromium picolinate (B) (0-10 μM) in the presence and absence of insulin (1 μg/ml) for 4 days. The cellular triglyceride levels were then measured. * Significantly different from no drug well (p<0.05).
Fig. 112: Effect of treatment with chromium chloride and chromium picolinate on glucose transport by muscle cells. C2C12 myoblasts were incubated with chromium chloride and chromium picolinate along with 2-(1,2-H)deoxy-D-glucose for 30 min and radiolabeled glucose in the cells was measured as explained in the materials and methods section. n = 3. Values are the mean ± SEM. * significantly different from basal; # significantly different from insulin (p<0.05).
STZ-induced type I diabetic rats showed multifocal areas of cortical tubular vacuolation with dilatation at corticomedullary junction (Fig. 27, 31). Mononuclear cell infiltration was also seen (Fig. 28, 32). Kidney sections of type I diabetic rats treated with chromium chloride (Fig. 63, 64) and chromium picolinate showed similar pathological changes, however of lower incidence and intensity (Fig. 67, 68).

Kidney sections of type II diabetic control rats showed multiple areas of tubular vacuolation with tubular hypertrophy (Fig. 34, 38). Sections of type II diabetic rats treated with chromium compounds showed similar pathological changes of lower intensity (Fig. 69, 70, 73, 74). The incidence and intensity of pathological changes in case of type I and type II diabetic rats treated with chromium chloride and chromium picolinate were not different from each other.

5.2.5.2 Liver

Microscopically livers of control rats showed no pathological changes such as congestion, inflammation, cellular necrosis or cholestasis (Fig. 75, 76). Liver sections of type I diabetic rats (Fig. 81, 82) were similar to that of control rats. However, untreated type II diabetic rats showed focal areas of hepatocellular vacuolations and hypertrophy (Fig. 87, 88). Livers of type II diabetic rats treated with chromium chloride and chromium picolinate (Fig. 91, 92) showed similar pathological changes as those of type II diabetic control rats. Liver sections of type I diabetic rats (85, 86) and control rats (Fig. 79, 80) treated with chromium chloride and chromium picolinate showed normal sections comparable to those of untreated control rats.