Effect of aluminum chloride on blood glucose level and lipid profile in normal, diabetic and treated diabetic rats

Venugopala Rao Konda, Madhavi Eerike, R. Prasanth Chary¹, Ruckmani Arunachalam, Venkata Ramana Yeddula², Vinayak Meti, T. Sobita Devi

Abstract:
OBJECTIVES: The objectives of the study were to assess evaluate the effects of aluminum chloride (AlCl₃) on blood glucose and lipid levels in normal, diabetic, and glibenclamide-treated diabetic rats.

MATERIALS AND METHODS: Forty-two male Wistar rats were divided into seven groups of six each. Group I was normal control, Groups II and III were given AlCl₃ 50 and 100 mg/kg, and Group IV to VII were administered with streptozotocin (STZ) (60 mg/kg) intraperitoneally. Group IV was diabetic control, Group V in addition was given AlCl₃ 50 mg/kg, Group VI glibenclamide (10 mg/kg), and Group VII glibenclamide and AlCl₃ (50 mg/kg) per-oral daily for 28 days. Blood glucose and lipid levels were estimated at base line, after diabetes was set in and on the last day of study. Histopathological changes in pancreas, liver, and kidney were studied.

RESULTS: No significant change was observed in blood glucose and lipid levels in Group I. Group II and III showed a dose-dependent significant increase in blood glucose was observed. Group V had a reduction in blood glucose but not to the nondiabetic level. Group VI had significant reduction in blood sugar. In Group VII, treated with glibenclamide and AlCl₃, there was no significant change in blood glucose reduction compared to Group VI. Lipid levels were reduced in groups treated with AlCl₃ and glibenclamide and not in other groups. Gross tissue damage was seen in pancreas in STZ group and in liver and kidney in AlCl₃ groups.

CONCLUSION: AlCl₃ administration in Wistar rats caused in significant hyperglycemia in normal rats, hypoglycemia in diabetic rats, and did not influenced hypoglycemic effect of glibenclamide and in addition, resulted in reduction in lipid levels.

Keywords: AlCl₃, blood glucose, diabetes, glibenclamide, lipid profile

Introduction

Aluminum (Al) is the third most abundant metal present naturally in the Earth’s crust.[¹]

It is also present in air, water, several eatables, and commercial products such as food storage materials, cookware, and medicinal products including drugs.[²] Exposure to humans occurs through different routes. The common routes of exposure include inhalation, oral, and skin. Exposure is more common among people working in Al industries.[³] The extensive use of Al cookware leads to ingestion of small quantities of Al every day. Food samples tested were found to contain Al levels in the range of 0.01 to 1.06 mg/g in 27 out of the total 90 samples tested.[⁴] The use of antiperspirants, drying agents, and cosmetics contributes to percutaneous and inhalational exposure.[³] Al is found to be a component of commonly used medications such as antiulcer drugs such as sucralfate, antacids containing Al hydroxide, hemodialysis fluid, total parenteral nutrition

How to cite this article: Konda VR, Eerike M, Chary RP, Arunachalam R, Yeddula VR, Meti V, et al. Effect of aluminum chloride on blood glucose level and lipid profile in normal, diabetic and treated diabetic rats. Indian J Pharmaco 2017;49:357-65.
solutions, phosphate binders, and vaccines. Al is also found in anticaking agents, preservatives, fillers, coloring agents, emulsifiers, and baking powders and also soy-based infant formula. Such extensive use of Al in consumable and nonconsumable products will certainly lead to Al entry and deposition in human body in the long term.

Al does not have any physiological role in the body. Al gets stored mainly in the lungs, liver, bones, brain, spleen, kidney, and muscles. It may act as a competitive inhibitor for elements such as magnesium, iron, and calcium because of its atomic size and electric charge and may result in anemia and bone damage.

High level of exposure can cause toxicity such as nephrotoxicity and hepatotoxicity. Al-induced neurotoxicity has already been reported in patients with chronic kidney disease who were on dialysis with Al-containing dialysis fluid. Al toxicity has been associated with Alzheimer’s disease, bone disease, and anemia. Al toxicity is due to oxidative stress and lipid peroxidation in tissues.

Exposure to heavy metals such as arsenic, cadmium, mercury, and nickel has been linked to the development of diabetes. Oxidative stress produced by these metals results in decreased insulin release, damage to insulin receptors, and insulin resistance, leading to diabetes. It is reported that higher levels of lead, nickel, Al, copper, and chromium were present in diabetic patients as well as prediabetics compared to normal population. In vitro studies conducted on the effect of Al, magnesium, and manganese have revealed that all the three elements can affect amylin deposition in beta cells of pancreas which could lead to beta cell destruction.

An autopsy study on 12 dialysis-associated encephalopathy patients had shown deposition of Al in various tissues including pancreas in 9 patients.

However, there are no in vivo studies linking Al either to the development or treatment of diabetes. According to National diabetic statistics report-2014, 29 million people suffer from diabetes and more than 8 million people are in prediabetic state. Taking into consideration the disease load of diabetes and increasing exposure to Al, the current study was undertaken to study the effect of Al chloride (AlCl₃) on blood glucose and lipid profile in normal and diabetic rats and assess the impact of AlCl₃ on the antidiabetic activity of glibenclamide in diabetic rats.

Materials and Methods

The study was initiated after getting approval from the Institutional Animal Ethics Committee, Approval letter No. IAEC2/Desp. No. 52/Dt. 29.07.2013. Animals were handled according to the CPCSEA guidelines, India.

Drugs and chemicals

AlCl₃, anhydrous (granular) was purchased from SD Fine-Chem Ltd., Mumbai, streptozotocin (STZ) from Sinco Research Pvt., Ltd., Mumbai, Maharashtra, India, and glibenclamide from the Institutional Pharmacy. Diagnostic kits for the estimation of total cholesterol (TC), triglyceride (TG), and high-density lipoprotein-cholesterol (HDL-C) were obtained from Coral Ltd., Goa, India.

Animals

Forty-two Wistar albino adult male rats of weight 200–250 g were procured from the central animal house and housed in polypropylene cages at 27°C ± 1°C and 12 h light and dark cycles. The animals were allowed to acclimatize to the environment for 7 days and supplied with standard pellet diet and water. 42 Wistar albino rats were divided into 7 groups with six in each [Table 1].

Dose selection

Doses of AlCl₃, selected for this study were 50 mg/kg and 100 mg/kg based on the previous study report (Nehru B).

Experimental design

Methodology

STZ was freshly prepared by dissolving it in 0.1 M citrate buffer (pH 4.5) and was administered intraperitoneally once a day for 2 consecutive days to induce diabetes in 24 animals (Groups IV–VII). The animals were considered as diabetic, if their blood glucose values were above 200 mg/dl on the 5th day, 3 days after the second STZ injection.

AlCl₃, aqueous solution was freshly prepared by dissolving 400 mg of AlCl₃ in 16 ml of distilled water and administered to the rats at doses of 50 and 100 mg/kg through direct oral feeding once daily in the morning for 28 days to Groups II and III rats, respectively. Groups V and VII received AlCl₃ at the dose of 50 mg/kg. The volume of solution administered was from 0.5 to 1 ml according to the body weight of the rats.

Group I received normal saline through direct oral feeding once daily in the morning for 28 days. A total of 45 mg of glibenclamide was dissolved in 15 ml of distilled water and administered through direct oral feeding once daily in the morning from day 5 for 28 days (up to day 33) to Groups VI and VII. The volume of solution administered ranged from 0.5 to 1 ml, according to the rats body weight.

The baseline blood glucose and serum lipid profile were measured in all the groups on day 0. The blood
glucose level and serum lipid profile were measured for Groups II and III on day 0 and 28. For the diabetic rats (Group IV to VII), blood glucose was measured on day 0, 5, and 33 and serum lipid profile was measured on day 0 and 33. In total, 1 ml of blood was collected by retro-orbital sinus puncture under halothane anesthesia. 0.2 ml was used for blood glucose estimation, and the remaining blood was used for serum separation and estimation of lipid profile. Serum was separated by centrifugation at 2500 rpm for 10 min. All the animals were sacrificed using high dose of halothane. Liver and pancreas were removed for histopathological examination.

Blood glucose level was estimated using glucometer (Accu-Check Active). TC, HDL-C, and TG levels were estimated using a spectrophotometer with diagnostic kits (Coral Ltd., Goa, India). The low-density lipoprotein-cholesterol (LDL-C) and very low-density lipoproteins-cholesterol (VLDL-C) in serum were estimated according to the following formula:

\[ \text{VLDL-C concentration (mg/dl) = TGs/5} \]
\[ \text{LDL-C concentration (mg/dl) = TC concentration –} \]
\[ \text{(VLDL-C + HDL-C)} \]

Statistical analysis
The results were analyzed using ANOVA followed by the Tukey–Kramer multiple comparison test. Paired t-test was used for comparison before and after the treatment. Differences were considered significant at \( P < 0.05 \). All values were presented as a mean ± standard error of mean.

| Table 1: Experimental design |
|-----------------------------|
| Groups | Treatment |
|------|----------|
| Group I | Normal saline |
| Group II | AlCl\(_3\) 50 mg/kg |
| Group III | AlCl\(_3\) 100 mg/kg |
| Group IV | STZ 60 mg/kg |
| Group V | STZ 60 mg/kg + AlCl\(_3\) 50 mg/kg |
| Group VI | STZ 60 mg/kg + glibenclamide 10 mg/kg |
| Group VII | STZ 60 mg/kg + AlCl\(_3\) 50 mg/kg + glibenclamide 10 mg/kg |

STZ=Streptozotocin, AlCl\(_3\)=Aluminum chloride

Results
AlCl\(_3\) administration did not affect the general behavior of the animals; however, histopathological examination of kidney and liver showed changes suggestive of hepatotoxicity [Figure 1] and nephrotoxicity [Figure 2].

STZ successfully induced type II diabetes with two doses of 30 mg/kg.

Effect on blood glucose
There was no significant change in the blood glucose level in the control group (Group I). A significant increase in the level of blood glucose was observed in Group II (AlCl\(_3\) 50 mg) and Group III (AlCl\(_3\) 100 mg) compared to the baseline value. A significant increase in the blood glucose level well above 200 mg/dl was seen in diabetic rats (Groups IV–VII). The change in blood glucose in groups IV to VII was compared with that of post-STZ blood glucose. Following treatment with glibenclamide, a significant decrease in blood glucose was observed in Group VI (\( P < 0.01 \)). The Group V animals treated with Al also had a reduction in the blood glucose level which was found to be significant, \( P < 0.01 \), but the animals were still in the diabetic state. The group treated with a combination of AlCl\(_3\) 50 mg + glibenclamide 10 mg (Group VII) also had a reduction in blood glucose with \( P < 0.001 \) [Table 2].

Percentage change in blood glucose was calculated by:

\[ \text{Percentage change in blood glucose} = \frac{\text{Initial value} - \text{Final value} \times 100}{\text{Initial value}} \]

In Group 3 animals treated with AlCl\(_3\) 100 mg/kg, 58.2% increase in blood glucose was noted, but the animals did not develop the diabetic state. There was a decrease in blood glucose in diabetic rats on treatment (Groups VI and VII) and it was slightly higher (61.8%) in Group VII compared to Group VI (59.4%) however this change was not significant [Table 3].

Al-treated groups did not show any change in behavior, food intake, and other activities at both the doses.

| Table 2: Effect of aluminum chloride on blood glucose of rats |
|------------------|
| Groups | Treatment given | Basal | Post-STZ | After 28 days (Day 33) |
|------|---------------|-------|---------|----------------------|
| I | Normal saline | 83.1±3.80 | 88.3±3.36 |
| II | AlCl\(_3\) 50 mg | 94.83±2.414 | 113.00±5.586\(^a\) |
| III | AlCl\(_3\) 100 mg | 77.25±2.562 | 104.5±3.476\(^a\) |
| IV | STZ 60 mg/kg | 96.3±1.085 | 309.3±8.58\(^***\) | 466.3±16.6\(^***a\) |
| V | STZ + AlCl\(_3\) 50 mg | 83.6±0.7483 | 386.8±58.379\(^***\) | 203.4±25.177\(^b\) |
| VI | STZ + glibenclamide 10 mg | 87.33±5.129 | 304.5±55.174\(^***\) | 123.5±7.496\(^b\) |
| VII | STZ + AlCl\(_3\) 50 mg + glibenclamide 10 mg | 81.33±3.955 | 338.5±59.827\(^***\) | 129.1±7.227\(^b\) |

Values are expressed as mean±SEM, n=6. \(^*P<0.05\), \(^**P<0.01\) and \(^***P<0.001\). \(^a\) Compared to 0 day, \(^b\) Compared to post-STZ level. STZ=Streptozotocin, SEM=Standard error of mean, AlCl\(_3\)=Aluminum chloride
Effect of lipid profile

In the control group, there was no significant change in serum lipid profile. A significant decrease (*P < 0.05, **P < 0.01, and ***P < 0.001) in the level of TC, TG, HDL-C, and VLDL-C was observed in AlCl₃ alone (Groups II and III) administered groups compared to pretreatment values. The effect on LDL-C was not significant. 100 mg of AlCl₃ decreased TC, TG, HDL-C, LDL-C, and VLDL-C to a greater extent than 50 mg/kg [Tables 4 and 5].

The level of TGs and VLDL significantly reduced (p < 0.001) in AlCl₃-treated Groups II and III when compared to STZ-induced group animals. The percentage reduction in TGs and VLDL-C was more than 75% in Group III treated with 100 mg/kg of AlCl₃ [Table 4] compared to other groups.

In Group IV (diabetic control), there was a significant increase (P < 0.01 and P < 0.001) observed in TC, TGs, LDL-C, and VLDL-C. HDL-C was slightly decreased but not significantly. The level of TGs and LDL-C was significantly increased (P < 0.001) in the STZ-treated (diabetic control) group. In Group V diabetic rats treated with AlCl₃, there was a significant reduction in TC, HDL-C, LDL-C (P < 0.01) and TG and VLDL-C (P < 0.05) [Table 5].

Glibenclamide (Groups VI and VII) also exhibited a hypocholesterolemic effect. A significant decrease in the lipid profile was also found in Group V (STZ + glibenclamide 10 mg/kg) with P < 0.01 and in Group VII (AlCl₃ 50 mg + STZ + glibenclamide 10 mg/kg) animals (P < 0.001). The level of TGs and VLDL-C significantly reduced (p < 0.001) in Group VII [Table 5].

The percentage reduction in TC (42.6%), HDL-C (43.1%), and LDL-C (44.4%) was more in diabetic rats treated with glibenclamide compared to diabetic rats treated

| Groups | Percentage change in blood glucose |
|--------|-----------------------------------|
| I      | No changes                        |
| II     | 19.9 (increase)*                  |
| III    | 58.2 (increase)*                  |
| IV     | 50.7 (increase)*                  |
| V      | 47.4 (decrease)*                  |
| VI     | 59.4 (decrease)*                  |
| VII    | 61.8 (decrease)*                  |

*In Group I–III percentage change was calculated from basal and final values,
*Diabetic rats Group IV–VII percentage change was calculated from values after STZ and end of treatment. STZ=Streptozotocin
Konda, et al.: Effect of AlCl₃ in diabetic rats

In Group V, the percentage reduction was higher with TGs (47%) and VLDL-C (53.6%) compared to Group VI. In the glibenclamide-treated group, it was 35.9 and 35.9%, respectively. In diabetic rats treated with glibenclamide and AlCl₃, percentage reduction in TC (34.2%), HDL-C (34.4%), and LDL-C (29.6%) was reduced compared to Group VI and the effect was higher with TG (50.8%) and VLDL-C (50.8%) compared to Group V [Table 6].

with AlCl₃ and it was 29.5%, 29.6%, and 21.8%, respectively [Table 6].

Table 4: Effect of aluminum chloride on lipid profile in Group I–III

| Groups | TC Basal | TG Basal | After 28 days Basal | HDL-C After 28 days Basal | LDL-C After 28 days Basal | VLDL-C After 28 days Basal |
|--------|---------|---------|---------------------|------------------------|-------------------------|--------------------------|
| I      | 68.2±2.70 | 64±2.39 | 66.5±5.2           | 13.63±0.54            | 41.73±1.6               | 42.97±3.37               |
| II     | 76.1±5.4  | 97.7±2.0| 41.3±4.3***        | 15.2±1.0              | 11.3±1.1**              | 14.07±1.1                |
| III    | 96.3±7.4  | 97.3±2.1| 24.1±3.7***        | 19.2±1.4              | 11.1±1.3*               | 41.3±4.2                 |

n=6, values were expressed as mean±SEM. *P<0.05, **P<0.01, ***P<0.001. HDL-C=High-density lipoprotein-cholesterol, LDL-C=Low density lipoprotein-cholesterol, VLDL-C=Very low-density lipoprotein-cholesterol, SEM=Standard error of mean, TC=Total cholesterol, TG=Triglyceride, NS=Not significant

Table 5: Effect of aluminum chloride on lipid profile in Group IV–VII

| Groups | TC Basal | TG Basal | After 33 days Basal | HDL-C After 33 days Basal | LDL-C After 33 days Basal | VLDL-C After 33 days Basal |
|--------|---------|---------|---------------------|------------------------|-------------------------|--------------------------|
| IV     | 79.4±4.15| 133.7±1.61***| 97.7±2.09        | 152.65±1.52***        | 15.89±0.83              | 43.9±3.15                |
| V      | 91.4±2.6 | 64.4±6.7**  | 88.9±5.1          | 47.1±7.8              | 18.2±0.5                | 55.3±2.6                |
| VI     | 96.3±3.6 | 55.2±3.9*** | 76.7±2.8          | 49.1±7.1**            | 19.2±1.2                | 61.7±5.5                |
| VII    | 104.7±6.5 | 68.8±4.5*** | 88.5±3.3          | 43.5±5.9***           | 20.9±1.3                | 66.0±5.7                |

n=6, values were expressed as mean±SEM. *P<0.05, **P<0.01, ***P<0.001. HDL-C=High-density lipoprotein-cholesterol, LDL-C=Low density lipoprotein-cholesterol, VLDL-C=Very low-density lipoprotein-cholesterol, SEM=Standard error of mean, TC=Total cholesterol, TG=Triglyceride
Histopathological examination

Pancreas

In STZ-induced diabetic rats, a decrease in pancreatic islet numbers and size and necrotic changes of pancreatic islets, especially in the center of islets were observed. Residue of destroyed cells and severe reduction of beta cells were clearly seen, and invasion of connective tissues in the parenchyma of pancreatic islets was detected, but these abnormal histological signs were not seen in AlCl₃ alone-treated groups. Significant but lesser effects compared to AlCl₃ supplemented group were observed in the glibenclamide-treated group [Figure 3].

Liver

Histopathological examination of liver in AlCl₃-treated rats showed formation of granuloma in hepatic lobule, microsteatosis, and mild sinusoidal dilatation. In the STZ-treated group, there was severe sinusoidal dilatation, infiltration with lymphocytes, and Kupffer cell hyperplasia and which was reduced in Group V. In glibenclamide treated group, Groups VI and VII, those changes were mild [Figure 1].

Kidney

AlCl₃-treated groups showed tubular degeneration, modest congestion of blood vessels, necrosis of the renal cells, degeneration of glomeruli, intrarenal arterial vessel showed modest thickening of the walls, and dose related tubulointerstitial damage. In diabetic control group, there were degenerated glomeruli and edema of the renal tubules and infiltration seen. In diabetic rats treated with AlCl₃, glomerular degeneration and tubulointerstitial damage, and congestion were present. These changes were minimal in glibenclamide-treated group [Figure 2].

Table 6: Percentage reduction in serum lipid levels in Group I–VII

| Groups | TC (%) | TG (%) | HDL-C (%) | LDL-C (%) | VLDL-C (%) |
|--------|--------|--------|-----------|-----------|------------|
| I      | No changes |        |           |           |            |
| II     | 25.2   | 57.7   | 25.6      | 9.6       | 57.9       |
| III    | 42     | 75.2   | 42.1      | 30.9      | 75.7       |
| V      | 29.5   | 47     | 29.6      | 21.8      | 53.6       |
| VI     | 42.6   | 35.9   | 43.1      | 44.4      | 35.9       |
| VII    | 34.2   | 50.8   | 34.4      | 29.6      | 50.8       |

HDL-C=High-density lipoprotein-cholesterol, LDL-C=Low-density lipoprotein-cholesterol, VLDL-C=Very low-density lipoprotein-cholesterol, TC=Total cholesterol, TG=Triglyceride

Figure 3: Histopathological examination of pancreatic tissue of rats - pancreas: Group I-III: no changes, it showed normal pancreas with normal islet of Langerhans, Group IV: decrease in pancreatic islet numbers and size, inflammation, and necrotic changes of pancreatic islets, especially in the center of islets, Group V: pancreatic islet cell number reduced and necrosis present, Group VI: reduced inflammation and changes were less than Group IV, Group VII: reduced inflammation and changes were less than Group IV.
Discussion

The current study was undertaken to evaluate the effect of AlCl₃ on blood glucose and lipid profile in normal, STZ-induced diabetic rats and glibenclamide-treated diabetic rats. Two doses of AlCl₃, 50 and 100 mg/kg, were selected based on previous studies.

Effect on blood glucose

A significant increase ($P < 0.05$) in blood glucose level was observed in rats treated with 50 and 100 mg/kg of AlCl₃, and the percentage of increase was 58% in the 100 mg/kg treated group. Although there was an increase in the blood glucose level, it was not elevated to the diabetic level.

The present result is in agreement with those reported by Clayton and Clayton[16] and Kalaiselvi et al.,[27] who reported that plasma glucose levels were significantly elevated in rats fed with AlCl₃ for 60 days when compared with the normoglycemic group. The percentage increase was only 25% in the previous study, whereas in our study, it was 58%.

The increase in blood glucose level could be due to pancreatic islet damage caused by AlCl₃-induced oxidative damage. Al is a strong oxygen acceptor and also binds to other oxygen donors and produces reactive oxygen species causing oxidative damage.[18]

Metwally and Mazhar also showed that Al toxicity caused a disruption in carbohydrate metabolism, through enhancement of breakdown of liver glycogen, possibly mediated by an increase in adrenocorticotropic and glucagon hormones and/or reduced insulin activity.[19] The reason for the increased blood glucose could be due to inhibition of insulin release from the beta cells and altered carbohydrate metabolism.

Animals treated with two doses of STZ at 30 mg/kg-induced mild impairment of insulin secretion mimicking type II diabetes mellitus.[20] STZ causes damage to beta cells of pancreas through DNA alkylation, resulting in decreased insulin secretion. In our study, STZ-induced damage is clearly seen in histopathological examination [Figure 3], and only a few islet cells were preserved.

The purpose of inducing type II diabetes mellitus in our study is due to the fact that the selected antidiabetic drug glibenclamide is insulin secretogogue. For the activity of glibenclamide a few functional islet cells should be there in the pancreas. Moreover, type II diabetes mellitus is the most commonest type. Interestingly, in our study, it was observed that, in diabetic rats treated with AlCl₃ alone, there was a decrease in blood glucose from 386 to 203 mg/dl but not to the normal range. The decrease in blood glucose may be due to spontaneous recovery of pancreatic damage induced by STZ, and it also denotes that AlCl₃ did not adversely affect the recovery of pancreas. Whether the decrease in blood glucose is independent of AlCl₃ is not known.

Nampoothiri et al. have observed a significant reduction in acetylcholinesterase enzyme (AChE) activity following the Al administration. Reduction in AChE activity will result in increased level of ACh.[21] ACh is reported to increase the insulin secretion when glucose level is above 7 mM. The blood glucose level in the AlCl₃ and STZ-treated group at baseline was 21.24 mM (386.8 mg/dL). At this high level of blood glucose, inhibition of AChE by Al would have caused increased secretion of insulin by the elevated level of ACh. This could be the reason why blood glucose was reduced in this group. However, in the isolated Al group, the oxidative damage on normal pancreatic tissue by Al would have been responsible for the elevated blood glucose.

Diabetic rats treated with glibenclamide had a decrease in blood glucose level, which is an expected response to the drug. Glibenclamide acts by increasing insulin secretion from pancreatic islet cells by blocking K⁺ ATP channels. When AlCl₃ was given along with glibenclamide, it did not significantly affect the hypoglycemic effect of glibenclamide. The small elevation in the percentage of reduction in blood glucose observed in STZ + glibenclamide + AlCl₃-treated group could be explained by the action of Al on insulin secretion as discussed above.

Effect on Lipid profile

Interestingly, in our study, a highly significant reduction ($P < 0.001$) in TG and VLDL-C levels was observed in AlCl₃-treated group (Group II and III). However, the reduction in the LDL-C was not found to be statistically significant [Table 3]. This could be due to the hepatotoxic effect of Al which resulted in decreased synthesis of TC.

Chronic Al exposure has been reported to cause depletion of glutathione in liver and a significant reduction in the synthesis of bile acids and this can be due to the reduction in cholesterol level due to Al.[22]

Sperber had observed a significant reduction in LDL-C and to a lesser extent HDL-C following 2-month administration of antacid containing a combination of Al hydroxide along with simethicone and magnesium hydroxide in hypercholesterolemic individuals.[23] However, in our study, the hypocholesterolemic effect on LDL-C was not observed in rats.

In untreated diabetic rats, there was a significant increase in TC, TGs, LDL-C, and VLDL-C except HDL-C. In diabetes, hyperlipidemia occurs due to
increased lipolysis, leading to increased free fatty acids and glycerol which are taken up by liver to synthesize acetyl Co A. Acetyl Co A is a precursor for cholesterol synthesis. It has been reported hyperlipidemia that occurs in STZ-induced diabetic rats is due to the increase in intestinal acyl coenzyme A activity.\[24\]

Group V diabetic rats treated with AlCl$_3$ also showed decreased lipid levels. The exact mechanism of reduction is not known. Probably, AlCl$_3$ can cause a decrease in cholesterol synthesis by damaging the liver cells, and in addition, absorption of fats from the intestine is altered in diabetics.

In diabetic rats treated with glibenclamide also, there was a significant reduction in lipid levels. Glibenclamide acts by increasing insulin secretion. It has been already known that insulin inhibits lipolysis in adipose tissue and favors TG synthesis. Insulin alters both esterification and lipolysis pathways.\[35\] Insulin enhances the transcription of vascular endothelial lipoprotein lipase which is involved in the clearance of VLDL-C.

Group VII rats treated with glibenclamide and AlCl$_3$, also showed a reduction in serum lipid levels. This is due to glibenclamide that controls blood glucose and AlCl$_3$ that helps in decreasing the absorption of fats. The percentage reduction in TC, HDL-C, and LDL-C was higher in diabetic rats treated with glibenclamide which shows that it decreases cholesterol synthesis in liver. In diabetic rats treated with AlCl$_3$, the percentage reduction was higher with TGs and VLDL-C. This may be due to the increase in esterification of fatty acids and decreased VLDL-C clearance from the circulation. In diabetic rats treated with both glibenclamide and AlCl$_3$, there was a mild alteration in antihyperlipidemic action of glibenclamide. The percentage reduction in TC, HDL-C, and LDL-C was reduced compared to Group VI, and it was increased with TG and VLDL-C.

From our study, it was clearly seen that diabetic rats treated with glibenclamide had a higher reduction in TC, HDL-C, and LDL-C while AlCl$_3$-treated diabetic rats had a reduction in TGs and VLDL-C. Treatment with both glibenclamide and AlCl$_3$ had an additive effect on TG and VLDL-C.

**Conclusion**

From our findings, it can be concluded that AlCl$_3$ administration had produced a dose-dependent elevation of blood glucose and reduction of lipid levels in normal rats. Diabetic rats treated with AlCl$_3$, showed a reduction of blood glucose. AlCl$_3$ was not found to affect the antidiabetic activity of glibenclamide. A hypolipidemic effect was seen in all the groups except in the normal control and diabetic control group. AlCl$_3$ significantly produced a higher reduction of TG and VLDL-C in normal rats.

In diabetic rats treated with glibenclamide, the reduction was higher in TC, HDL, and LDLD-c. Glibenclamide and AlCl3 had an additive effect in reducing TG and VLDL-C in diabetic rats.

Therefore, exposure to AlCl$_3$ may not adversely affect the antidiabetic activity of glibenclamide but may contribute to reduction in lipid levels. Further studies are needed to elucidate the mechanism of hypolipidemic action of Al.

**Acknowledgment**

We would like to thank Chettinad Academy of Research and Education, for providing the facility and Dr. Vijayshree, Professor of pathology, for providing her expert opinion on histopathological findings of our work and Mr. Vijayvel, animal house lab technician, for his support during the work.

**Financial support and sponsorship**

Nil.

**Conflicts of interest**

There are no conflicts of interest.

**References**

1. Verstraeten SV, Aimo L, Oteiza PI. Aluminium and lead: Molecular mechanisms of brain toxicity. Arch Toxicol 2008;82:789-802.
2. Krewski D, Yokel RA, Nieboer E, Borchelt D, Cohen J, Harry J, et al. Human health risk assessment for aluminium, aluminium oxide, and aluminium hydroxide. J Toxicol Environ Health B Crit Rev 2007;10 Suppl 1:1-269.
3. Wesdock JC, Arnold IM. Occupational and environmental health in the aluminum industry: Key points for health practitioners. J Occup Environ Med 2014;56:55-11.
4. Ogimoto M, Suzuki K, Haneshii N, Kikuchi Y, Takanashi M, Tomioka N, et al. Aluminium content of foods originating from aluminium-containing food additives. Food Addit Contam Part B Survivell 2016;9:85-90.
5. Geyikoglu F, Türeke H, Bakır TO, Cicek M. The genotoxic, hepatotoxic, nephrotoxic, haematoxic and histopathological effects in rats after aluminium chronic intoxication. Toxicol Ind Health 2013;29:780-91.
6. Pierides AM, Edwards WG Jr., Cullum UX Jr., McCall JT, Ellis HA. Hemodialysis encephalopathy with osteomalacic fractures and muscle weakness. Kidney Int 1980;18:115-24.
7. Tomljenovic L. Aluminium and Alzheimer’s disease: After a century of controversy, is there a plausible link? J Alzheimers Dis 2011;23:567-98.
8. Malluche HH. Aluminium and bone disease in chronic renal failure. Nephrol Dial Transplant 2002;17 Suppl 2:21-4.
9. Kaiser L, Schwartz KA. Aluminium-induced anemia. Am J Kidney Dis 1985;6:348-52.
10. Yousef MI. Aluminium-induced changes in hemato-biochemical parameters, lipid peroxidation and enzyme activities of male rabbits: Protective role of ascorbic acid. Toxicology 2004;199:47-57.
11. Mirhashemi SM, Shahabaddin ME. Evaluation of aluminium,
manganese, copper and selenium effects on human islets amyloid polypeptide hormone aggregation. Pak J Biol Sci 2011;14:288-92.
12. Mirhashemi SM, Aarabi MH. To study various concentrations of magnesium and aluminium on amylin hormone conformation. Pak J Biol Sci 2011;14:653-7.
13. Reusc H, Lindner B, Arnholdt H. Widespread aluminium deposition in extracerebral organ systems of patients with dialysis-associated encephalopathy. Virchows Arch 1994;424:105-12.
14. Serdar MA, Bakir F, Hasimi A, Celik T, Akin O, Kenar L, et al. Trace and toxic element patterns in nonsmoker patients with noninsulin-dependent diabetes mellitus, impaired glucose tolerance, and fasting glucose. Int J Diabetes Dev Ctries 2009;29:35-40.
15. Nehru B, Bhalla P, Garg A. Further evidence of centrophenoxine mediated protection in aluminium exposed rats by biochemical and light microscopy analysis. Food Chem Toxicol 2007;45:2499-505.
16. Clayton GD, Clayton FE, editors. Patty’s Industrial Hygiene and Toxicology: Volume 2A, 2B, 2C: Toxicology. 3rd ed. New York: John Wiley Sons; 1981-1982. p. 1496.
17. Kalaiselvi A, Aadhinath Reddy G, Ramalingam V. Ameliorating effect of ginger extract (Zingiber officinale Roscoe) on liver marker enzymes, lipid profile in aluminium chloride induced male rats. Int J Pharm Sci Drug Res 2015;7:52-8.
18. Kawahara M, Kato-Negishi M. Link between aluminium and the pathogenesis of Alzheimer’s disease: The integration of the aluminum and amyloid cascade hypotheses. Int J Alzheimers Dis 2011;2011:276393.
19. Metwally FM, Mazhar MS. Effect of aluminium on the levels of some essential elements in occupationally exposed workers. Arh Hig Rada Toksikol 2007;58:305-11.
20. Srinivasan K, Viswanath B, Asrat L, Kaul CL, Ramarao P. Combination of high-fat diet-fed and low-dose streptozotocin-treated rat: A model for type 2 diabetes and pharmacological screening. Pharmacol Res 2005;52:313-20.
21. Nampoothiri M, Kumar N, Venkata Ramalingayya G, Gopalan Kutty N, Krishnadas N, Mallikarjuna Rao C, et al. Effect of insulin on spatial memory in aluminum chloride-induced dementia in rats. Neuroreport 2017;28:540-4.
22. Gonzalez JA, Roma MG, Bernal CA, Alvarez Md L, Carrillo MC. Biliary secretory function in rats chronically intoxicated with aluminum. Toxicol Sci 2004;79:189-95.
23. Sperber AD, Henkin Y, Ziuli I, Bearman JE, Shany S. The hypocholesterolemic effect of an antacid containing aluminum hydroxide. Am J Med 1991;91:597-604.
24. Kusunoki J, Aragane K, Kitamine T, Kozono H, Kano K, Fujinami K, et al. Postprandial hyperlipidemia in streptozotocin-induced diabetic rats is due to abnormal increase in intestinal acyl coenzyme A: cholesterol acyltransferase activity. Arterioscler Thromb Vasc Biol 2000;20:171-8.
25. Otto-Buczkowska E, Jarosz-Chobot P. Lipid metabolism. I. Role of insulin in lipid metabolism. Pol Merkur Lekarski 2001;10:180-4.