Researchers investigated the effects of titanium on biochemical parameters related to lipid metabolism. Male Wistar rats were treated with different doses of titanium for a period of up to 60 days. Blood samples were collected for analysis. Lipid-related parameters in plasma were measured by standard methods. It was shown that titanium reduced plasma VLDL and triglycerides concentrations but increase in LDL-C and cholesterol levels were seen in all experimental groups. Titanium also showed to inhibit lipoprotein lipase activity. The finding that titanium increases LDL and cholesterol concentrations should be considered seriously, especially in people exposing to titanium compounds for a long period.
titanium intake could induce dyslipidemic profile at in vivo condition.

**MATERIALS AND METHODS**

Male Wistar rats (200-250 g) were used for this study. They were kept under standard conditions having free access to food and water but were fasted the night before experiment. The experimental animals received daily intraperitoneal dose of 2.5 mg/kg body weight of titanium for a period of 10 days (acute dose) and 0.75 mg/kg body weight of titanium for a period of 30 and 60 days (chronic dose). In the day of experiment, animals were killed, bloods were collected and centrifuged at 2000-2500×g and their plasma was separated from blood cells. Samples were used directly or kept refrigerated for the analysis. Free fatty acids were measured by the method of Felix [21] and plasma protein by the method reported by Lowry et al. [22]. Plasma cholesterol and triglyceride levels were determined by the enzymatic methods using commercial laboratory kits purchased from Ziest Chimie (Tehran, Iran). HDL-C was measured in the supernatant after the precipitation of the Apo-B containing lipoproteins (LDL and VLDL) using polyanions in the presence of a divalent cation [23]. LDL-cholesterol was determined by calculation using the Friedewald equation [24].

**RESULTS**

Plasma levels of lipid related parameters were changed in animals treated with different doses of titanium (Tables 1-3). As indicated in Table 1, cholesterol and LDL-C increased significantly in animals treated with acute dose of titanium in short time whereas triglyceride and free fatty acids were decreased in this condition. Changes in lipid fractions in animals chronically treated with titanium for 30 and 60 days are shown in Tables 2 and 3 respectively. It can be seen that the pattern of changes is similar to acutely-treated animals.

**DISCUSSION**

The present results demonstrated that titanium interferes with lipid metabolism. This interference might be initiated by the changes in the activity of lipoprotein lipase, a key enzyme that plays an important role in the metabolism, transport and tissue uptake of lipid fractions. Our previous study showed that titanium reduced the activity of this enzyme by 19.6-36.1 percent (p < 0.005) [20]. The exact mechanism by which titanium inhibits lipoprotein lipase activity is not known exactly, however the activity of this enzyme depends on the presence of free SH groups [25]. It is probable that titanium by interacting with some essential SH groups interferes with lipid metabolism. This interference could be attributed to either the lowered activity of lipoprotein lipase in the presence of titanium or the inhibition of adenylate cyclase system leading to the reduction in intracellular levels of cAMP and the inhibition of adenylate cyclase system leading to the reduction in intracellular levels of cAMP.
inactivation of HSL [26]. Although the concentrations of different lipid and lipoprotein fractions are changed following the administration of titanium, the main clinically-important consequence is the significant increase in LDL levels of titanium treated animals. This effect of titanium should be considered seriously. It is well documented that there is a relationship between lipoprotein levels and the incidence of cardiovascular disease [27]. There are many reports indicating that the progression of atherosclerosis is well correlated with high plasma LDL/HDL ratio [27-29]. So, our results showed that titanium elevated the ratio of LDL/HDL should be considered seriously in patients taking this drug for a long period of time.

Our results also showed that the liver content of triglycerides decreased following the administration of titanium. Triglycerides are synthesized from the esterification of glycerol phosphate and acyl CoA. Glycerol phosphate in cells is partly maintained by glycolytic reactions, and titanium probably inhibits glycolytic enzymes. Therefore, the intracellular level of glycerol phosphate is limited. Titanium, on the other hand, inhibits lipoprotein lipase and lowers the plasma levels of free fatty acids. It is probable that the limitation of triglyceride synthesis may result in lower levels of liver triglycerides. Substrates that could not reach the triglyceride synthesis pathways may contribute to phospholipid synthesis. Our results showed that titanium increased phospholipid contents of liver.

Considering our data, it is concluded that the systemic changes in plasma lipid parameters, at the cellular level, may induce changes in cell membrane and metabolism and this could be the start of metabolic disorders in patients who are using titanium for a long period of time.

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CURRENT AUTHOR ADDRESSES
H. Ahmadvand, department of Biochemistry, faculty of medicine, Lorestan University of medical science, Lorestan, Iran. E-mail: hassan_a46@yahoo.com (Corresponding author)
M. Ani, Department of clinical Biochemistry, School of pharmacy, Isfahan University of Medical Sciences, Isfahan, Iran.
A. A. Moshtaghi, Department of clinical Biochemistry, School of pharmacy, Isfahan University of Medical Sciences, Isfahan, Iran.