



## Effect of Dietary Cholesterol and Niacin Supplementation on Serum Enzymatic Alterations in Experimentally Induced Renal Dysfunction in Wistar Rats

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### ABSTRACT

Study was carried out to evaluate the effect of dietary cholesterol and niacin supplementation and renal dysfunction in wistar rats. Eighty-four adult healthy wistar male rats were divided into twelve equal groups. Experiment was carried out as per  $2 \times 3 \times 2$  factorial design with two clinical conditions (Kidney-Normal and Kidney-Compromised); three levels of cholesterol supplementation (0%, 0.5% and 1.0%) and two niacin levels (unsupplemented and supplemented @ 100 mg/kg body weight), respectively. At the start of the experiment, renal dysfunction was induced in respective rats by daily injection of gentamicin for 8 days. Blood samples were collected from experimental animals on zero, 20<sup>th</sup>, 40<sup>th</sup> and 60<sup>th</sup> days of trial to study liver specific serum enzyme profile *viz* aspartate amino transaminase (AST), alanine amino transaminase (ALT), alkaline phosphatase (ALP) and acid phosphatase (ACP). Gentamicin injection resulted in significantly increase in levels of enzymes. Also cholesterol supplementation @ 0.5% and 1% resulted in significantly higher levels of enzymes studied. However, treatment with niacin @ 100 mg/kg body weight resulted in marked improvement in level of enzymes studied.

**Keywords:** Gentamicin, renal dysfunction, niacin, Wistar rats

Kidneys perform various functions in the body such as osmoregulation, excretion of end products including urea and creatinine, synthesis of hormones such as rennin and erythropoietin and for the metabolism of vitamin D. Thus, the kidneys maintain water and electrolyte balance as well as pH to regulate metabolic activities. To perform their function well, the kidneys have the richest blood supply per unit weight of tissue in the body. Renal arteries supply blood supply to kidneys and venous drainage is performed by the renal veins. There are many environmental contaminants and chemical variables such as drugs, alter the functions of the kidney (Mahmood and Waters, 1994).

Nephrotoxicity is characterized by any adverse functional or structural change in the kidney due to the effect of various chemical and biological products, that is inhaled, ingested or absorbed or which yields metabolite with an identifiable toxic effect on the kidney (Aslam *et al.*,

2013). Drug induced nephrotoxicity is an important cause of renal failure. Nephrotoxic drugs include antiretrovirals (example, tenofovir), antimicrobials (example, aminoglycosides) and chemotherapeutic agents (example, cisplatin) (Perazella, 2009). Aminoglycosides including gentamicin are potential agents for the treatment of gram negative bacterial infections. Nephrotoxicity is the major side effect of aminoglycosides, which accounts for about 10-15% of all cases of acute renal failure (Homes and Weinberg, 1986). The specificity of gentamicin renal toxicity is apparently related to its preferential accumulation in the renal convoluted tubules and its effect on biological membranes. The excretion of gentamicin is through kidneys without degradation and about 5- 10 % is concentrated in the proximal convoluted tube, highly exceeding serum levels (Costa *et al.*, 1987). Aminoglycosides have highly basic charge and thus they poorly penetrate cell membranes (Erdem *et al.*, 2000). The

proximal tubular cells of the renal cortex have a greater ability to concentrate aminoglycosides several folds more than plasma levels (Erdem *et al.*, 2000).

Cholesterol is the most abundant steroid in the body. Far from being harmful, when properly regulated, it is a critically important molecule as an integral component of cellular membranes where it helps in maintenance of membrane structural integrity and fluidity. Cholesterol homeostasis in the body is maintained by the balance between cholesterol biosynthesis, and its metabolism. Additionally it also serves as precursor for several important biomolecules such as steroid hormones, bile acids, and vitamin D. Hypercholesterolemia is well-known to be an independent risk factor for renal injury (Oda and Keane, 1999) and to aggravate the pathogenesis of a variety of clinical and experimental renal diseases (Stulak *et al.*, 2001). Several studies indicated that abnormalities in lipid metabolism can often accompany and exacerbate renal disease (Vazquez-Perez *et al.*, 2001). Hypercholesterolemia is well-known to be an independent risk factor for renal injury (Oda and Keane, 1999) and to aggravate the pathogenesis of a variety of clinical and experimental renal diseases. There are many evidences that supports the fact that high cholesterol diet exacerbates kidney damage in animal models of kidney disease (Mori and Hirano, 2012). Previous data showed that even a short exposure to high cholesterol diet supplementation is associated with an increase in oxidative stress and renal inflammation (Wilson *et al.*, 2003). Liver enzymes such as AST, ALT, ACP and ALP are marker enzymes for assessing liver function and integrity (Kim *et al.*, 2006). These enzymes are usually elevated in acute hepatotoxicity or mild hepato-cellular injury (Kim *et al.*, 2006).

Chronic kidney disease results in profound alterations in lipid metabolism and plasma lipid profiles characterized by hypertriglyceridemia, diminished HDL cholesterol, impaired HDL maturation, and depressed HDL antioxidant and anti-inflammatory activities (Vaziri, 2006). Nephrotic syndrome is also found to be associated with profound dysregulation of lipid/lipoprotein metabolism, severe hyperlipidemia, and lipiduria. Common features of dyslipidemia in nephritic syndrome are hypercholesterolemia, increased plasma low-density lipoprotein (LDL), impaired LDL and high-density lipoprotein (HDL) clearance, and depressed maturation of HDL (Vaziri, 2003). These abnormalities are due to

acquired hepatic LDL receptor and HDL docking receptor (SRB1) deficiencies as well as urinary excretion and reduced plasma concentration and enzymatic activity of lecithin cholesterol acyltransferase (LCAT) (Vaziri and Liang, 2002).

Niacin (nicotinic acid, vitamin B3) is a water-soluble vitamin that is critical for cellular metabolism (Maiese *et al.*, 2009). It has been used successfully to regulate abnormalities in plasma lipid metabolism and is frequently referred to as a “broad spectrum anti-hyperlipidemic drug”. In pharmacological doses, niacin reduces total plasma cholesterol, triglyceride, VLDL, and LDL concentrations (Carlson, 1969; Figge *et al.*, 1988). Niacin and its coenzymes NAD and Nicotinamide Adenine Dinucleotide Phosphate (NADP) have fundamental roles as a part of reduction/oxidation coenzymes involved in energy metabolism, amino acid metabolism, detoxification reactions for drugs and other substances as well as antioxidant protection (Permul *et al.*, 2005). Many studies have examined the effects of niacin on various diseases such as anemia (Arun *et al.*, 1999), hypertension (Cho *et al.*, 2009), cardiovascular diseases (Brown *et al.*, 2001) and liver diseases (Ganji *et al.*, 2015). However, one of the roles through which niacin can have a potential effect on human health is that as an antioxidant, which has not been clearly investigated. However, there is no published information available on the pharmacokinetics of niacin in patients with renal disease. Although there is a lot of information available regarding the altered lipid metabolism in renal dysfunction but there is a gap with respect to the metabolic profile at different levels of cholesterol feeding and its interaction with niacin/nicotinic acid as such and also in renal dysfunction.

## MATERIALS AND METHODS

The study was conducted in the Division of Veterinary Physiology and Biochemistry, faculty of Veterinary sciences and animal husbandry, Sher-e-kashmir University of Agricultural Sciences and Technology- Jammu, R.S. Pura, J&K, India.

### Ethical approval

The animals were treated humanely during the whole period of experimental study and the work was approved

by the institutional Animal Ethics Committee vide No. 862/ac/04/CPCSEA on ethical standards in animal experimentation.

### Experimental material

Specialized rat feed containing 3 levels of cholesterol supplementation @0%, 0.5% and 1% was procured from CSK HPKV, Palampur (H.P.), India. Diets were made equi-calorie by supplementation with groundnut oil to match the energy content of the diet at three different cholesterol levels. Nicotinic Acid (as source of niacin) and all the other chemicals (analytical grade) used in the present study were procured from SD Fine-Chem Ltd., India and Sigma Aldrich Corporation, India. Gentamicin sulphate was procured from Genticyn company. Diagnostic Kits were procured from Erba diagnostics Mannheim.

### Experimental design

The study was conducted on 84 adult healthy Wistar male rats with a mean body weight of  $200 \pm 5$ gms. Animals were procured from Indian Institute of Integrative Medicine (IIIM), Council of Scientific & Industrial Research (CSIR,) Lab, Jammu. All the animals were provided standard pelleted ration and clean drinking water *ad libitum*. All the animals were maintained under standard managemental conditions. A daily cycle of 12 h of light and 12 h of darkness was provided to animals. Prior to start of experiment, the animals were acclimatized in the laboratory conditions for a period of more than 1 week. All the experimental animals were kept under constant observation during entire period of study. Study was carried out for a duration of sixty days excluding the time required for acclimatization of animals and induction of renal dysfunction. Prior to the start of the experiment renal dysfunction was induced in rats from (Group VII to group XII) by daily intra-peritoneal injection of gentamicin @ 80mg/kg body weight for 8 days. Niacin was supplemented in group II, group IV, group VI, group VIII, group X and group XII @ 100 mg/kg body weight for 60 days. Dose of niacin was selected as per Yanardag *et al.* (2005). Blood collection was made from retro-orbital fossa of all experimental rats on 0<sup>th</sup> day, 20<sup>th</sup> day, 40<sup>th</sup> day and 60<sup>th</sup> day of the experiment. Blood was collected and allowed to clot. This was followed by centrifugation at 3000 rpm for 15 minutes. The serum samples was collected and used

to study enzymatic parameters. Estimation of serum AST, ALT, ALP and ACP were carried out using Erba diagnostic kits. Animals were slaughtered on 60<sup>th</sup> day of experiment and liver tissue was collected for histopathological analysis.

**Table 1:** Group-wise treatment details of animals

Group	Clinical condition	Cholesterol supplementation	Niacin supplementation
I	Kidney-Normal	0%	Un-supplemented
II	Kidney-Normal	0%	Supplemented
III	Kidney-Normal	0.5%	Un-supplemented
IV	Kidney-Normal	0.5%	Supplemented
V	Kidney-Normal	1.0%	Un-supplemented
VI	Kidney-Normal	1.0%	Supplemented
VII	Kidney-Compromised	0%	Un-supplemented
VIII	Kidney-Compromised	0%	Supplemented
IX	Kidney-Compromised	0.5%	Un-supplemented
X	Kidney-Compromised	0.5%	Supplemented
XI	Kidney-Compromised	1.0%	Un-supplemented
XII	Kidney-Compromised	1.0%	Supplemented

### Statistical analysis

Statistical analysis was performed using generalized linear model analysis of variance (Snedecor and Cochran, 1994) and Duncan's multiple range test (Duncan, 1955).

### RESULTS AND DISCUSSION

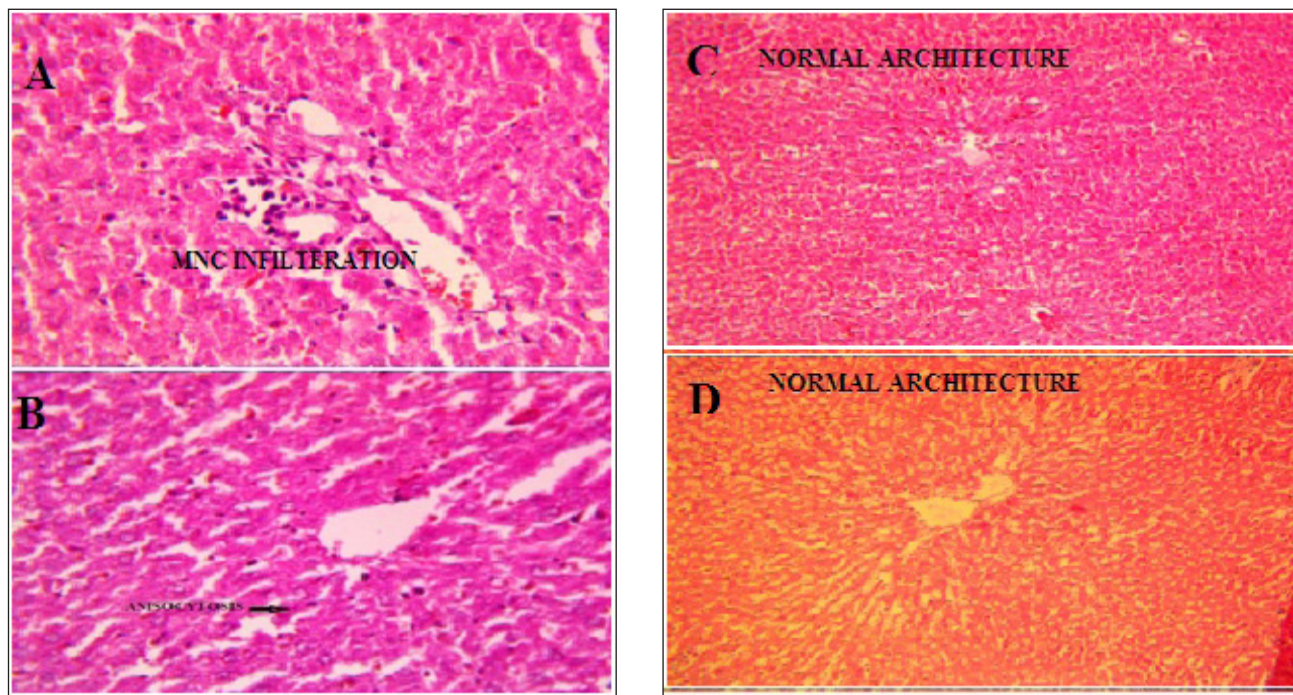
The results are presented in the light of main effects and the interaction effects. The main effects are Kidney condition (K), Cholesterol level (C), Niacin supplementation (N) and Period of observation (P). The two way interaction effects studied are Kidney  $\times$  Cholesterol (KC), Kidney  $\times$  Niacin (KN), Kidney  $\times$  Period (KP), Cholesterol  $\times$  Niacin (CN), Cholesterol  $\times$  Period (CP) and Niacin  $\times$  Period (NP). The three way interaction effects studied are Kidney  $\times$  Cholesterol  $\times$  Niacin (KCN), Kidney  $\times$  Cholesterol

× Period (KCP), Kidney × Niacin × Period (KNP), Cholesterol × Niacin × Period (CNP), four way interaction effects studied are Kidney × Cholesterol × Niacin × Period (KCNP).

Renal dysfunction as well as cholesterol supplementation resulted in significant ( $P < 0.01$ ) elevation of serum AST, ALT and ALP levels (Table 2). Increment with cholesterol supplementation was dose dependent. Niacin Supplementation @ 100 mg/kg body weight significantly ( $P < 0.01$ ) reduced serum AST. Significant ( $P < 0.01$ ) two, three and four way interactions between factors were also observed except for KN and KP. KNP interaction was also found to be significant ( $P < 0.05$ ) (Table 2). Significant ( $P < 0.01$ ) two and three-way interactions between factors were also observed except for KCN. KCNP interaction was also significant ( $P < 0.05$ ) (Table 2). Significant ( $P < 0.01$ ) two and three-way interactions between most of the factors were observed except for KCP and KCNP. KC interaction was also found to be significant ( $P < 0.05$ ) (Table 2). Renal dysfunction resulted in significant ( $P < 0.01$ )

reduction of serum ACP levels (Table 2). No significant effect of cholesterol and niacin supplementation were observed. Renal dysfunction resulted in significant ( $P < 0.01$ ) reduction of serum ACP levels. No significant effect of cholesterol and niacin supplementation were observed (Table 2). Also no interaction between factors in ACP were observed.

In present study renal dysfunction resulted in significant ( $P < 0.01$ ) elevation of serum enzymes AST, ALT and ALP levels. Serum levels of AST, ALT, ALP and ACP are the indicators of functional efficiency of liver and kidney (Alarifi *et al.*, 2012). Similar findings have been documented in other studies also (Aboubakr and Abdelazem, 2016, Abbas *et al.* (2013). Gentamicin is reported to induce the production of ROS in the cells and the consequential damage to biological membrane. Therefore this elevation may be attributed to the release of these enzymes from the cell into the blood circulation after cellular damage and altered membrane permeability. The recorded increased level of ALT indicates functional disorders of the liver,



**Fig. 1 (A):** Photomicrograph of Liver of gentamicin toxic rats showing mononuclear cells infiltration (H&EX400), **(B):** Photomicrograph of Liver of 1% cholesterol fed rats showing anisocytosis (H&EX400), **(C):** Photomicrograph of Liver of gentamicin toxic rats along with niacin supplementation showing normal hepatocytes (H&EX100), **(D):** Photomicrograph of Liver of 1% cholesterol fed rats showing rats along with niacin supplementation showing normal architecture (H&EX100).

**Table 2:** Effect of cholesterol and niacin supplementation on serum enzymes in Wistar rats with renal dysfunction

Variables/ Parameters	Kidney		Cholesterol Supplementation (% of diet)				Niacin Supplementation (mg/kg b.wt.)		Period Mean $\pm$ SEM	P value
	Normal	Compromised	0.0	0.5	1.0	1.0	0	100		
<i>Aspartate aminotransferase (AST/SGOT; IU/L)</i>										
0 <sup>th</sup> day	48.14	59.40	52.80	53.91	54.59	54.12	53.42	53.77 <sup>a</sup> $\pm$ 0.998		
20 <sup>th</sup> day	65.15	73.66	60.32	71.01	76.89	77.18	61.64	69.41 <sup>b</sup> $\pm$ 1.894	<0.01: K; C; N; P; KC; CN; CP; NP; KCN; KCP; CNP; KCNP	
40 <sup>th</sup> day	67.98	77.25	63.93	75.78	78.13	87.38	57.85	72.61 <sup>c</sup> $\pm$ 2.406	<0.05: KNP	
60 <sup>th</sup> day	69.15	82.46	66.97	79.69	80.76	95.02	56.60	75.81 <sup>d</sup> $\pm$ 2.787	>0.05: KN; KP	
Mean $\pm$ SEM	62.61 $\pm$ 1.683	73.19 $\pm$ 1.483	61.01 <sup>a</sup> $\pm$ 1.779	70.10 <sup>b</sup> $\pm$ 1.863	72.59 <sup>c</sup> $\pm$ 2.192	78.42 $\pm$ 1.840	57.37 $\pm$ 0.810	67.90 $\pm$ 1.157		
<i>Alanine aminotransferase (ALT/SGPT; IU/L)</i>										
0 <sup>th</sup> day	25.53	39.77	32.84	31.10	34.00	33.19	32.11	32.65 <sup>a</sup> $\pm$ 0.857		
20 <sup>th</sup> day	29.14	46.61	35.84	38.44	39.34	41.61	34.13	37.84 <sup>b</sup> $\pm$ 1.326	<0.01: K; C; N; P; KC; KN; KP; CN; CP; NP; KCP; KNP; CNP	
40 <sup>th</sup> day	35.57	53.13	36.94	42.54	53.57	52.39	36.31	44.35 <sup>c</sup> $\pm$ 1.839	>0.05: KCNP	
60 <sup>th</sup> day	36.17	58.13	36.98	45.31	59.17	58.46	35.85	47.15 <sup>d</sup> $\pm$ 2.233	>0.05: KCN	
Mean $\pm$ SEM	31.60 $\pm$ 0.993	49.41 $\pm$ 1.071	35.65 <sup>a</sup> $\pm$ 1.255	39.35 <sup>b</sup> $\pm$ 1.550	46.52 <sup>c</sup> $\pm$ 1.559	46.41 $\pm$ 1.468	34.60 $\pm$ 0.714	40.51 $\pm$ 0.876		
<i>Alkaline phosphatase (ALP; IU/L)</i>										
0 <sup>th</sup> day	87.19	119.89	99.78	106.58	104.26	102.45	104.64	103.54 <sup>a</sup> $\pm$ 2.473		
20 <sup>th</sup> Day	93.39	109.55	94.95	103.86	105.60	112.20	90.75	101.47 <sup>a</sup> $\pm$ 2.328	<0.01: K; C; N; P; KN; KP; CN; CP; NP; KCN; KNP; CNP	
40 <sup>th</sup> day	98.28	108.05	101.40	100.80	107.29	117.60	88.72	103.16 <sup>a</sup> $\pm$ 2.232	<0.05: KC	
60 <sup>th</sup> day	110.86	119.75	101.82	120.73	123.37	146.98	83.63	115.31 <sup>b</sup> $\pm$ 4.162	>0.05: KCP; KCNP	
Mean $\pm$ SEM	97.43 $\pm$ 1.967	114.31 $\pm$ 2.013	99.49 <sup>a</sup> $\pm$ 1.984	107.99 <sup>b</sup> $\pm$ 2.760	110.13 <sup>b</sup> $\pm$ 2.769	119.81 $\pm$ 2.153	91.93 $\pm$ 1.345	105.87 $\pm$ 1.479		
<i>Acid phosphatase (ACP; IU/L)</i>										
0 <sup>th</sup> day	0.72	0.66	0.69	0.68	0.70	0.71	0.67	0.69 $\pm$ 0.018		
20 <sup>th</sup> day	0.69	0.66	0.64	0.70	0.69	0.69	0.66	0.68 $\pm$ 0.014	<0.05: K	
40 <sup>th</sup> day	0.69	0.65	0.66	0.69	0.65	0.65	0.69	0.67 $\pm$ 0.016	>0.05: C; N; P; KC; KN; KP; CN; CP; NP; KCN; KCP; KNP; CNP; KCNP	
60 <sup>th</sup> day	0.69	0.66	0.69	0.63	0.71	0.67	0.68	0.67 $\pm$ 0.014		
Mean $\pm$ SEM	0.70 $\pm$ 0.010	0.66 $\pm$ 0.012	0.67 $\pm$ 0.014	0.67 $\pm$ 0.014	0.69 $\pm$ 0.014	0.68 $\pm$ 0.011	0.68 $\pm$ 0.011	0.68 $\pm$ 0.008		

#Means bearing different superscripts (abc) within a row of this column differ significantly. ^Means bearing different superscripts (ABC) within the column differ significantly.

\*Main effects (K: Kidney condition; C: cholesterol supplementation; N: Niacin supplementation; P: Period) and respective interaction effects.

kidney and heart (Mayne, 1994). Significant elevated levels of ALT and AST is usually concurred with renal damage (Smith *et al.*, 1988). Kadhkhoaee *et al.* (2005) has also shown a positive correlation between gentamicin induced acute renal dysfunction and elevated ALP levels. Nephrotoxin induced changes in ALP activity in proximal renal tubules has been reported (Taylor, 1965). ALP has been suggested as an early and sensitive index of nephrotoxicity and it could be used for diagnosing early renal tubular damage (Gyrd-Hansen, 1974). These facts are also supported by histopathological findings in hepatic tissue in gentamicin treated rats (Fig. A) as mononuclear cells infiltration in portal area was observed. A significant ( $P<0.01$ ) reduction of serum ACP levels was also observed in our study under renal dysfunction. Sadava *et al.* (1996) has reported decreased activity of acid phosphatase in renal cortex as well as in renal medulla in progressive renal damage in rats. Decreased ACP activity in serum of chronic renal failure patients has been reported previously (Hasan and Abdul-Sattar, 2015). Decreased activity of ACP may be as a result of progressive impairment of phagocyte ability of neutrophils under renal dysfunction associated hyperuremia (Sharma *et al.*, 2000).

Cholesterol supplementation in our study resulted in significant ( $P<0.01$ ) elevation of serum AST, ALT and ALP levels. Our results are in agreement to the findings of Shanker and Debnath (2016). As AST, ALT and ALP are the marker enzymes of hepatotoxicity, our findings directly links the hepatotoxic activity of dietary cholesterol. High dietary cholesterol induced oxidative damage to liver must have resulted in release of these enzymes in the blood and their elevated levels (Ali, 2016). High cholesterol diets has been reported to increase lipid peroxidation in liver due to increased cholesterol accumulation in hepatocytes and lipotoxicity (Arguello *et al.*, 2015). These facts are also supported by histopathological findings in hepatic tissue of cholesterol fed rats (Fig. B) as liver of cholesterol fed rats developed hepatocytic degeneration and anisocytosis. Nwozo *et al.* (2015) also documented similar findings in liver of hypercholesterolemic rats. Niacin supplementation @ 100 mg/kg body weight significantly ( $P<0.01$ ) reduced serum levels of AST, ALT and ALP. Our results are also supported by our histopathological findings in which niacin supplementation resulted in improvement (Fig. C and D) in liver in gentamicin and 1% cholesterol fed

group. Similar findings have been documented by De Paula *et al.* (2016). Antioxidant activity by inhibiting hepatic lipid accumulation of niacin may be credited to its hepatoprotective activity.

## CONCLUSION

Niacin treatment of rats @ 100 mg/kg BW has resulted in significant normalization of enzyme levels in gentamicin and cholesterol fed rats.

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