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Effect of Cholesterol and Niacin Supplementation on Serum Lipid Profile in Experimentally Induced Renal Dysfunction in Wistar Rats

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A B S T R A C T

Study was conducted on 84 adult male Wistar rats for duration of sixty days. Animals were divided into twelve equal groups and treatments were applied as 2x3x2 factorial design with 2 renal conditions (Normal and Compromised); 3 cholesterol supplementation levels (0%, 0.5% and 1% w/w on DM basis) and 2 niacin supplementation levels (Unsupplemented and Supplemented @ 100 mg/kg body weight per day orally). Renal dysfunction was induced in respective groups by daily intra-peritoneal injection of gentamicin @ 80mg/kg body weight for 8 days. Blood samples were collected on 0^{th}, 20^{th}, 40^{th} and 60^{th} day of experiment to study lipid profile. Renal dysfunction as well as cholesterol supplementation resulted in significant ($p<0.01$) elevation of total cholesterol (TC), triglycerides (TG), low density lipoprotein (LDL-c), very low density lipoprotein (VLDL-c) and a significant lowering of high density lipoprotein (HDL-c) levels. Niacin Supplementation @ 100 mg/kg body weight, however led to significant improvement in lipid profile.

Introduction

Cholesterol is the most abundant steroid in the body. It is a critically important molecule as an integral component of cellular membranes where it helps in maintenance of membrane structural integrity and fluidity. Additionally, it also serves as precursor for several important biomolecules such as steroid hormones, bile acids, and vitamin D (Tabas,

2002). However, cholesterol is widely implicated as a mediator of various lifestyle disorders, including coronary heart diseases (Yusuf *et al.*, 2004), leading to restrictive dietary guidelines with respect to daily cholesterol intake (USDA, 2010). However, this perceived notion is currently being challenged often (Berger *et al.*, 2015) and it is being recommended to remove restrictions over its dietary levels. This warrants that risk factors associated with dietary cholesterol, its relationship with serum lipid profile and its safe levels in healthy and diseased individuals needs to be reassessed. Kidneys are a vital organ in health and disease. They perform crucial functions such as osmoregulation, excretion of end products including urea and creatinine, synthesis of hormones such as rennin and erythropoietin and are the pivotal organ in the metabolism of vitamin D. They maintain water and electrolyte balance as well as pH to regulate metabolic activities. Being a site of continuous metabolic activity, compromised functioning of kidneys can have devastating effects over whole body metabolism with severe cascading consequences. There are many environmental contaminants and chemical variables that are known to alter the functions of the kidney (Mahmood and Waters, 1994).

Nephrotoxicity is characterized by any adverse functional or structural alteration in the kidney due to any chemical and biological agent or its metabolite having an identifiable toxic effect on the kidney (Aslam *et al.*, 2014). Nephrotoxicity is the major side effect of aminoglycosides such as gentamicin, which accounts for about 10-15% of all cases of acute renal failure even at therapeutic doses (Shu-Hui *et al.*, 2007). The specificity of gentamicin renal toxicity is apparently related to its preferential accumulation in the renal convoluted tubules and its effect on biological membranes. Reactive oxygen metabolites such as superoxide, free radical species, hydroxyl radical anion and hydrogen peroxide have been implicated as important mediators of gentamicin induced renal tissue injury (Walker and Shah, 1987).

Cholesterol levels in serum and renal health shares a two-way relationship, with either affecting the other. Several studies reported that abnormalities in lipid metabolism can often accompany and exacerbate renal disease (Mori and Hirano, 2012). Hypercholesterolemia is well-known to be an independent risk factor for renal injury and to aggravate the pathogenesis of a variety of clinical and experimental renal diseases (Stulak *et al.*, 2001). On the other hand, chronic kidney disease results in profound alterations in lipid metabolism and plasma lipid profiles characterized by hypertriglyceridemia, diminished high density lipoprotein (HDL) cholesterol, impaired HDL maturation, and depressed HDL antioxidant and anti-inflammatory activities (Vaziri, 2006). These abnormalities are due to acquired hepatic low density lipoprotein receptor and HDL docking receptor (SRB1) deficiencies as well as urinary excretion and reduced plasma concentration and enzymatic activity of lecithin cholesterol acyltransferase (Vaziri and Liang, 2002).

Niacin (nicotinic acid, vitamin B_3), a water-soluble vitamin that is critical for cellular metabolism (Maiese *et al.*, 2009), has been used successfully to regulate abnormalities in plasma lipid metabolism (Wadhera *et al.*, 2016) and is frequently referred to as a 'broad-spectrum anti-hyperlipidemic drug' (Ganji *et al.*, 2003). In pharmacological doses, niacin reduces total plasma cholesterol, triglyceride, VLDL (Very Low Density Lipoprotein), and LDL (Low Density Lipoprotein) concentrations (Figge *et al.*, 1988). It is the most potent clinically used agent that increases circulating HDL cholesterol and apo A-I, the major protein of HDL.

It appears that there is sufficient basis to hypothesize a three-way inter-relationship between dietary cholesterol levels/serum lipid profile; renal health and niacin.

Understanding of this relationship may help in designing customized dietary management and supplementation strategies for individuals suffering from or exposed to risk of renal disorders. The present study, therefore, explores the effect of these variables and their interrelationship with respect to blood lipid profile.

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±5gms. 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 @ 100mg/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^{th} day, 20^{th} day, 40^{th}day and 60^{th}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 lipid profile. Estimation of total cholesterol, and triglycerides and LDL-C was done by using Erba diagnostic kits. Serum high density lipoprotein HDLc level and VLDLc was calculated as per Kaur (2014), through difference method using Friedewald equation.

Statistical analysis

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

Results and Discussion

Renal dysfunction also resulted in significant elevation of total cholesterol, triglycerides, LDL and VLDL levels, concurrent with significant ($P<0.01$) reduction in plasma HDL levels (Table 1). These results are corroborated by the finding of previous workers (Aboubakr and Abdelazem, 2016 and Ahmadvand *et al.,* 2016). Abnormal lipid metabolism and associated dyslipidaemias are frequent finding in nephrotic syndrome and chronic renal failure (Merzah and Hasson, 2015). Altered lipid profile may be a consequence of urinary protein loss (Keane, 1994), with increased synthesis and altered receptor dependent and receptor independent catabolism of various lipid and apoprotein components of lipoprotein as the underlying cause (Warwick *et al.*, 1992).

High cholesterol levels have been reported in proteinuric patients. Hypoalbuminemia leads to an upregulation of HMG Co-A reductase (regulatory enzyme in cholesterol biosynthesis) resulting in elevated cholesterol levels (Vaziri, 2003). Urinary protein loss stimulates compensatory increase in low density lipoprotein (LDL) synthesis in liver (Trevisan *et al.*, 2006). Urinary loss of the enzyme lecithin cholesterol acyl transferase (LCAT) required for maturation of high density lipoprotein (HDL) particles have been credited for lowered HDL levels (Vaziri *et al.,* 2001). Increased plasma concentration of very low density lipoprotein (VLDL) and impaired clearance of chylomicrons and VLDL during kidney diseases results in elevated levels of triglycerides (Trevisan *et al.*, 2006).

Dietary cholesterol supplementation also resulted in significant elevation of serum total cholesterol, LDL, VLDL, and triglyceride levels while HDL levels were found to be significantly lowered (Table 1). Bobadoye *et al.,* 2016 have reported similar observations. High cholesterol diet leads to dyslipidemic syndrome and hyperlipidemia characterized by increased triglyceride and decreased HDL (Halcox and Misra, 2015) levels. Dietary cholesterol supplementation increases the synthesis of fatty acids and triglycerides in liver and enhances cholesterol absorption (Senthil Kumaran *et al.,* 2009). Collapse of oxidative defence system and augmented inflammation in hypercholesterolemia has also been suggested as the cause of elevated lipid profile (Rajeswari *et al.,* 2017). Supplementation of cholesterol in the diet rapidly results in marked increase in production of cholesteryl ester rich VLDL by liver and intestine and a reduced rate of cholesterol removal by hepatic LDL receptors (Brown and Goldstein, 1983). Triglyceride accumulation caused by dietary cholesterol may contribute to the reduction of fatty acid β-oxidation and the preference of cholesterol esters to afflux to LDL during the onset of biosynthesis and secretion of LDL (Wang *et al.,* 2010).

Niacin Supplementation in the present study, however, significantly reduced levels of serum total cholesterol, triglyceride, LDL and VLDL levels. It also resulted in significantly improved HDL levels (Table 1). These findings are in agreement with previous reports of antihyperlipidemic action of niacin (Shah *et al.,* 2013). Niacin acts at different but interrelated stages of lipid and lipoprotein metabolism, including, inhibition of lipolysis in adipose tissue, inhibition of the synthesis and secretion of VLDL by the liver, lowering of serum levels of lipoprotein (a), a variant form of LDL, and an increase in serum levels of HDL accompanied by a shift in HDL

Subtype distribution (DiPalma and Thayer, 1991).

Number of studies in animals as well as in hyperlipidemic patients has indicated that niacin (or nicotinic acid) inhibits endogenous synthesis of cholesterol (Hotz, 1983) and/or increases hepatic secretion of biliary cholesterol leading to enhanced reverse cholesterol transport. Niacin is reported to inhibit receptor dependent as well as independent lipolysis in adipose tissue by lowering cellular cyclic adenosine monophosphate levels.

This results in decreased availability of free fatty acids in the liver for triglyceride synthesis and their subsequent assembly into lipoproteins (VLDL). Since LDL are derived mainly from VLDL, a decrease in VLDL synthesis and secretion by the liver will eventually cause a decline in circulating levels of LDL (Dipalma and Thayer, 1991).

Niacin lowers triglyceride levels by reducing hepatic VLDL synthesis, thereby limiting the activity of cholesteryl ester transfer protein (CETP), which exchanges triglycerides in VLDL and LDL particles for cholesteryl esters in HDL particles (Digby *et al.,* 2009). Additionally niacin can also decrease triglyceride levels through inhibition of diacylglycerol O-acyltransferase 2 (DGAT2) (Ganji *et al.,* 2004). Inhibiting DGAT2 decreases triglyceride synthesis and thus reduces its availability for VLDL assembly, resulting in a reduced production of VLDL and its catabolic product, LDL. Furthermore, niacin increases apoB catabolism, thereby further impairing synthesis of apoB-containing lipoproteins, including VLDL and LDL (Jin *et al.,* 1999).

The group-wise treatment details are given below:

Group	Clinical condition	Cholesterol supplementation	Niacin supplementation
I	Normal	0%	Un-supplemented
II	Normal	0%	Supplemented
III	Normal	0.5%	Un-supplemented
IV	Normal	0.5%	Supplemented
V	Normal	1.0%	Un-supplemented
VI	Normal	1%	Supplemented
VII	Renal dysfunction	0%	Un-supplemented
VIII	Renal dysfunction	0%	Supplemented
IX	Renal dysfunction	0.5%	Un-supplemented
X	Renal dysfunction	0.5%	Supplemented
XI	Renal dysfunction	1.0%	Un-supplemented
XII	Renal dysfunction	1%	Supplemented

Table.1 Effect of cholesterol and niacin supplementation on serum lipid profile in Wistar rats with renal dysfunction

Variables/ Parameters	Kidney(K)		Cholesterol Supplementation(C) (% of diet)			Niacin Supplementation (mg/kg b.wt.)(N)		Period Mean ± SEM	P value
	Normal	Compromised	0.0	0.5	1.0	0	100		
Total cholesterol (mg dl^{-1})									
0th day	116.70	224.81	165.12	169.17	177.97	165.64	175.86	170.75^{a}±6.282	**<0.01:** K; C; N; P; KC; KN; KP; CN; CP; NP; KCN; KCP; KNP; CNP **>0.05:** KCNP
20th Day	156.65	223.41	164.75	189.22	216.13	216.47	163.59	190.03^{b}±5.995	
40th day	162.94	212.73	157.98	188.05	217.49	228.35	147.33	187.84^{b}±6.650	
60th day	165.73	202.99	152.34	188.79	211.94	232.96	135.76	184.36^{b}±7.440	
Mean±SEM	150.50±4.075	215.98±3.863	160.05^{a}±5.018	183.81^{b}±5.103	205.88^{c}±6.241	210.85±4.889	155.64±3.336	183.25±3.317	
Triglycerides (mg dl^{-1})									
0th day	71.32	145.49	113.18	110.07	101.97	101.62	115.19	108.41±4.558	**<0.01:** K; N; KC; KP; CN; CP; NP; KCN; KCP; KNP; CNP; KCNP **<0.05:** C **>0.05:** P; KN
20th Day	93.85	133.18	111.45	110.19	118.92	133.19	93.84	113.52±4.228	
40th day	96.83	127.14	107.01	109.52	119.42	137.92	86.05	111.98±4.410	
60th day	103.38	124.15	105.23	116.56	119.51	145.92	81.55	113.77±5.136	
Mean±SEM	91.35±2.789	132.49±2.864	109.22^{a}±4.025	111.58^{ab}±3.781	114.96^{b}±4.105	129.68±3.135	94.16±2.729	111.92±2.291	
Low density lipoprotein(LDL; mg dl^{-1})									
0th day	48.80	168.89	103.48	107.82	115.24	102.87	114.82	108.85^{a}±6.867	**<0.01:** K; C; N; P; KC; KN; KP; CN; CP; NP; KCN; KCP; KNP; CNP; KCNP
20th Day	88.83	159.95	95.22	127.73	150.22	158.23	90.54	124.39^{c}±6.530	
40th day	93.97	146.09	87.75	120.90	151.44	169.81	70.25	120.03^{bc}±7.590	
60th day	96.68	138.74	82.08	122.52	148.54	176.14	59.29	117.7^{b}±8.486	
Mean±SEM	82.07±4.341	153.42±4.564	92.13^{a}±5.230	119.74^{b}±5.665	141.36^{c}±7.315	151.76±5.315	83.73±3.578	117.74±3.700	
Very low density lipoprotein (VLDL; mg dl^{-1})									
0th day	14.26	29.10	22.64	22.01	20.39	20.32	23.04	21.68±0.912	**<0.01:** K; N; KC; KP; CN; CP; NP; KCN; KCP; KNP; CNP; KCNP **<0.05:** C **>0.05:** P; KN
20th Day	18.77	26.61	22.29	22.04	23.78	26.64	18.77	22.70±0.846	
40th day	19.37	25.43	21.40	21.90	23.88	27.58	17.21	22.40±0.882	
60th day	20.68	24.83	21.05	23.31	23.90	29.20	16.31	22.75±1.027	
Mean±SEM	18.27±0.558	26.50±0.573	21.84^{a}±0.805	22.32^{ab}±0.756	22.99^{b}±0.821	25.94±0.627	18.83±0.546	22.38±0.458	
High density lipoprotein (HDL; mg dl^{-1}l)									
0th day	53.65	26.82	39.01	39.33	42.35	42.45	38.01	40.23^{a}±1.774	**<0.01:** K; C; N; P; KC; KN; KP; CN; CP; NP; KCN; KCP; CNP **<0.05:** KCNP **>0.05:** KNP
20th Day	49.05	36.83	47.24	39.45	42.13	31.60	54.28	42.94^{b}±1.797	
40th day	49.61	41.22	48.83	45.25	42.16	30.96	59.87	45.51^{b}±2.311	
60th day	48.37	39.42	49.22	42.96	39.50	27.62	60.16	43.89^{b}±2.221	
Mean±SEM	50.17±1.308	36.07±1.369	46.07^{b}±1.410	41.75^{a}±1.805	41.53^{a}±2.017	33.16±1.178	53.08±1.267	43.12±1.021	

Niacin administration lowers serum levels of VLDL and LDL, as well as total cholesterol and triglycerides, but increases HDL and HDL-associated cholesterol (Alderman *et al.*, 1989). Apo A1 is an activator for LCAT. This enzyme plays a major role in removal of cholesterol from peripheral tissues through the process of HDL mediated reverse cholesterol transport. Thus, part of the antihyperlipidemic effect of nicotinic acid may arise from inhibition of apo A1 degradation, which, in turn, facilitates LCAT activity and mobilization of cholesterol for subsequent removal through the hepatic LDL receptor system (Dipalma and Thayer, 1991).

Most of the two, three and four-way interactions were significant for serum lipid profile, which indicates towards the aggravated negative effects of dietary cholesterol supplementation under renal dysfunction on lipid profile. The relationship of renal diseases and lipid is complicated. High dietary cholesterol induced hyperlipidemia/ dyslipidemia may be considered as cause as well as the consequence of renal diseases/disorders (Trevisan *et al.,* 2006). Under the conditions of renal damage, the urinary albumin loss leads to compensatory increase in hepatic lipoprotein synthesis and could in effect be a part of a positive feed-back loop causing further renal injury (Moorhead *et al.,* 1982) and possibly further dyslipidemia.

Niacin was able to counteract these effects of dietary cholesterol supplementation on lipid profile under renal dysfunctions. These beneficial effects of niacin may be due to its hyperlipidemia/dyslipidemia corrective (Shah *et al.,* 2013) and renoprotective action (Cho *et al.,* 2009) by its direct and indirect effects on lipid/lipoprotein metabolism (DiPalma and Thayer, 1991). The main effects were further modulating with the advancement of period of supplementation as suggested by significant interactions with period of observation. For triglyceride and VLDL, KN interaction was not observed, suggesting that impact of kidney dysfunction over these parameters was non-responsive to niacin supplementation.

It was concluded that cholesterol supplemented diet aggravate the damage inflicted by renal dysfunction in Wistar rats with respect to serum lipid profile. Niacin supplementation @ 100mg/kg body weight *per os* was effective in ameliorating aberrations in serum lipid profile caused by cholesterol supplemented diet in Wistar rats suffering with renal dysfunction, however, it may not extend similar benefits over deviations caused by renal dysfunction only with respect to triglycerides and VLDL levels.

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