



EFFECT OF BETA-CAROTENE ON LIPID LEVELS IN DIET INDUCED HYPERLIPIDEMIC RATS

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ABSTRACT

This study attempt to evaluate the effect of beta-carotene in lipids level in diet induced hyperlipidemic rats. The rats were randomly divided into three groups of 6 animals each. Group 1 Normal control, Group II as positive control and Group III as test group. Blood samples were collected to perform lipid profile analysis. HDL levels significantly increased (51.50 ± 3.94) and LDL levels reduced in test group (73.33 ± 4.84) when compared to the control group. Atherogenic index (0.11 ± 0.04), MDA (5.40 ± 0.32) and Total cholesterol/HDL ratio (3.06 ± 0.31) and TGL/HDL ratio (2.99 ± 0.27) were also significantly reduced. Beta-carotene showed positive cardio protective effect by improving HDL value and reducing TAG/HDL ratio, atherogenic index and LDL cholesterol. Our results support the claim of the researchers who have found beta carotene administration to be effective in improving dyslipidemia. But further studies can be designed to test the effectiveness of beta carotene at various doses.

KEYWORDS: Beta-carotene, Hyperlipidemia, Atherogenic index, HDL, LDL, antioxidants.



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INTRODUCTION

Hyperlipidemia has been ranked as one of the greatest risk factors contributing to prevalence of atherosclerosis.¹ It is characterized by elevated serum total cholesterol (TC), low density lipoprotein (LDL) and very low-density lipoprotein (VLDL) and decreased high density lipoprotein (HDL) levels.² Abnormalities in lipid metabolism lead to a series of metabolic disorders.³ Reduced HDL-C is associated with inflammation causes disruption of endothelium leading to atherosclerosis and high levels of LDL-C and triacylglycerol (TAG) causes insulin resistance leading to metabolic and cardiac disorders.⁴ Increase in free radicals in the cells causes damage to the biomolecular structure associated with many conditions like aging, heart diseases, cancers and gastric problems.⁵ Disorders in lipid metabolism lead to the formation of oxidative compounds like aldehyde, such as malondialdehyde (MDA) and conjugated dienes during free radical stress on membrane lipoproteins and polyunsaturated fatty acids (PUFA). Oxidative stress in hyperlipidemia is thought to be a factor in development of atherosclerotic plaques.⁶ Antioxidants are scavengers which counter the effect of free radicals and protect the tissues.⁵ Antioxidants like beta carotene, vitamins E and C have protective counter effect against reactive oxygen species in hyperlipidemic conditions. Antioxidants reduce lipid peroxidation and its supplementation provides protective effects against hyperlipidemia.⁷ Beta-carotene also called pro vitamin A is found abundant in many fruits and vegetables. It is chemically classified as a hydrocarbon and specifically as a terpenoid (isoprenoid), reflecting its derivation from isoprene units. β -Carotene is biosynthesized from geranyl geranyl pyrophosphate.⁸ A recent study showed that beta carotene regulates the expression of HMG-CoA reductase in rat liver by post transcription mechanism and reduces the cholesterol synthesis and also increases macrophages LDL receptor activity which enhances clearance of LDL from plasma.⁹ Another study showed that addition of β -carotene along with lipid lowering drug atorvastatin did not show additional benefits on serum lipid profile, lipid and antioxidant status.¹⁰ Thus there are conflicting reports about the effect of beta carotene on lipid levels in hyperlipidemia. So the present study was designed to evaluate the effect of beta carotene on lipid profile and lipid peroxidation in hyperlipidemic rats.

MATERIALS AND METHODS

Experimental animals

A total number of 18 Sprague Dawley (SD) rats of age 8 -10 weeks and weighing 200-250 g were purchased from King's Institute Guindy, Chennai, India. They were maintained in central animal house, as per the Committee for the purpose of control and supervision on experimental animals (CPCSEA) guidelines. The temperature was maintained at 22°C \pm 2°C and relative humidity at 50-70% with alternate 12-hour light-dark cycles with proper ventilation. Rats were fed with pellet chow diet and water ad libitum. Rats were acclimatized for one week before starting the study. Ethical clearance was obtained from Institutional Animal Ethical

Committee 686/02/a/CPCSEA before commencement of study. Drugs and chemicals β -carotene (20% beadlets) was obtained from Biorigine Life Sciences Private Limited, Pondicherry, India. Cholesterol powder and Cholic acid (25 Grams in each container) were procured from Loba Chemie Laboratory Reagents and Fine Chemicals, Mumbai, India. Tablet Propylthiouracil from Macleods Pharmaceuticals Ltd, Mumbai, India. All reagents and chemicals used were of analytical grade. Preparation of high cholesterol diet (HCD) and test drug High Cholesterol diet was prepared by mixing 30 g propylthiouracil which was ground to powder and mixed with 100 g Cholic acid + 100 g Cholesterol. Finally, this mixture was made into solution by adding one litre of peanut oil and stored in appropriate measure.¹¹ The beta-carotene 20% beadlets were crushed into powder and administered along with HCD.

Experimental procedures

The rats were divided into three groups of 6 animals each. Group 1 received normal diet for 30 days and served as Normal control. Group II was fed with normal pellet diet with water, additionally high cholesterol diet (HCD) 1 ml/100 g BW/day by intra-gastric gavage.¹¹ for 7 days and served as positive control. Group III received High cholesterol diet 1 ml/100 g BW/day for 7 days with normal pellet diet alone on remaining days and β -carotene 300 mg/kg BW/day by orally and served as test group.^{6, 12} Weight of the animals was taken by electronic balance before commencement of the experiment (day 0) and on 7th, 14th and 30th day of the experiment. After overnight fasting, blood was taken from the lateral tail vein as per the method of Diehl K. H. et al.¹³ The first sample was taken in all groups of rats on day 0 (zero) to analyze baseline data before administration of drug and HCD. Samples were collected on 7th day, 14th and 30th day to assess lipid levels – TC, HDL, TAG and TBARS assay.

Bio chemical analysis

The blood sample was assayed for TC by cholesterol oxidase method. TAG was estimated by glycerol kinase method. HDL was analysed by Poly anion precipitation method.

LDL was calculated using Friedewald's Formula:¹⁴

$$\text{LDL} = \text{TC} - (\text{HDL} + \text{TG}/5).$$

VLDL by using standard formula:

$$\text{VLDL} = \text{TGL}/5.$$

Atherogenic index was calculated by using formula =log (TG/HDL-C).¹⁵

TBARS Assay Kit was used in the direct quantitative measurement of Malondialdehyde (MDA) in blood samples and measured in nM/ml.^{16,6}

STATISTICAL ANALYSIS

Parameters were tabulated in the excel sheet and analysed by using SPSS version 16.0. Data obtained were expressed as mean \pm SD. Significance of the results was evaluated using one way analysis of variance (ANOVA) followed by post hoc Bonferroni's test. P value < 0.05 was considered as statistically significant.

RESULTS

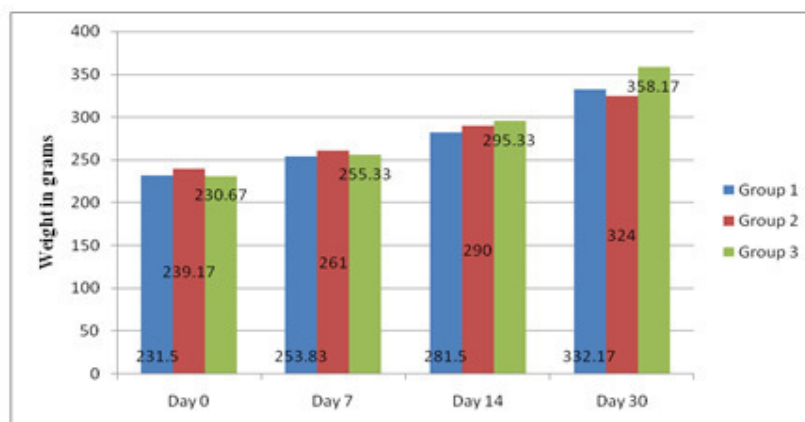


Figure 1
Showing Changes in Weight of Normal Control, Positive Control and Test group on Day 0, 7, 14 and 30. (n=6)

At 0, 7, 14 days there were no significant changes in the weight between the groups. At 30th day the weight in test group increased when compared to other groups but it was not statistically significant.

Table 1
Showing Total cholesterol, HDL, LDL, VLDL & TAG level (mg%) in Normal Control, Positive Control and Test group on Day 0, 7, 14 and 30. (n=6)

DAYS	INVESTI	GRUOP-1	GROUP-2	GROUP-3
DAY-0	TOTAL CHOLESTROL	65.00±8.10	65.50±9.84	65.33±5.34
	HDL	28.00±3.90	26.83±6.37	22.67±2.58
	LDL	19.50±8.12	21.50±10.13	26.33±3.44
	VLDL	16.97±1.73	16.07±1.269	15.37±2.378
	TAG	84.83±8.64	80.33±6.35	76.83±11.89
DAY-7	TOTAL CHOLESTROL	72.33±9.52	103.50±9.12*	100.07±4.88*
	HDL	26.00±3.58	28.00±2.83	29.50±4.23
	LDL	27.83±7.03	52.67±8.04*	48.17±7.36*
	VLDL	18.00±1.66	22.27±2.16*	22.767±2.15*
	TAG	90.00±8.32	111.33±10.78*	113.83±10.48*
DAY-14	TOTAL CHOLESTROL	68.83±8.13	128.00±6.44*	130.00±9.55*
	HDL	26.50±4.23	34.17±3.25*	42.83±4.45* [#]
	LDL	25.17±10.46	65.33±6.92*	60.50±9.01*
	VLDL	16.800±1.15	27.03±0.89*	26.00±0.63*
	TAG	84.00±5.76	135.67±5.13*	131.00±3.16*
DAY-30	TOTAL CHOLESTROL	71.50±8.44	164.00±5.73*	154.83±5.49*
	HDL	29.33±4.5	43.17±3.31*	51.50±3.94* [#]
	LDL	24.17±8.11	90.67±7.15*	73.33±4.84* [#]
	VLDL	17.97±1.72	31.10±1.29*	30.200±2.13*
	TAG	89.83±8.59	156.33±6.15*	151.00±10.64*

Results were expressed in Mean ± SD; *Highly Significant P value (< 0.001) with Post hoc Bonferroni test when positive control and test group is compared with normal control on Days 14 and 30. [#]Highly Significant P value (< 0.001) with Post hoc Bonferroni test when test group is compared with positive control group on Days 14 and 30. The total HDL level gradually increased in test group and positive control group when measured on days 14 and 30. Although HDL levels increased in both groups, in test group it increased significantly more when compared with positive control

group. The VLDL level increased significantly in test group and positive control group on days 7, 14 and 30 when compared with normal control group. But no significant difference noted when test group compared with positive control. TC level increased significantly in test group and positive control group on days 7, 14 and 30 when compared with normal control group. TAG level increased significantly in test group and positive control group on days 7, 14 and 30 when compared with normal control group. But no significant difference noted when test group compared with positive control.

Table 2
Total cholesterol/HDL (TC/HDL), HDL/LDL and TAG/HDL ratios in three groups studied

Group	Ratio	Day-0	Day-7	Day-14	Day-30
1	TC/HDL	2.31±0.38	2.77±0.41	2.65±0.72	2.53±0.48
	HDL/LDL	1.70±0.98	0.98±0.24	1.26±0.64	1.29±0.41
	TAG/HDL	2.94±0.37	3.51±0.56	3.27±0.77	3.25±0.67
2	TC/HDL	2.55±0.57	3.73±0.62*	3.77±0.41*	3.92±0.29*
	HDL/LDL	1.43±0.99	0.56±0.12*	0.51±0.07*	0.47±0.06*
	TAG/HDL	3.11±0.72	4.10±0.77	3.99±1.04	3.75±0.27
3	TC/HDL	2.66±0.53	3.44±0.63	0.13±0.05 [#]	3.06±0.31 [#]
	HDL/LDL	1.05±0.33	0.64±0.19*	0.72±0.12	0.68±0.06*
	TAG/HDL	3.25±0.83	3.95±0.81	3.09±0.35	2.99±0.27 [#]

Results were expressed in Mean ± SD; *Highly Significant P value (< 0.001) with Post hoc Bonferroni test when positive control and test group is compared with normal control.

TC/HDL ratio increased significantly in positive control group on days 7, 14 and 30 when compared with normal control group. The same was increased significantly in test group on 14th day when compared with normal control group. There was a significant increase in the ratio in the test group when compared with positive control on days 14 and 30. HDL/LDL ratio decreased significantly in positive control group on days 7, 14 and 30 when compared with normal control

group. The ratio decreased significantly in test group on days 7 and 30 when compared with normal control group. But no significant difference noted when test group compared with positive control. No significant difference was noted in the TAG/HDL ratio in the test and positive control group when compared with normal control. The TAG/HDL ratio was decreased significantly in the test group when compared with positive control on day 30.

Table 3
Atherogenic index and MDA levels in Normal group, Control group and Test group.

Days	GROUP-1		GROUP-2		GROUP-3	
	Atherogenic index	MDA	Atherogenic index	MDA	Atherogenic index	MDA
Day-0	0.12±0.04	2.78±0.35	0.11±0.01	2.97±0.20	0.17±0.05	2.65±0.41
Day-7	0.18±0.07	3.12±0.49	0.22±0.04*	4.17±0.26*	0.29±0.17 [#]	3.05±0.34 [#]
Day-14	0.15±0.09	2.92±0.51	0.24±0.03*	5.20±0.28*	0.13±0.05 [#]	4.17±0.27 [#]
Day-30	0.13±0.07	3.23±0.41	0.22±0.03*	7.78±0.24*	0.11±0.04 [#]	5.40±0.32 [#]

Results were expressed in Mean ± SD; *Highly Significant P value (< 0.001) with Post hoc Bonferroni test when positive control and test group is compared with normal control. [#]Highly Significant P value (< 0.001) with Post hoc Bonferroni test when positive control is compared with test group. Atherogenic index level raised significantly in positive control group on days 7, 14 and 30 when compared with normal control group. It is significantly reduced in test group when compared with positive control group on days 7, 14 and 30. The MDA level increased in test group and positive control group when compared with normal control on days 14 and 30. But significant reduction of MDA levels was seen in the test group on days 7, 14 and 30 when compared with the positive control group.

DISCUSSION

This study was designed to assess the effect of oral beta-carotene on lipid levels and oxidative stress in diet induced hyperlipidemic rats. At the end of the study, we noticed that there were no significant changes in the weight of the animals in all the groups. We found that there was a significant increase in HDL values, and reduction of the atherogenic index. The high cholesterol diet supplemented group (positive control) showed that Serum total cholesterol, TAG, LDL, VLDL and plasma MDA levels were significantly increased by 7th day, indicating successful induction of hyperlipidemia and lipid peroxidation. In our study, supplementation of beta-

carotene (test group) showed significant improvement of HDL level and this result was similar to a study conducted by Salem SA, *et. al.* on SD rats with different types of antioxidants including beta-carotene.⁶ Ringer TV, *et. al.* also reported similar findings in a clinical trial with various doses of beta-carotene.¹⁷ HDL-cholesterol the transporter of cholesterol and cholesterol esters from the peripheral tissues and cells to the liver leads to metabolism of cholesterol. This pathway plays a very vital role in lowering cholesterol levels in the blood and peripheral tissues and favouring to cardiovascular system by inhibiting formation atherosclerotic plaque.⁶ LDL level increased on 7th, 14th and 30th day in positive control and test groups. LDL level in rats within the hyperlipidemic control group increased by about 3-folds when compared with the normal control group. The increased level of LDL is one of the indicators for lipid peroxidation.¹⁸ It is well-known that lipoprotein oxidation plays a major role in formation of atherosclerosis. Oxidized LDL in tissues, including the artery wall stimulates the release of oxidation products that activate an inflammatory response.¹⁸ In this study, the test group showed highly significant reduction of LDL when compared with control group, indicate that beta-carotene has the ability to scavenge the free radicals which promote the lipid peroxidation. This finding is similar to that of Salem SA *et al.*⁶ Lavy A, *et.al.*¹⁹ have explained that reduction of LDL by beta-carotene occurs by suppressing the cellular uptake of oxidized LDL by macrophages. Jaarsveld VH, *et.al.* in an experimental

study on SD rat had shown that iron induced lipid peroxidation at various doses was significantly reduced by Carotenoids (beta-carotene) whereas the control group showed high LDL-VLDL lipid peroxidation which was proven by measuring malondialdehyde and lipid hydroperoxide concentrations.²⁰ However, a study by *Anderson JW, et al.* on SD rat found that supplementation of beta carotene at a dose of 250 mg/kg BW/d does not produce significant effect on the oxidation of lipoproteins LDL-VLDL.²¹ In our study VLDL, TAG and total cholesterol levels increased significantly in test group and positive control group on days 7, 14 and 30 when compared with normal control group. But no significant difference noted when test group compared with positive control. This was controversial to the findings of a study done by *Tsai AC .et.al.* in spontaneously induced hypertensive rats. In that they have found beta-Carotene supplementation resulted in significant dose-related decrease in serum total cholesterol, LDL and HDL cholesterol concentrations and serum total, VLDL and LDL triacylglycerol concentrations.²² Our study shows there was significant reduction in atherogenic index in the test group. This indirectly proves reduced CVS mortality.¹⁴ The Atherogenic Index of plasma is a well known marker of atherosclerosis because it increases in people at higher risk for coronary heart disease and is inversely correlated with LDL particle size. Furthermore, insulin resistance is also often associated with increased TAG and decreased HDL concentrations and a predominance of small, dense LDL particles are at higher risk for CHD.²³ Seo JS.et.al Beta-Carotene reduced plasma triglycerides and total cholesterol in diabetic rats. HDL did not differ between groups. Fecal excretion of cholesterol and coprostanone were decreased in diabetic rats and beta-carotene tended to increase this excretion. The atherogenic index of diabetic rats was higher than that of control rats and beta-carotene feeding decreased the index.²⁴ We measured the MDA values by using TBARS assay and found significant reduction in MDA values in the test

group when compared with control. This is an effective indicator to analyse the antioxidant property of beta carotene. *Song YO, et.al.* performed an experimental study to evaluate the effect of dietary beta-carotene supplementation on lipid metabolism and activities of antioxidant enzyme in hyperlipidemic rats and concluded that beta-carotene supplementation partly decreases the serum lipid and lipid peroxide levels and increases the activities of antioxidant enzymes such as SOD (Superoxide Dismutase) and Glutathione peroxidase in hyperlipidemic rats.^{18,6} Beta-carotene showed positive cardio protective effect by improving HDL value and reducing TAG/HDL ratio, atherogenic index and LDL cholesterol. It also exhibits anti-oxidant property. Our results support the claim of the researchers who have found beta carotene administration to be effective in improving dyslipidemia via antioxidant mechanism. But further studies can be designed to test the effectiveness of beta carotene at various doses for a chronic period in larger number of animals and in humans before it can be routinely recommended for chronic cardiovascular diseases.

CONCLUSION

Beta-carotene showed positive cardio protective effect by improving HDL value and reducing TAG/HDL ratio, atherogenic index and LDL cholesterol. It also exhibits anti-oxidant property. Our results support the claim of the researchers who have found beta carotene administration to be effective in improving dyslipidemia via antioxidant mechanism. But further studies can be designed to test the effectiveness of beta carotene at various doses for a chronic period in larger number of animals and in humans before it can be routinely recommended for chronic cardiovascular diseases.

CONFLICT OF INTEREST

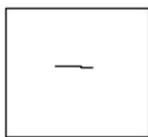
Conflict of Interest declared none.

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