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Original article

Dose effect relationship between high fluoride intake and biomarkers of lipid metabolism in endemic fluorosis

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ABSTRACT

Fluorosis is a metabolic hard tissue disease caused by ingestion of excessive amount of fluoride mainly through drinking water. We aimed to explore the dose effect correlation among some biochemical indexes of lipid metabolism in fluoride toxicity. Blood samples from 705 patients, age 20–60, with endemic fluorosis living in seven high fluoride (5.9–24.5 mg/L) areas of Punjab, India were examined and compared with 300 matched controls for total cholesterol, high-density lipoproteins (HDL), triglyceride, and low-density lipoproteins (LDL). One-way ANOVA with post Hoc Bonferroni multiple comparison test revealed that the amount of cholesterol declined significantly ($P < 0.05$ to 0.001) in fluorotic patients of all study groups. The amount of HDL declined significantly ($q = 7.07–78.64$, 95% CI = –1.32–40.03) in fluorotic patients. A statistically significant ($F\ 7{,}997 = 1001.8$, $t = 32.35–61.39$, 95%CI = 18.15–40.82, $P < 0.05–0.001$) accumulation of triglycerides was recorded whereas LDL concentration was reduced significantly ($P < 0.001$). Bonferroni multiple comparison test revealed that the value of TC/HDL ratio declined significantly ($t = 0.19$ to 0.56, $P < 0.01–0.001$) in patients of study groups (5.9–6.5 mg F/L) and subsequently elevated ($t = 0.41–2.71$, $P < 0.05–0.0001$) in fluorotic patients exposed to 7.9–24.5 mg F/L. Linear regression and correlation analysis indicated highly significant relationship of serum fluoride with total cholesterol ($r = –0.86$), HDL ($r = –0.90$), triglyceride ($r = 0.92$), LDL ($r = –0.55$) and TC/HDL ratio ($r = 0.74$) in fluorotic patients exposed to different levels of fluoride. Fluoride may cause disturbances in lipid metabolism. The decline in the cholesterol content may be due to inhibition of lipid synthesis by fluoride as well as increased utilization of stored lipids as a source of energy to conduct regular metabolic functions.

1. Introduction

Fluorine is a non-metallic element, also an essential trace element to human beings. But long-term excessive intake of fluoride will cause fluorosis to the body, which damage a variety of tissues and organs. It has been reported that fluoride causes injury to hepatic tissues [1]. The liver is the most effective organ of the body in synthesizing cholesterol. Thus liver ability to synthesize cholesterol would decrease, the cholesterol level would decrease. There are significantly adverse changes in the lipid and lipoprotein profiles, total cholesterol, high-density lipoprotein, low-density lipoprotein and triglycerides in postmenopausal women [2] and fluorotic patients [3,4]. Fluorides reduce lipoprotein lipase (LPL) activity and cause a decreased peripheral removal of lipoproteins in plasma [5]. Theoretically, the decrease in LPL activity could result from the direct inhibition of the enzyme by fluorides, or from the decreased levels of plasma apoprotein CII, known as an activator of LPL. Insulin is important for the synthesis and release of lipoprotein lipase. Insulin deficiency is associated with a decrease in plasma and adipose tissue lipoprotein lipase activity. Hyperglycemia in insulin deficiency induces an elevated production of very low-density lipoproteins from esterification of endogenous fatty acids. Serum cholesterol levels may be slightly increased in this type of hyperlipoproteinemia. The present study aimed to assess the status of lipid metabolism in blood of patients afflicted with skeletal fluorosis and its correlation with different water fluoride levels.

2. Materials and methods

2.1. Study group

Seven hundred and five patients (male = 393, female = 312, mean age of 39.35 ± 11.27) with clinical defined skeletal fluorosis exposed to 5.9 to 24.5 mg/L fluoride in drinking water and 300 age, sex matched healthy controls (male = 176, female = 124, mean age) with normal fluoride intake were enrolled in this prospective study. Informed written consent was obtained from all subjects. This study was approved by the Institutional Human Ethical Committee.

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2.2. Biochemical estimations

Blood samples of the subjects were collected by venipuncture into vacutainers. Blood was centrifuged at 2000 to 3000 rpm for 15 minutes to separate out the serum. Total cholesterol, high-density lipoprotein and triglyceride were determined with an auto-analyzer by using standard kit methods. Low-density lipoprotein cholesterol was then estimated by the Frieldewald formula.

$$\text{LDL} - \text{C} = \text{TC} - \text{HDL} - \left(\text{TG}/5\right)$$

2.3. Statistical analysis

All continuous data were represented as mean ± standard deviation (SD). Statistical tests for significance were performed by use of ANOVA with subsequent Tukey-Kramer and Bonferroni multiple comparison tests using Statistical Analysis System software (Version 9.0, SAS Institute, Cary, NC). A difference at $P < 0.05$ was considered statistically significant.

3. Results

3.1. Biochemical analysis

3.1.1. Total cholesterol

Cholesterol is a waxy steroid metabolite found in the cell membranes and transported in the blood plasma. It is an essential structural component of mammalian cell membranes, where it is required to establish proper membrane permeability and fluidity. Within cells, cholesterol is the precursor molecule in several biochemical pathways. In the liver, cholesterol is converted to bile, which is then stored in the gallbladder. The alteration in serum cholesterol of fluorotic patients and control are given in Table 1 and Fig. 1. The mean serum cholesterol level was declined significantly ($P < 0.001$) in fluorotic patients of all study groups vs control. There were non-significant differences in the cholesterol content in fluorotic patients of study group F 3 (7.9 mg/L) and F 5 (11.0 mg/L). Maximum percent decline of 33.14% was noted in fluorotic patients exposed to 24.5 mg/L fluoride. One-way ANOVA with post Hoc test showed a significant ($F_{7,997} = 240.39$, $P < 0.0001$) variance in the serum level of cholesterol in controls and fluorotic patients. Bonferroni multiple mean comparison test revealed that the amount of cholesterol declined significantly ($t = 11.89–30.68$, 95% CI = 18.43–72.44, $P < 0.05$ to 0.001 Table 1, Fig. 1) in fluorotic patients of all study groups when compared to control.

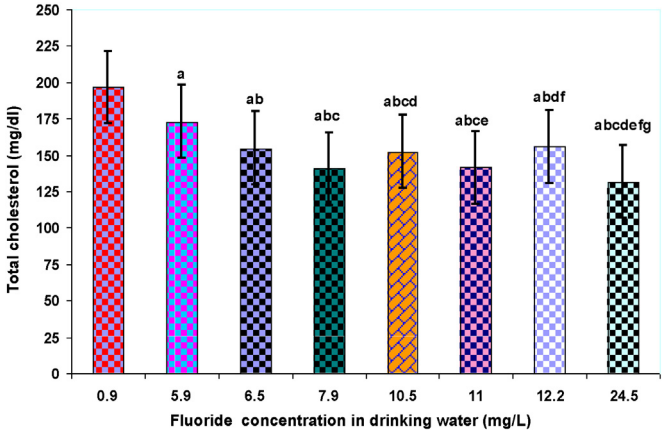

Fig. 1. Effect of fluoride concentration on serum total cholesterol in control and fluorotic patients of endemic fluoride areas.

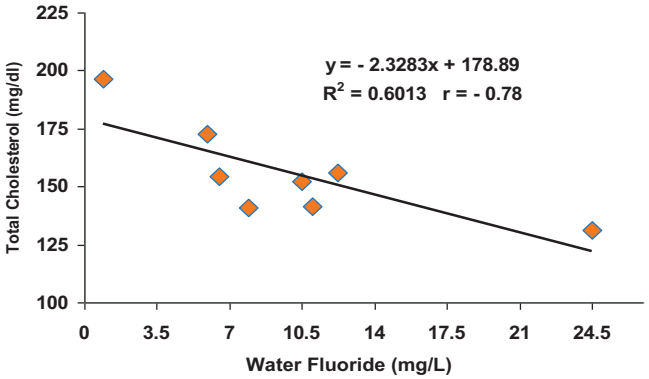

Fig. 2. Correlation and regression between the level of water fluoride and concentration of total cholesterol in serum of fluorotic patients.

Linear regression and correlation analysis indicated highly significant negative relationship between water fluoride and total cholesterol level where the coefficient correlation was $r = –0.78$. The regression equation for water fluoride and total cholesterol was $Y = –2.3283x + 178.89$, $R^2 = 0.60$, $P < 0.01$ (Fig. 2). A highly significant negative correlation was found between the serum fluoride and total cholesterol ($r = –0.86$, $P < 0.05$) (Fig. 3).

3.1.2. High-density lipoproteins

High-density lipoprotein (HDL) is the major vehicle for the transport of cholesterol from extra hepatic tissues in the liver. There was significant ($P < 0.001$) decrease in the mean serum HDL level in fluorotic patients when comparison was made with control (Table 2). Minimum percent decline of 4.8% in serum HDL level was noted in F 2 group, whereas maximum (63.4%) was recorded in fluorotic patients of study group F 7. One-way ANOVA with post hoc test showed a significant ($F_{7,997} = 676.81$, $P < 0.0001$) difference in the serum HDL levels in controls and fluorotic patients. Tukey-Kramer multiple mean comparison test revealed that the amount of HDL declined significantly ($q = 7.07–78.64$, $P < 0.05–0.001$, 95% CI = –1.32–40.030 (Table 2) in fluorotic patients of all fluoride exposed groups compared with control. Fig. 4 showed a great difference in the mean level of HDL in fluorotic patients of study group F 1–7 compared with each other as well as with control. Sharpest decline in HDL level was observed in study group F 7 exposed to 24.5 mg fluoride.

Linear regression and correlation analysis indicated the highly significant negative relationship between water fluoride and serum HDL content, where the coefficient correlation were $r = –0.86$

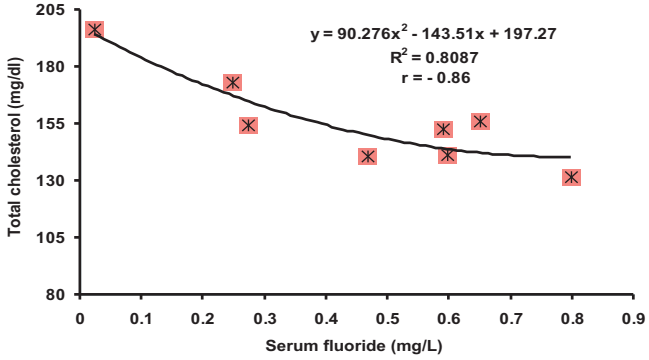

Fig. 3. Correlation and regression between the level of serum fluoride and concentration of total cholesterol in serum of fluorotic patients.

Table 1
Serum cholesterol (mg/dl) in control and fluorotic patients.

Study group	*n*	Water F mg/L	Cholesterol (mg/dl) Mean ± SD	*t*	95% CI	% age decrease
Control	300	0.9	196.65 ± 4.74			
F 1	105	5.9	172.95 ± 13.92[a]	11.89	–18.43–31.61	–12.05
F 2	95	6.5	154.56 ± 10.24[ab]	19.67	–36.13–49.81	–21.40
F 3	105	7.9	140.74 ± 6.98[abc]	27.02	–50.26–63.44	–28.43
F 4	95	10.5	152.46 ± 3.85[abcd]	20.09	–37.05–50.73	–22.47
F 5	105	11.0	141.48 ± 6.93[abce]	26.11	–48.86–62.19	–28.05
F 6	100	12.2	155.91 ± 5.83[abdf]	19.15	–34.32–47.74	–20.72
F 7	100	24.5	131.49 ± 9.10[abcdefg]	30.68	–59.02–72.44	–33.14

n: number of control and fluorotic patients in study groups; F 1–F 7: fluorotic groups; F: fluoride; *t*: Bonferroni Test value; means designated with different letters abcdefg are significantly different, $P < 0.05$–0.001 among study groups.

Table 2
Serum levels of high density lipoprotein (mg/dl) in control and fluorotic patients.

Study group	*n*	Water F mg/L	HDL (mg/dl) Mean ± SD	*q*	95% CI	% age decline
Control	300	0.9	60.81 ± 3.52			
F 1	105	5.9	57.84 ± 3.24[a]	7.07	–1.32–5.38	–4.88
F 2	95	6.5	56.70 ± 1.77[a]	10.60	–3.10–7.32	–6.76
F 3	105	7.9	37.96 ± 1.80[abc]	46.97	–20.23–24.30	–37.58
F 4	95	10.5	33.17 ± 2.41[abcd]	54.74	–24.83–29.05	–45.45
F 5	105	11.0	37.59 ± 2.11[abce]	47.41	–20.52–24.60	–38.18
F 6	100	12.2	45.93 ± 2.54[abcdef]	29.41	–12.13–16.26	–24.47
F 7	100	24.5	22.26 ± 2.84 [abcdefg]	78.64	–35.90–40.03	–63.39

n: number of control and fluorotic patients in study groups; F 1–F 7: fluorotic groups; F: fluoride; *q*: Tukey-Kramer Test value; means designated with different letters abcdefg are significantly different, $P < 0.05$–0.001 among study groups.

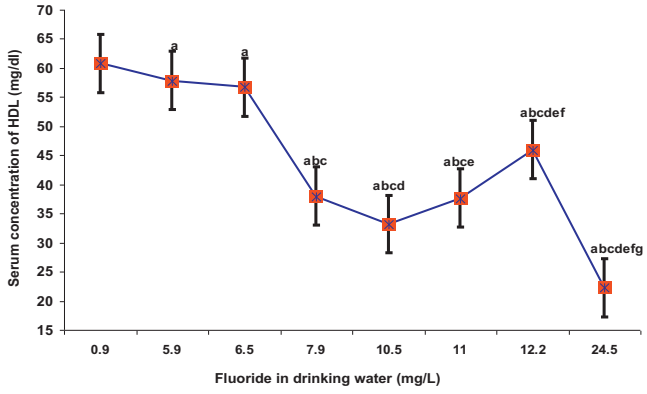

Fig. 4. Effect of fluoride on serum levels of high-density lipoprotein in control and fluorotic patients of high fluoride areas.

(Fig. 5). A highly significant ($P < 0.05$) negative relationship between serum fluoride and serum HDL concentration (Regression equation: $Y = -48.034x + 65.294$, $R^2 = 0.80$, $r = -0.90$ (Fig. 6) was also noted.

3.1.3. Triglyceride

Triglycerides (Tg), as major components of very low-density lipoprotein (VLDL) and chylomicrons, play an important role in metabolism as energy sources and transporters of dietary fat. Triglycerides function as storage lipids. Patients of fluorosis in all study groups showed a significant ($P < 0.001$) accumulation of triglyceride (Table 3, Fig. 7). However, fluoride showed maximum effect on percentage elevation of triglycerides (37.3%) in patients of group F 7. One-way ANOVA with post hoc test depicted highly significant variance ($F_{7,997} = 1001.8$, $P < 0\ 0001$) to null hypothesis in serum level of triglyceride with increase in water fluoride concentration. Bonferroni multiple comparison analysis revealed a significant ($t = 32.35$–61.39, 95%CI = 18.15–40.82, $P < 0.05$–0.001, Table 3) enhancement in the amount of triglycerides in patients of fluorosis of all study groups and also compared with control.

Pearson's correlation analysis indicated the highly significant positive relationship between water fluoride and triglyceride level ($r = 0.80$, Fig. 8). A highly significant ($P < 0.05$) positive relationship between serum fluoride and triglyceride level (Regression equation: $Y = 44.709x + 111.49$, $R^2 = 0.84$, $r = 0.92$, Fig. 9) was noted in fluorotic patients.

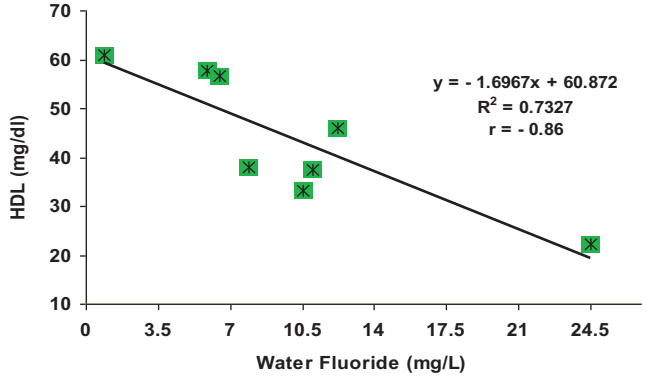

Fig. 5. Correlation and regression between the level of water fluoride and concentration of HDL in serum of fluorotic patients.

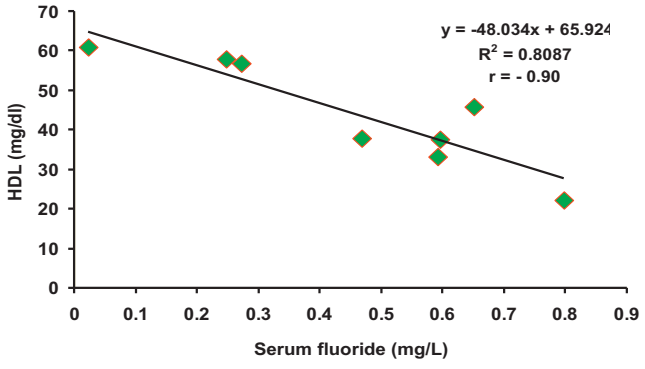

Fig. 6. Correlation and regression between serum fluoride and concentration of HDL in serum of fluorotic patients.

Table 3
Serum levels of triglyceride in control and fluorotic patients.

Study group	*n*	Water F mg/L	Triglyceride (mg/dl) Mean ± SD	*t*	95% CI	% age increase
Control	300	0.9	105.83 ± 4.15			
F 1	105	5.9	126.31 ± 1.86[a]	32.35	18.15–22.04	+ 19.35
F 2	95	6.5	127.79 ± 1.50[a]	33.02	19.27–23.31	+ 20.75
F 3	105	7.9	139.68 ± 0.96[abc]	53.51	31.29–35.18	+ 31.99
F 4	95	10.5	132.66 ± 2.10[abcd]	40.63	24.18–28.23	+ 25.35
F 5	105	11.0	134.89 ± 1.15[abcde]	46.15	26.72–30.61	+ 27.46
F 6	100	12.2	142.53 ± 1.70[abcdef]	56.65	33.85–37.61	+ 34.69
F 7	100	24.5	145.28 ± 1.70[abcdefg]	61.39	36.85–40.82	+ 37.28

n: number of control and fluorotic patients in study groups; F 1–F 7: fluorotic groups; F: fluoride; *t*: Bonferroni Test value; means designated with different letters abcdefg are significantly different, $P < 0.05$–0.001 among study groups.

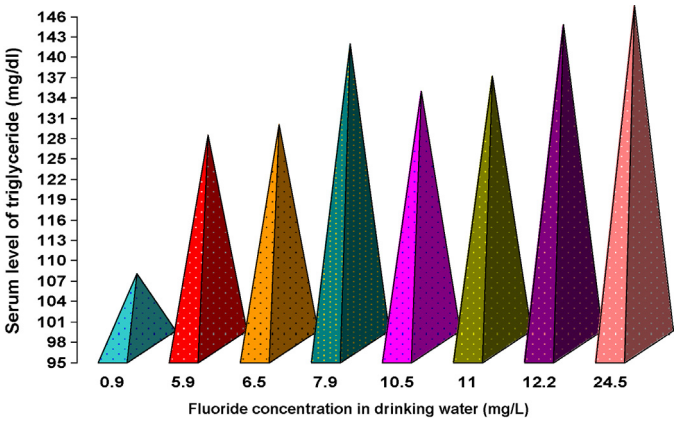

Fig. 7. Effect of fluoride on serum levels of triglyceride in control and fluorotic patients of high fluoride areas.

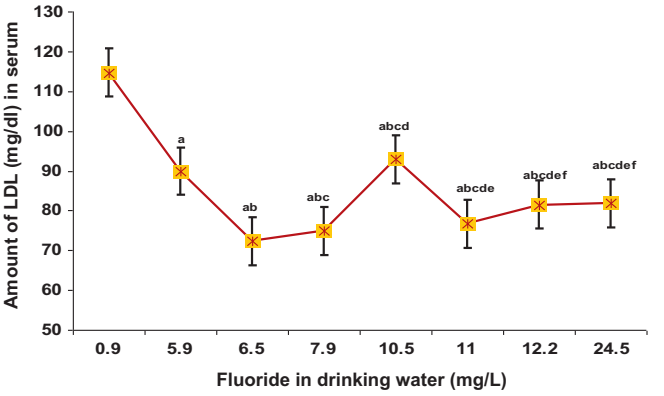

Fig. 10. Effect of high fluoride concentration in drinking water on serum levels of LDL (mg/dl) in control and patients of fluorosis.

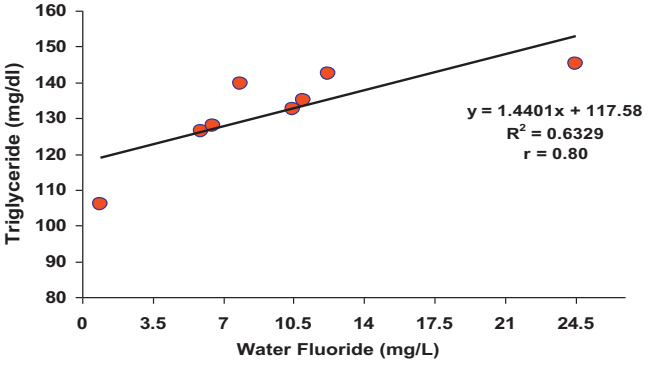

Fig. 8. Correlation and regression between the level of water fluoride and serum triglyceride in serum of fluorotic patients.

3.1.4. Low-density lipoproteins

One-way ANOVA with post hoc test depicted a highly significant ($F_{7,997} = 1115.20$, $P < 0.0001$) difference in the serum level of low-density lipoprotein in control and patients of fluorosis. Tukey- Kramer multiple comparison test revealed that low-density lipoprotein content was significantly ($q = 44.61$–80.39, 95% CI = 20.08–44.17, $P < 0.05$–0.001, Table 4) declined in all fluorotic patients compared with in different study group as well as compared with controls (Fig. 10). Maximum percent decline of 36.9% was recorded in fluorotic patients exposed to 6.5 mg/L of fluoride. Pearson's correlation demonstrated significant ($P < 0.05$) negative relationship between water fluoride and serum LDL ($r = -0.43$, Fig. 11) and serum fluoride versus LDL ($r = 0.55$, Fig. 12).

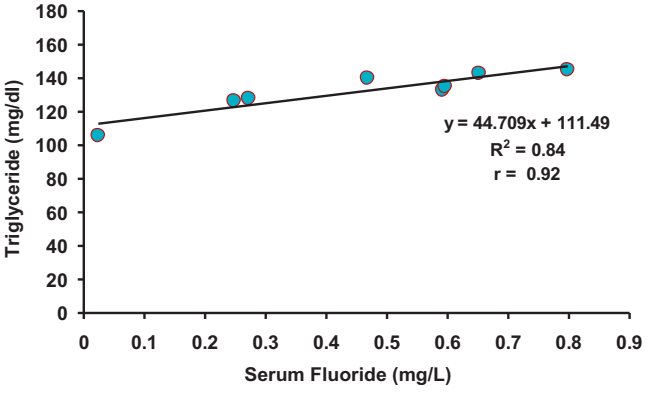

Fig. 9. Correlation and regression between serum fluoride and triglycerides in fluorotic patients.

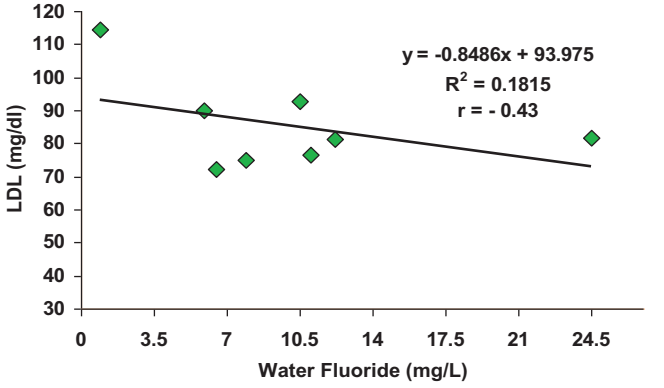

Fig. 11. Correlation and regression between the level of water fluoride and concentration of LDL in serum of fluorotic patients.

Table 4
Serum low-density lipoproteins in control and fluorotic patients.

Study group	*n*	Water F mg/L	LDL (mg/dl) Mean ± SD	*q*	95% CI	% age decline
Control	300	0.9	114.66 ± 2.20			
F 1	105	5.9	89.84 ± 11.55[a]	52.49	–23.07–26.56	–21.65
F 2	95	6.5	72.30 ± 8.89[ab]	86.29	–40.54–44.17	–36.94
F 3	105	7.9	74.84 ± 5.41[abc]	84.22	–38.07–41.56	–34.73
F 4	95	10.5	92.76 ± 1.90[abcd]	44.61	–20.08–23.71	–19.09
F 5	105	11.0	76.65 ± 5.42[abcde]	80.39	–36.26–39.75	–33.15
F 6	100	12.2	81.47 ± 3.55[abcdef]	68.93	–31.41–34.96	–28.95
F 7	100	24.5	80.16 ± 6.54[abcdef]	71.65	–32.72–36.27	–30.09

n: number of control and fluorotic patients in study groups; F 1–F 7: fluorotic groups; F: fluoride; *q*: Tukey-Kramer Test value; means designated with different letters abcdefg are significantly different, $P < 0.05$–0.001 among study groups.

Table 5
Mean value of TC/HDL (mg/dl) in serum of control and fluorotic patients.

Study group	*n*	Water F mg/L	TC/HDL ratio Mean ± SD	*t*	95 % CI	% age change
Control	300	0.9	3.23 ± 0.11			
F 1	105	5.9	2.98 ± 0.12[a]	13.66	–0.19–0.30	–7.74
F 2	95	6.5	2.72 ± 0.11[ab]	26.83	–0.45–0.56	–15.79
F 3	105	7.9	3.70 ± 0.05[abc]	25.68	0.41–0.52	+14.55
F 4	95	10.5	4.60 ± 0.22[abcd]	42.09	1.31–1.43	+42.41
F 5	105	11.0	3.76 ± 0.05[abce]	28.95	0.47–0.58	+16.81
F 6	100	12.2	3.39 ± 0.06[bcdef]	18.58	0.10–0.21	+ 4.95
F 7	100	24.5	5.93 ± 0.38[abcdefg]	74.87	2.64–2.75	+83.59

n: number of control and fluorotic patients in study groups; F 1–F 7: fluorotic group; F: fluoride; *t*: Bonferroni Test value; means designated with different letters abcdefg are significantly different, $P < 0.05$–0.001 among study groups.

3.1.5. Total cholesterol/high-density lipoprotein

The patients of fluorosis had a significantly ($P < 0.001$) higher mean value of TC/HDL ratio when compared with control group except in two study groups (F 1– 2) in which the mean value of TC/HDL ratio was decreased in fluorotic patients exposed to 5.9–6.5 mg/L of fluoride. Maximum percent elevation of 83.6% was observed at highest fluoride level (24.5 mg/L). One-way ANOVA with post hoc analysis revealed a highly significant ($F_{7,997} = 4362.0$, $P < 0.0001$) variance in TC/HDL ratio in controls and fluorotic patients with the increase of water fluoride levels. Bonferroni multiple comparison test revealed that the ratio of TC/HDL declined significantly ($t = 0.19$ to 0.56, $P < 0.01$, $P < 0.001$, Table 5) in patients of study group (F 1–F 2) and subsequently elevated ($t = 0.41$–2.71, $P < 0.05$–0.001) in fluorotic patients exposed to 7.9–24.5 mg/L of fluoride. A non-significant ($P > 0.05$) difference was found in mean value of TC/HDL ratio in control and fluorotic patients of study group F 6 (Fig. 13). Pearson's correlation demonstrated highly significant positive relationship between water fluoride and TC/HDL ratio (regression equation: $Y = 0.1289x + 2.5092$, $R^2 = 0.73$; $r = 0.84$, $P < 0.05$, Fig. 14). The TC/HDL ratio in fluorotic patients increased

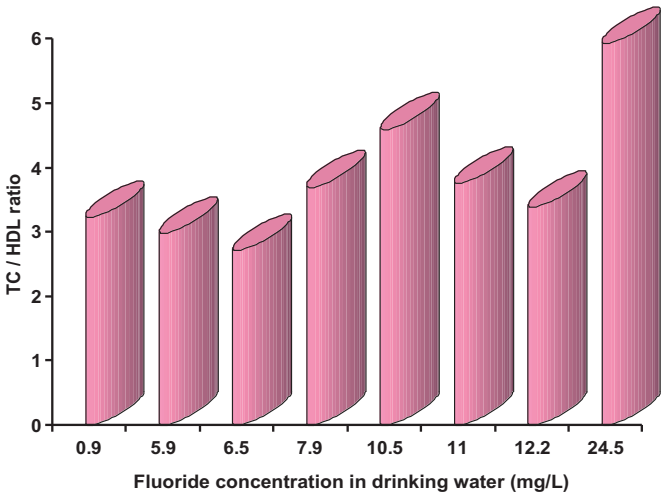

Fig. 13. Effect of fluoride concentration on TC/HDL ratio in control and fluorotic patients of high fluoride areas.

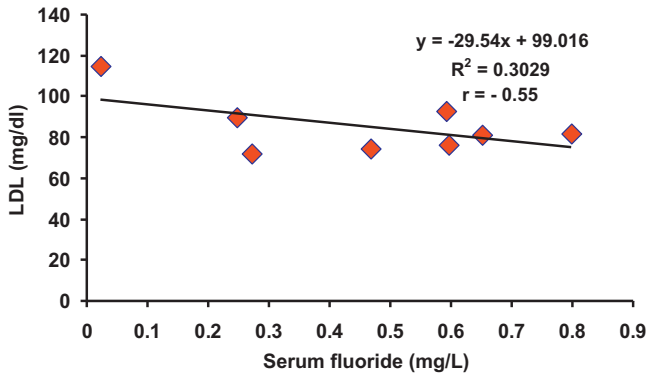

Fig. 12. Correlation and regression between serum fluoride level and concentration of serum LDL in fluorotic patients.

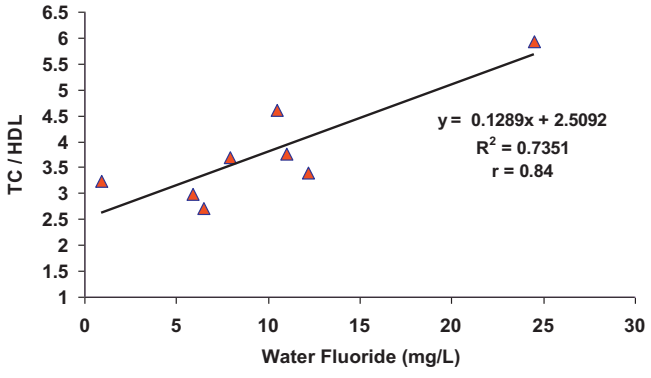

Fig. 14. Correlation and regression between the level of water fluoride and mean value of TC/HDL ratio in of fluorotic patients.

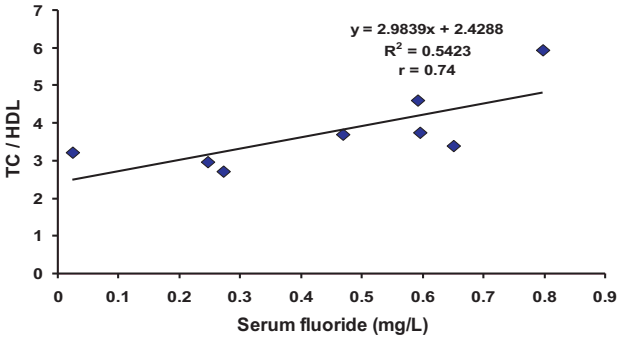

Fig. 15. Correlation and regression between serum fluoride and mean value of TC/HDL ratio serum of fluorotic patients.

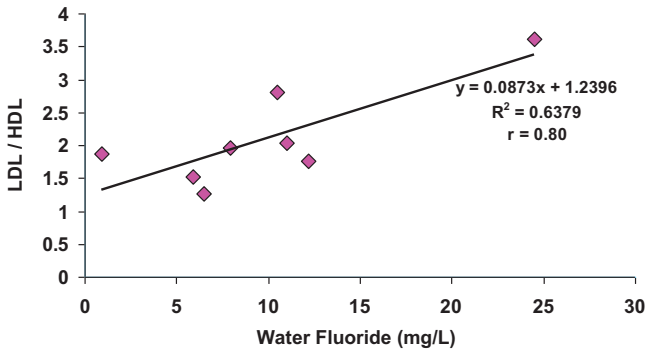

Fig. 17. Correlation and regression between water fluoride and serum LDL/HDL ratio in fluorotic patients.

significantly ($P < 0.05$) with increasing serum fluoride (regression equation: $Y = 2.9839x + 2.4288$, $R^2 = 0.54$; $r = 0.74$ Fig. 15).

3.1.6. Low-density lipoprotein/high density lipoprotein ratio

The results showed fluctuation in the mean values of LDL/HDL ratio in fluorotic patients of all fluoride exposed groups when compared with controls. Maximum percent increase of 92% in LDL/HDL ratio was noticed in fluorotic patients exposed to 24.5 mg/L. LDL/HDL ratio in all fluoride exposed groups differed significantly ($F_{7,997} = 5444.2$, $P < 0.0001$), which is proved by the results of One-way ANOVA with post hoc test. Tukey-Kramer multiple comparison test demonstrated a highly significant ($P < 0.001$) decline in LDL/HDL ratio of fluorotic patients exposed to 5.9, 6.5 and 12.2 mg/L F but at 7.9 to 11.0 and 24.5 mg/L fluoride exposed group, there was a significant ($P < 0.001$) increase in the LDL/HDL ratio in patients of fluorosis when comparison was made within all fluoride groups as well as controls (Table 6, Fig. 16).

Correlation analysis revealed that high fluoride was strongly associated with increased level of LDL/HDL ratio ($r = 0.80$, Fig. 17). Simple linear correlation and regression model showed that higher levels of LDL/HDL ratio in fluorotic patients were strongly associated with the increases serum fluoride ($r = 0.80$, Fig. 18).

4. Discussion

The present study showed hypocholestrolemia and hypolipidemia, and hypertriglyceridemia, TC/HDL, and LDL/HDL ratio revealed a significant increase in fluorotic patients. High fluoride in drinking water may prevent atherosclerosis. Hypocholesterolemia was observed in patients affected with fluorosis due to high fluoride intake through drinking water. Fluoride may cause disturbances in lipid metabolism. The decline in the cholesterol content may be due to inhibition of lipid synthesis by fluoride as well as increased utilization of stored lipids as a source of energy to conduct regular metabolic functions. Fluoride is a well known inhibitor of lipases, phosphatases, esterases, and acetyl Co-A synthetase. It interferes with fatty acid oxidation which results in decreased synthesis of cholesterol from Acetyl Co-A [6]. Fluoride decreases the absorption of cholesterol and bile salt from plasma and intestine which could result in an increased conversion of bile acids in the liver and bile acids are known to inhibit cholesterol synthesis in the intestine. This is indicative of hepato-biliary disturbances in fluoride intoxication [7]. Flavonoids reduce the levels of cholesterol in plasma and thus slow down the process of atherosclerosis in blood vessels. Biochemical work on lipid metabolism endemic fluorosis is limited and results are conflicting. Earlier workers demonstrated decreased levels of cholesterol in the patients of skeletal fluorosis [8]. Michael et al. [9] observed normal level of serum cholesterol among fluorotic individuals at 6.53 ppm fluoride in drinking water.

A high intake of fluoride result in various biochemical changes including alternation in lipid metabolism. Townsend and Singer [10] recorded an increase in serum triglycerides in guinea pigs fed high fluoride concentration. Vatassery et al. [11] reported increased levels of serum cholesterol and total lipids in the sera and liver of fluoridated guinea pig. Kessabi et al. [12] noted a significant decrease in the levels of serum cholesterol in sheep in fluoride intoxication. Singh et al. [13] found significant decrease in the levels of cholesterol and triglycerides in the livers of albino rabbits. Kumari et al. [14] demonstrated a decrease in plasma free fatty acids as well as total lipids, and an increase in serum cholesterol, in rat supplemented with fluoride in drinking water for sixty days. Chinoy and Sequiera [15] noted decrease in the levels of cholesterol and triglycerides in experimental male mice after fluoride intoxication.

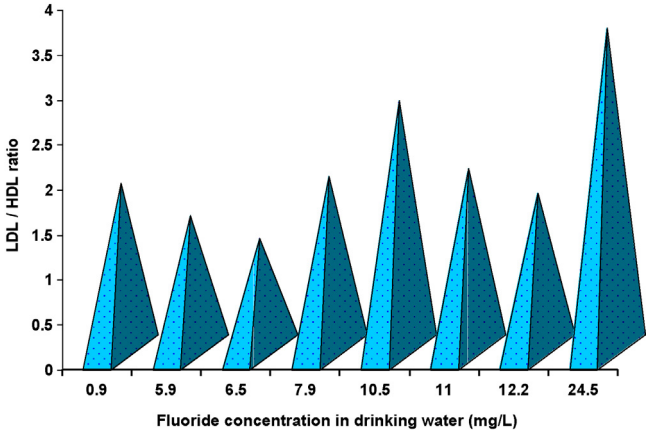

Fig. 16. Effect of fluoride on serum LDL/HDL ratio in control and fluorotic patients.

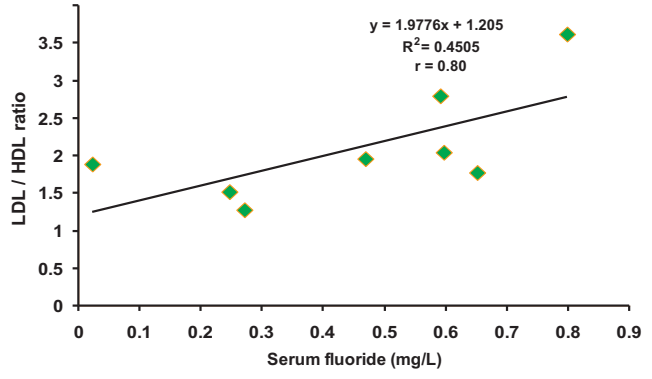

Fig. 18. Correlation and regression between serum fluoride and mean value of LDL/HDL ratio serum of fluorotic patients.

Table 6
LDL/HDL ratio in control and fluorotic patients.

Study group	*n*	Water F mg/L	LDL/HDL ratio Mean ± SD	*q*	95 % CI	% age change
Control	300	0.9	1.88 ± 0.07			
F 1	105	5.9	1.52 ± 0.09[a]	43.75	−0.32–0.39	−19.15
F 2	95	6.5	1.27 ± 0.12[ab]	71.40	−0.57–0.64	−32.45
F 3	105	7.9	1.96 ± 0.07[abc]	9.72	0.04–0.12	+ 4.26
F 4	95	10.5	2.80 ± 0.15[abcd]	107.6	0.88–0.95	+48.94
F 5	105	11.0	2.04 ± 0.04[abcde]	19.44	0.12–0.19	+ 8.51
F 6	100	12.2	1.77 ± 0.03[abcdef]	13.12	−0.07–0.14	−5.85
F 7	100	24.5	3.61 ± 0.20[abcdefg]	206.45	1.69–1.76	+92.02

n: number of control and fluorotic patients in study groups; F 1–F 7: fluorotic group; F: fluoride; *q*: Tukey-Kramer Test value; means designated with different letters abcdefg are significantly different, $P < 0.05$–0.001 among study groups.

Shashi [16] demonstrated hyperphospholipidemia, hypertriacyl-glycerolemia, and hypercholesterolemia in testes being indicative of increased biosynthesis of lipids in response to the toxic action of fluoride. After ingestion of food, fatty acids – both those synthesized *de novo* from excess glucose and those provided to the liver from residual chylomicrons or particles of the LDL fraction – are usually utilized for the synthesis of triacylglycerols. Some of these acids are used for the production of phospholipids and the esterification of cholesterol. Besides degradation of residual chylomicrons, liver plays a vital role in the metabolism of cholesterol. Although nearly all of the cells of body tissues contain enzymes necessary for the synthesis of cholesterol, that process takes place most rapidly in the liver, which produces 85% of the body's cholesterol [17]. Mysliwiec et al. [18] reported that the amount of total cholesterol, low-density protein, and triglyceride rose by 69%, 102% and 45% while the level of high density lipoprotein reduced by 19% in fluoride intoxicated rats. Czerny et al. [19] described that the sodium fluoride (20 mg/kg/24 hr) therapy increased the amount of total cholesterol, low-density lipoprotein, and triglyceride in blood of ovariectomized rats. Grucka-Mamczar et al. [20] observed the hypertriacylglycerolemia in long term fluoride intoxication, thereby indicating disturbances of lipid metabolism under the influence of sodium fluoride.

Bouaziz et al. [21] reported decrease in the levels of serum cholesterol in adult mice and their suckling pups when they were exposed to sodium fluoride. In a study by Tao et al. [22], the growing pigs consuming diets with 100 and 150 mg/kg fluoride group, revealed a lower content of serum cholesterol and triglyceride than those of the controls. Shashi and Kumar [3] observed that the levels of cholesterol, low-density lipoprotein, and high-density lipoprotein revealed a significant ($P < 0.01$) decline, while there was increase in serum triglycerides in the patients of skeletal fluorosis in all age groups. The level of total cholesterol, low-density lipoprotein, very low-density protein, and triglyceride was enhanced in renal failure fluorosis patients exposed to 2.37 to 6.74 ppm fluoride in drinking water [4].

5. Conclusions

We found a consistent association between biomarkers of lipid metabolism and fluoride exposure. Fluorosis can directly influence the lipid parameters up to some extent.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

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