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CLINICAL AND BIOCHEMICAL PARAMETERS IN RELATION TO SERUM Lp(a) LEVELS IN INDIAN CHILDREN AND ADOLESCENTS.

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ABSTRACT

The incidence of obesity, type 2 diabetes and cardiovascular diseases among childhood in India is largely increasing. The serum Lp(a) and its correlation with biochemical, clinical and anthropometric parameters were evaluated in 338 children and adolescents (Controls-103, obese-96, Overweight-97, Congenital heart disease-42) of age group between 10 – 17 years. The levels of serum Lp(a) were measured by Latex Immunoturbidimetry method. Serum Lp(a) levels were found to be significantly elevated in obese, overweight and congenital heart disease children than controls. Serum Lp(a) levels showed positive correlation with BMI, WHR, TC, TG, LDL-C, TCHR and no association with fasting glucose, HDL-C, systolic and diastolic blood pressure. Our findings suggest that Lp(a) levels are genetically determined, not related to gender differences and sexual maturation. Childhood obesity is associated with lipid patterns. Therefore, it has been suggested that physical activity in overweight and obese children is associated with significant changes in Lp(a) levels.

KEY WORDS

Serum Lp(a), Overweight, Obesity, Congenital Heart Disease

INTRODUCTION

Reports from different parts from India suggested a rising trend prevalence of obesity, type 2 diabetes, cardiovascular diseases among childhood is largely increasing. Epidemiological studies have described that obesity in childhood is associated with an increased mortality due to cardiovascular disease in adulthood, independent of adult weight[1]. Recent reports suggest that adverse patterns of blood lipids and atherosclerosis itself begin in childhood**. S**tudies of population and individual differences in the early onset and progression of risk factors through adolescence are important[2].Elevated levels of Lipoprotein-a (Lp(a)) is considered to be an independent and novel risk factor for cardiovascular diseases and diabetes. Obese children suffer from abnormalities of the cardiovascular system during childhood and adolescence. Children who are at risk for the development of accelerated atherosclerosis in early adult life may need early treatment[3]. There is now evidence from many studies, weight reduction in obese children is associated with significant changes in LP(a) concentrations[4,5,6,7]. Lp(a) is a lipoprotein

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subclass and is a modified form of LDL that contains apoB100 and linked to glycoprotein molecule called apolipoprotein a(apo-a) by disulfide bridges[8]. Lp(a) is known to be genetically determined and the risk for coronary artery disease appeared to increase progressively beyond a level of 30mg/dl[5,6,9]. The present study aims to investigate serum Lp(a) levels in children and adolescents of Indian population and its correlation with anthropometric and biochemical parameters. To the best of our knowledge, till date, no data are available with respect to serum Lp(a) levels in Indian children and adolescents.

MATERIALS & METHODS

A total of 338 school children belongs to different states of India with age ranging from 10 to 17 years were enrolled as study participants. Informed written consent from the parents was obtained before the commencement of the study. Children with overweight, obesity and congenital heart disease were included in the study. The study was carried out at the International Centre for Cardio-Thoracic and Vascular Diseases, a unit of Dr.K.M.Cherian Heart Foundation, Chennai. Children with secondary causes of obesity, insulin dependent and independent diabetes mellitus and also, children undergoing treatment for any other disorder were excluded from the study. Anthropometric measurements such as height, weight, body mass index (BMI), and Waist-to-hip ratio were recorded. Weight was measured using a beam balance to the nearest 0.1 kg and height to the nearest centimeter using a tape stuck to the wall. Abdominal girth was measured at the level of umbilicus with the subject relaxed and in a standing posture. Hip girth was measured at widest point of the hips at the level of the greater trochanter with the patient standing with both feet together. Waist–to-hip ratio (WHR) was calculated from these measurements. Children with BMI>85th percentile for age and gender, were considered as overweight and children with BMI >95th percentile for age and gender considered as obese by using CDC growth charts. Blood pressure levels were also recorded for all the children using mercury sphygmomanometer. A detailed questionnaire regarding the medical history of the parents and the children were recorded. This study was approved by the Institutional Ethics Committee.

Twelve hour fasting samples were collected from all the children, serum separated and the samples stored at -20^{0}c until analysis. Lipid profile which includes total cholesterol, LDL and HDL were analyzed by enzymatic methods and triglycerides by GPO-PAP method and fasting glucose levels were analyzed by GOD-POD method using an auto analyzer (Randox Daytona). Serum Lp(a) levels were measured using Latex Immunoturbidimetry method (Spinreact, Spain), TCHR (Total cholesterol to HDL ratio) calculated by following formula.

TCHR = Total Cholesterol (mg/dl) / HDL-Cholesterol (mg/dl).

STATISTICAL ANALYSIS

Statistical analysis of the data was carried out using SPSS package 9.0. Results are expressed as Mean ± SD and P value of < 0.05 was considered to be statistically significant. Data of significance among the groups were analyzed by one way ANOVA and Bonferroni Comparison. Correlation analysis was done by Pearson correlations at 5% level of significance. Since some of the parameters are slightly

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skewed, we have applied logarithmic transformations for all statistical analysis.

Table I shows the study population of different groups.

RESULTS

Groups	Description	Number of Subjects
I	Control	103
II	Overweight	97
III	Obese	96
IV	Congenital Heart Disease	42

The biochemical and anthropometric characteristics of study subjects are described in Table II. Out of 338(103 control, 96 obese, 97 overweight, 42 congenital heart disease children and adolescents, the age ranged between 10-17 years. The anthropometric measurements were found to be significantly higher in overweight and obese children compared to controls. In addition, the anthropometric parameters were found to be decreased in children with congenital heart disease than controls.

Serum Lp(a) levels were increased in obese (23.51±4.79mg/dl), overweight (19.98±5.13mg/dl) and in children with congenital heart disease (22.65±4.79mg/dl) ($p<0.001$) on comparison with control children (16.09±5.71mg/dl).

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Table II

Comparison of various parameters between different Groups.

	I	II	III	IV
Age	14.5±1.4	13.9±1.5	14.0±1.6	13.3±1.5
BMI(Kg/m^2)	18.0±2.1	24.1±1.4**	28.4±2.6**	15.9±2.6**
WHR	0.85±0.09	0.99±0.13**	1.02±0.13**	0.87±0.05 ^{NS}
S.B.P(mmHg)	117.6±5.5	120.5±7.1†	124.5±8.8**	108.7±9.4**
D.B.P(mmHg)	75.4±6.7	77.9±9.0 ^{NS}	76.6±9.0 ^{NS}	66.5±8.0**
Lp(a)(mg/dl)	16.1±5.7	20.0±5.1**	23.5±4.8**	22.7±4.8**
TCHR	3.6±0.5	3.93±0.7**	4.3±0.7**	3.44±0.5 ^{NS}
TC(mg/dl)	140.9±18.2	151.9±21.8**	164.2±22.0**	139.1±23.6^{NS}
TG(mg/dl)	75.7±26.9	90.0±32.3†	103.3±36.2**	96.2±44.2*
LDL-c(mg/dl)	87.9±12.3	90.7±12.3 ^{NS}	92.6±12.3 ^{NS}	76.2±17.9**
HDL-c(mg/dl)	39.5±4.8	39.0±4.0 ^{NS}	38.4±3.5 ^{NS}	40.6±4.9 ^{NS}
Fasting glucose(mg/dl)	87.8±6.6	82.0±6.2**	80.9±6.5**	89.7±12.0 ^{NS}
Non Veg(%)	64.0	74.2	86.4	88.0

Results are expressed in Mean ± SD.
***P<0.001; *P<0.005; ††P<0.01; †P<0.05; NS-Non - significant.*
BMI- Body Mass Index, WHR-Waist-to-hip ratio, TC- Total Cholesterol, TG- Triglycerides, TCHR- Total Cholesterol to HDL Ratio.

On further comparison between boys and girls, even marginal differences of serum Lp(a) levels were not found between the boys and girls in all the groups. The descriptive statistics are summarized in Table III.

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Table III

Comparison of various parameters between boys and girls of different groups.

	I		II		III		IV	
	Boys(55)	**Girls(48)**	**Boys(47)**	**Girls(50)**	**Boys(54)**	**Girls(42)**	**Boys(22)**	**Girls(20)**
Age	**14.5±1.4**	**14.4±1.3**	**14.0±1.4** ^{NS}	**13.8±1.5** ^{NS}	**14.2±1.5** ^{NS}	**13.9±1.6** ^{NS}	**13.8±1.7** ^{NS}	**12.8±2.1** **
BMI (Kg/m^2)	**18.1±2.2**	**18.0±2.0**	**24.0±1.4** **	**24.2±1.4** **	**28.1±2.6** **	**28.7±2.4** **	**15.5±2.0** **	**16.6±3.1** †
WHR	**0.86±0.1**	**0.84±0.1**	**0.97±0.1** **	**1.0±0.2** **	**0.99±0.1** **	**1.05±0.2** **	**0.87±0.04** ^{NS}	**0.88±0.05** ^{NS}
S.B.P (mmHg)	**116.7±5.8**	**118.5±5.1**	**120.9±6.7** †	**120.2±7.4** ^{NS}	**124.3±8.8** **	**124.8±8.9** **	**107.2±9.7** **	**110.5±9.1** **
D.B.P (mmHg)	**74.4±7.6**	**76.7±5.2**	**77.0±9.5** ^{NS}	**78.8±8.5** ^{NS}	**73.9±8.1** ^{NS}	**80.0±9.1** ^{NS}	**66.0±6.1** **	**67.2±9.8** **
Lp(a) (mg/dl)	**16.6±5.7**	**15.6±5.7**	**20.0±5.0** *	**20.0±5.3** **	**23.2±4.5** **	**23.9±5.1** **	**21.8±4.0** **	**23.6±5.5** **
TCHR	**3.59±0.51**	**3.61±0.46**	**3.83±0.64** ^{NS}	**4.03±0.70** ††	**4.2±0.59** **	**4.43±0.72** **	**3.32±0.34** ^{NS}	**3.58±0.64** ^{NS}
TC (mg/dl)	**139.2±19.7**	**142.9±16.4**	**148.6±18.5** ^{NS}	**155.1±24.2** †	**159.4±20.8** **	**170.3±22.4** **	**134.3±16.7** ^{NS}	**144.5±29.0** ^{NS}
TG (mg/dl)	**77.5±28.6**	**73.7±24.9**	**85.6±32.0** ^{NS}	**94.1±32.4** †	**98.0±32.2** ††	**110.1±40.1** **	**96.0±43.4** ^{NS}	**96.5±46.1** ^{NS}
LDL-c (mg/dl)	**86.6±13.6**	**89.4±10.5**	**89.2±12.9** ^{NS}	**92.2±11.6** ^{NS}	**90.7±12.1** ^{NS}	**95.0±12.4** ^{NS}	**75.0±9.7** **	**77.5±24.2** ††
HDL-c (mg/dl)	**39.1±4.9**	**39.9±4.7**	**39.3±4.5** ^{NS}	**38.7±3.6** ^{NS}	**38.1±3.5** ^{NS}	**38.7±3.5** ^{NS}	**40.6±4.3** ^{NS}	**40.6±5.5** ^{NS}
Fasting Glucose (mg/dl)	**86.4±6.2**	**89.5±6.7**	**80.5±6.0** **	**83.4±6.0** **	**80.2±6.3** **	**81.9±6.7** **	**89.9±11.3** ^{NS}	**89.5±3.2** ^{NS}

Results are expressed in Mean ± SD.
***P<0.001; *P<0.005; ††P<0.01; †P<0.05; NS-Non - significant.*
BMI- Body Mass Index, WHR-Waist-to-hip ratio, TC- Total Cholesterol, TG- Triglycerides, TCHR- Total Cholesterol to HDL Ratio.

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The relationship between serum Lp(a) and biochemical and anthropometric parameters for all the groups are shown in Table IV. serum Lp(a) levels showed positive correlation with BMI, WHR, TC, TG, LDL-C, TCHR and no association with fasting glucose, HDL-C, systolic and diastolic blood pressure.

Table IV

Pearson's correlation analysis between Serum Lp(a) and anthropometric and biochemical variables of the study subjects

	Overall(338)		**Boys(178)**		**Girls(160)**	
	r value	**P value**	**r value**	**P value**	**r value**	**P value**
BMI(kg/m^2)	0.30	0.001	0.34	0.001	0.26	0.001
WHR	0.18	0.001	0.19	0.01	0.18	0.02
Systolic B.P(mmHg)	0.08	0.15	0.09	0.22	0.06	0.43
Diastolic B.P(mmHg)	-0.05	0.32	-0.09	0.21	-0.01	0.83
TCHR	0.28	0.001	0.26	0.001	0.31	0.001
TC (mg/dl)	0.32	0.001	0.31	0.001	0.34	0.001
TG (mg/dl)	0.28	0.001	0.17	0.02	0.37	0.001
LDL-C (mg/dl)	0.20	0.001	0.19	0.01	0.22	0.006
HDL-C (mg/dl)	0.01	0.81	0.04	0.64	-0.01	0.90
Fasting Glucose(mg/dl)	-0.03	0.58	-0.03	0.65	-0.02	0.74

BMI- Body Mass Index, WHR-Waist-to-hip ratio, TC- Total Cholesterol, TG- Triglycerides, TCHR- Total Cholesterol to HDL Ratio.

Family history of obesity, diabetes, hypertension and heart disease of all children enrolled for the study are summarized in Table V. Socio-economic status and physical training programme of all children enrolled for the study were found to be almost similar.

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Table V

Comparison of family history between different Groups.

	I (%)	II (%)	III (%)	IV (%)
Obesity	20.3	56.7	55.2	23.8
Diabetes	11.6	36	30.2	28.6
Hypertension	15.5	32	37.5	26.2
Heart disease	4.0	9.2	7.3	9.5

Figure 1and 2 show the correlation of serum Lp(a) with total cholesterol and triglyceride levels in obese boys and girls.

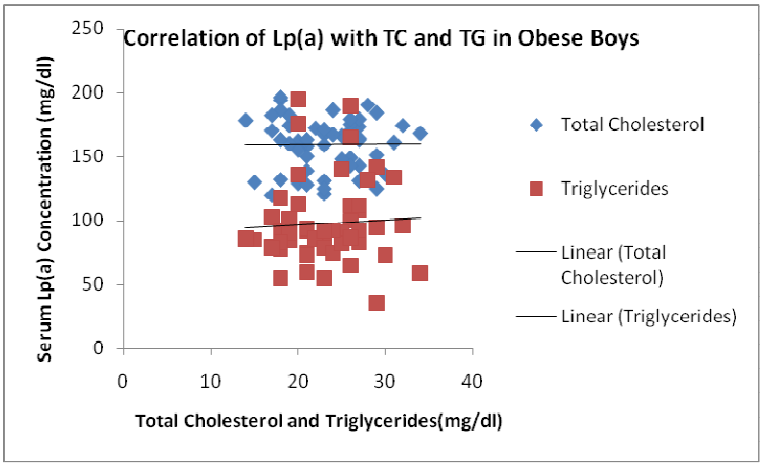

Figure 1
Correlation of Serum Lp(a) with total cholesterol, triglyceride levels in Obese Boys.

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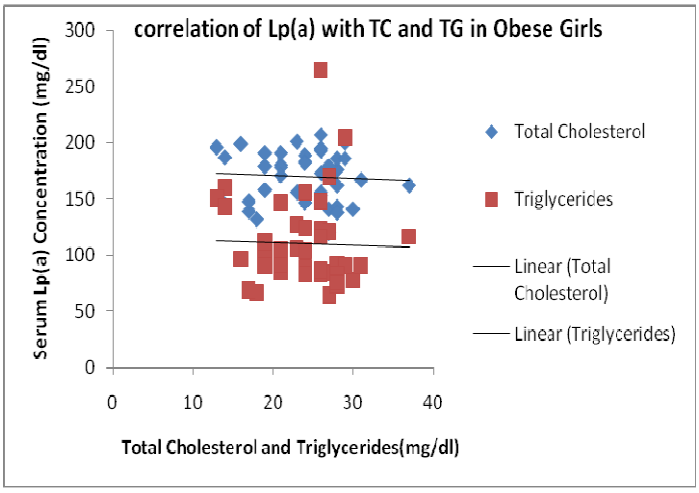

Figure 2
Correlation of Serum Lp(a) with total cholesterol, triglyceride levels in Obese Girls.

DISCUSSION

Recent studies demonstrated significantly higher Lp(a) levels are strongly associated with the development of early atherosclerosis, especially for cardiovascular diseases.[5,6,10,11] Unfortunately, sparse information is available particularly in children and adolescents. The present study aims to analyse the association between serum Lp(a) levels and anthropometric, clinical and biochemical parameters in Indian children and adolescents. Data reported in the present study show significantly elevated Lp(a) levels in overweight, obese and children with congenital heart disease. Our observations strongly suggest that atherosclerotic process begins very early in life and although clinical manifestations of cardiovascular diseases do not usually emerge until middle age and our data agree with those reported by others.[12,7] The mechanism behind elevated Lp(a) levels in children with congenital heart disease is unclear. Probably, family history of cardiovascular diseases is associated with higher levels of Lp(a).[13] It has been consistently observed that anthropometric parameters such as BMI and WHR were significantly elevated in obese, overweight children and adolescents than controls. This is natural as per diagnostic criteria. On the other hand, BMI and WHR were decreased in children with congenital heart disease on comparison with controls.

The current data show elevated systolic and diastolic blood pressure in obese and overweight children and adolescents than controls. Furthermore, children with congenital heart disease showed lower systolic and

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diastolic blood pressure levels than controls. Many studies have reported on hypertension in obese children which may occur due to increased intravascular volume, increased sympathetic nervous system activity, sodium retention and hyperinsulinemia.[14] Lp(a) levels were found to be not significantly correlated with systolic and diastolic blood pressure. This indicates Lp(a) levels are genetically determined, not involved in the pathophysiological mechanism of hypertension and our data closely agree with earlier reports.[9]

Serum TC, TG and LDL-C were found to be elevated in obese and overweight children on comparison with controls and no notable difference of HDL-C levels were observed between obese, overweight and controls. Despite, we observed good correlation between serum Lp(a) and TC,TG and LDL-C, TCHR. There is now evidence from many studies that childhood obesity is associated with dyslipidemia and our data are also in agreement with the earlier reports.[15] One of the major observations of this study is that, fasting glucose levels are found to be decreased in both obese and overweight children and adolescents and there was no association between serum Lp(a) and fasting glucose levels. The possible explanatory mechanism could be that obesity causes insulin resistance. In obesity, probably insulin decreases blood glucose concentrations by reducing hepatic gluconeogenesis and glycogenolysis and by enhancing glucose uptake into striated muscles and adipocytes.[16]

Children with congenital heart disease showed higher Triglycerides, HDL-C and glucose levels and decreased total cholesterol and LDL-C levels than controls. The reason for this variation is still not clear. However the variations may possibly be due to excessive intake of macronutrients.

On further comparison of serum Lp(a) levels between boys and girls. We noticed less specific sex differences and our data indicate that Lp(a) levels are not altered by hormonal changes during sexual maturation and our findings are in par with other investigators[17,18,19].Among overweight, obese children and adolescents, the parental history of obesity, hypertension, diabetes, heart diseases was 56%, 35%, 33%, 8.5% respectively and this confirms the strong genetic influence on childhood obesity, diabetes and cardiovascular diseases.[20] The main limitation of our study was the lack of puberty assessment and measurement in detail of the dietary habits of children and adolescents. Moreover investigation on the larger sample size of congenital heart disease would be more appropriate to draw valid conclusions.

Thus to conclude, serum Lp(a) levels showed positive correlation with BMI, WHR, TC, TG, LDL-C, TCHR and no association with fasting glucose, HDL-C, systolic and diastolic blood pressure. These findings suggest that Lp(a) levels are genetically determined, not related to gender differences and sexual maturation. However, childhood obesity is associated with changes in lipid patterns. Therefore, it has been suggested that physical activity in overweight, obese children and adolescents is associated with significant changes in Lp(a) levels. However, further prospective studies on larger sample size are needed to elucidate the role of Lp(a) in childhood obesity and its complications.

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