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Non-HDL Cholesterol Versus LDL Cholesterol as a CVD Risk Factor in Diabetic Subjects

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Summary:

Objective: *Serum low density lipoprotein (LDL) cholesterol is considered as the primary target of lipid lowering therapy and non-high density lipoprotein (HDL) cholesterol is the recommended second target. Recent studies claimed that non-HDL cholesterol is a better predictor of cardiovascular diseases (CVD) than LDL cholesterol. In this study we aimed to compare non-HDL cholesterol and LDL cholesterol as a CVD risk factor in confirmed diabetic subjects.*

Materials and methods: *In this cross-sectional observational study, 1042 confirmed diabetic subjects selected randomly were included. HbA_{1c} concentrations were measured by modified high-performance liquid chromatography. Serum total cholesterol (TC) and triglycerides (TG) concentrations were measured by enzymatic end point method. Serum HDL cholesterol was measured by a direct automated method and LDL cholesterol was calculated by Friedewald's formula. Subjects having TC d" 150 mg/dL and TG > 400 mg/dL were excluded. Selected subjects were divided into 5 groups depending on TG values (up to TG concentrations of 150 mg/dL, 151-200 mg/dL, 201-250 mg/dL, 251-300 mg/dL and 301-400 mg/dL respectively). In each group, number of individuals with LDL cholesterol d" 100 mg/dL, non HDL cholesterol d"130 mg/dL and LDL cholesterol >100 mg/dL, non-HDL cholesterol >130 mg/dL were calculated and compared by Fisher's exact test.*

Results: *In the total subjects, 767 (74%) subjects had LDL cholesterol > 100 mg/dL and 822 (79%) subjects had non-HDL cholesterol > 130 mg/dL. HbA_{1c} values were different (p<0.02) in five groups and showed upward trend (p<0.01). All the lipid parameters studied were significantly different in five groups (p<0.0001) and TC, TG and non-HDL cholesterol showed upward trend (p<0.0001), but HDL cholesterol and LDL cholesterol showed downward trend (p<0.0001). Odds ratio (OR) of likelihood of risk individuals regarding non-HDL cholesterol compared to LDL cholesterol were 0.50 (p<0.001), 1.32 (p>0.05), 2.96 (p<0.001), 6.49 (p<0.001) and 9.37 (p<0.001) for TG concentrations of up to 150 mg/dL, 151-200 mg/dL, 201-250 mg/dL, 251-300 mg/dL and 301-400 mg/dL respectively with relative risk of 0.60, 1.24, 2.43, 4.83, 5.10.*

Conclusion: *LDL cholesterol is a better tool for the detection of high-risk individuals than non-HDL cholesterol at TG concentration up to 150 mg/dL, whereas non-HDL cholesterol is better than LDL cholesterol at TG concentration above 200 mg/dL as a CVD risk factor.*

Key words: *CVD risk factors, Non-HDL cholesterol, LDL cholesterol, Diabetes mellitus*

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Introduction:

Non-high density lipoprotein (HDL) cholesterol is defined as the difference between total cholesterol (TC) and HDL cholesterol. Non-HDL cholesterol contains all cholesterol in lipoprotein particles considered to be atherogenic, that is low-density lipoprotein (LDL), lipoprotein(a), intermediate-density lipoprotein (IDL), and very low density lipoprotein (VLDL), chylomicron remnants, small dense LDL. Traditionally, elevated LDL cholesterol is considered as the most potent risk factor for cardiovascular diseases (CVD), but recent epidemiologic study,[1] The Strong Heart population based Study in American Indians,[2] longitudinal study[3] and meta-analysis[4-6] showed that non-HDL cholesterol is a stronger predictor of CVD than LDL cholesterol. Comparison of cardiovascular risk markers between control and diabetic and hypertensive subjects showed that non-HDL cholesterol was higher in diseased group than in control group, LDL cholesterol showed no significant difference between diseased and control groups.[7] According to the recommendation of ATPIII,[8] non-HDL cholesterol is the second target of lipid lowering therapy in subjects with hypertriglyceridemia and target of non-HDL cholesterol is 30 mg/dL higher for all risk groups than LDL cholesterol.[8] The National Cholesterol Education Panel (NCEP),[8] the American Diabetes Association (ADA)[9] and the American College of Cardiology (ACC) Foundation[10] recommended to reduce LDL cholesterol to a goal of < 100 mg/dL and non-HDL cholesterol to a goal of < 130 mg/dL. In this study we aimed to compare non-HDL cholesterol and LDL cholesterol risk for CVD in Bangladeshi diabetic subjects.

Materials and methods:

This cross-sectional observational study was conducted in the department of Clinical Biochemistry, Bangladesh Institute of Health Sciences (BIHS), Dhaka, Bangladesh. One thousand and forty two specimens obtained during April 2010 to August 2010 from confirmed diabetic subjects (both treated and untreated for the management diabetes mellitus or dyslipidemia) were analyzed. For lipid profile measurement blood specimens were collected after 10 to 12 hours fast and serum was collected after centrifugation. For HbA_{1c} measurement blood specimens were collected in blood collection tubes (BD Vacutainer® containing 3.6 mg K_2EDTA; BD, Franklin Lakes, NJ USA). All biochemical analyses were performed on same day. HbA_{1c} was measured by modified cation-exchange high performance liquid chromatography (HPLC) using D-10™ glycosylated hemoglobin testing system (Bio-Rad Laboratories, Inc., Hercules, CA, 94547, USA). Serum TC and TG were measured by enzymatic end point method by Dimension RxL Max automated chemistry analyzer (Siemens Healthcare Diagnostics Ltd. USA), HDL cholesterol was measured by direct automated method using Dimension RxL Max analyzer. LDL cholesterol was calculated by Friedewald's formula[11] and non-HDL cholesterol was calculated as, non-HDL cholesterol = Total cholesterol – HDL cholesterol. Subjects having TC d"150 mg/dL and TG >400 mg/dL were excluded. Study subjects were divided into 5 groups depending on TG values. In each group, number of individuals with LDL cholesterol d" 100 mg/dL, non-HDL cholesterol d"130 mg/dL and LDL cholesterol >100 mg/dL, non-HDL cholesterol >130 mg/dL were calculated and compared by Fisher's exact test. Data analyses were performed using GraphPad Prism version 5.03 for Windows, GraphPad Software, San Diego California USA.

Results:

Of the total subjects, 48% were male and 52% were female. The mean ± SD of age of the total study subjects was 49.8 ± 11.5 years. Demographic characteristics, mean ± SD of HbA_{1c}, lipid parameters and results of statistical analyses of different groups are shown in Table I. HbA_{1c} values were different (p<0.02) in five groups and showed upward trend (p<0.01). Nineteen percent (19%) subjects had LDL cholesterol d" 100 mg/dL and 81% had LDL cholesterol > 100 mg/dL; 32% had non-HDL cholesterol d" 130 mg/dL and 68% had non-HDL cholesterol > 130 mg/dL in Group I. Number of non-HDL cholesterol classified risk individuals were significantly lower than LDL cholesterol classified risk individuals in Group I (OR: 0.50, 95% CI: 0.37-0.69, p<0.001). Twenty six percent (26%) individuals had LDL cholesterol ≤100 mg/dL, 74% had LDL cholesterol >100 mg/dL and 21% individuals had non-HDL cholesterol ≤130 mg/dL, 79% had non-HDL cholesterol

> 130 mg/dL in Group II. No statistically significant difference of the number of non-HDL cholesterol classified risk individuals and LDL cholesterol classified risk individuals was observed in Group II (OR: 1.32, 95% CI: 0.86-2.01, $p>0.05$). In Group III, 27% individuals had LDL cholesterol d" 100 mg/dL, 73% had LDL cholesterol >100 mg/dL and 11% individuals had non-HDL cholesterol d" 130 mg/dL, 89% had non-HDL cholesterol > 130 mg/dL. Number of non-HDL cholesterol classified risk individuals were significantly higher than LDL cholesterol classified risk individuals in Group III (OR: 2.96, 95% CI: 1.70-5.16, $p<0.001$). In group IV, 30% individuals had LDL cholesterol ≤ 100 mg/dL, 70% had LDL cholesterol >100 mg/dL and 7% individuals had non-HDL cholesterol ≤130 mg/dL, 93% had non-HDL cholesterol > 130 mg/dL. Number of non-HDL cholesterol classified risk individuals were significantly higher than LDL cholesterol classified risk individuals in Group IV (OR: 6.49, 95% CI: 2.55-16.53, $p<0.001$). In Group V, 51% individuals had LDL cholesterol ≤100 mg/dL, 49% had LDL cholesterol >100 mg/dL and 10% individuals had non-HDL cholesterol ≤130 mg/dL, 90% had non-HDL cholesterol > 130 mg/dL. Number of non-HDL cholesterol classified risk individuals was significantly higher than LDL cholesterol classified risk individuals in Group V (OR: 9.37, 95% CI: 4.37-20.07, $p<0.001$). The relative risk of residual risk individuals regarding non-HDL cholesterol compared to LDL cholesterol were 0.6, 1.24, 2.43, 4.83 and 5.10 in different groups respectively (Table-I).

Trend line of lipid parameters with incremental TG groups is shown in Fig. 1. The trends for TC, TG and non-HDL cholesterol were upward ($p<0.0001$) and that for HDL cholesterol and LDL cholesterol were downward ($p<0.0001$).

Table-I

Demographic characteristics, mean ± SD of biochemical parameters and statistical analyses of different groups

	Group I TG: ≤150 (mg/dL)	Group II TG: 151-200 (mg/dL)	Group III TG: 201-250 (mg/dL)	Group IV TG: 251-300 (mg/dL)	Group V TG: >300 (mg/dL)
Age (Years)	50.23±11.15	50.73±11.89	49.12±11.78	48.59±11.93	48.22±11.16
Sex (M/F)%	45/55	42/58	54/46	57/43	49/51
No. of Subjects	414	244	188	96	100
HbA_{1c}%	9.02±2.41	9.23±2.41	9.53±2.53	9.73±2.51	9.61±2.47
TC (mg/dL)	190.3±29.7	199.7±33.9	205.2±35.1	210.0±36.4	212.1±43.0
TG (mg/dL)	115.4±22.5	174.3±14.1	221.5±15.0	272.8±14.5	344.0±28.9
HDLC (mg/dL)	41.97±8.19	39.86±8.02	37.34±7.95	36.82±7.16	35.68±7.70
LDLC (mg/dL)	125.01±28.20	125.03±32.63	122.61±32.78	119.03±32.83	108.42±39.71
Non-HDLC (mg/dL)	148.4±28.92	159.87±32.84	167.86±31.93	173.20±32.66	176.46±39.60
OR	0.50***	1.32^{NS}	2.96***	6.49***	9.37***
95% CI	0.37-0.69	0.86-2.01	1.70-5.16	2.55-16.53	4.37-20.07
Relative Risk	0.60	1.24	2.43	4.83	5.10

***, $p<0.001$; NS, Not significant

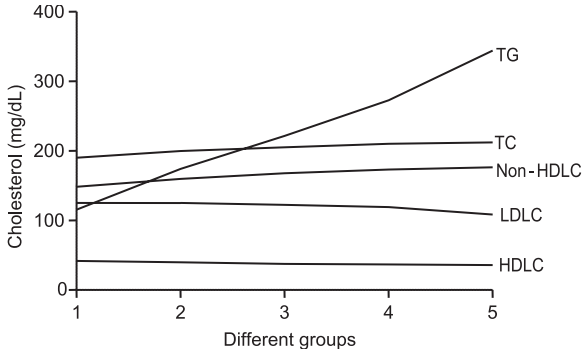

Fig.-1: *Trends of lipid parameters with the increase of serum TG*

Discussion:

With the increment of serum TG, the odds ratio of non-HDL cholesterol risk individuals compared to LDL cholesterol risk individuals increased from 0.5 to 9.37 (Table-I). Since odds ratio was 0.5 (p<0.001) at TG concentration d" 150 mg/dL, LDL cholesterol showed better performance than non-HDL cholesterol to evaluate risk factor more accurately. At serum TG concentrations of 151-200 mg/dL, or was not statistically significant (p>0.05), LDL cholesterol or non-HDL cholesterol can be used to include residual risk individuals but relative risk was 1.24 to exclude residual risk individual for LDL cholesterol. At serum TG > 200 mg/dL, ors were stronger and statistically highly significant (p<0.001), so that non-HDL cholesterol classified risk individuals more accurately than LDL cholesterol. It was also evident from Fig. 1 that, with the increase of TG, TC and decrease of serum HDL cholesterol, serum LDL cholesterol decreases which misleads the risk individuals whereas non-HDL cholesterol increases with the increase of TC, TG and with the decrease of HDL cholesterol.

In hypertriglyceridemic subjects, LDL cholesterol targeted therapy may mask the non-HDL cholesterol risk. Peters[12] described a diabetic subject whose TC concentration was 207 mg/dL, triglycerides was 364 mg/dL, HDL cholesterol was 36 mg/dL, LDL cholesterol was 98 mg/dL (<optimum level) and non-HDL cholesterol was 171 mg/dL (>130 mg/dL). Since his LDL cholesterol level was at goals, no steps were taken to reduce non-HDL cholesterol. Several years later unfortunately the patient was found to have severe CAD and required coronary artery bypass grafting.[12]

Since non-HDL contains all the atherogenic cholesterol, is highly correlated with more atherogenic apolipoprotein B,[13,14] effective to include residual high risk subjects and associated with an increased risk of cardiac death,[15] it would be the better target of classification of lipid risk individuals and lipid lowering therapy at TG concentration greater than 200 mg/dL.

Conclusion:

LDL cholesterol classified high-risk subjects better than non-HDL cholesterol at TG concentration up to 150 mg/dL. No significant difference is observed for LDL cholesterol and non-HDL cholesterol CVD risk classification at TG concentration of 151-200 mg/dL but non-HDL cholesterol classified high-risk subjects better than LDL cholesterol at TG concentration above 200 mg/dL for CVD risk.

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