Status of non-HDL-cholesterol and LDL-cholesterol among subjects with and without metabolic syndrome

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Abstract
Objective: To compare non-high-density lipoprotein and low-density lipoprotein cholesterol among subjects with or without metabolic syndrome, glycation status and nephropathic changes.
Methods: The comparative cross-sectional study was carried out from Dec 21, 2015, to Nov 15, 2016, at the department of pathology and medicine PNS HAFEEZ and department of chemical pathology and clinical endocrinology (AFIP), and comprised patients of either gender visiting the out-patient department for routine screening. They were evaluated for anthropometric indices, blood pressure and sampled for lipid profile, fasting plasma glucose, glycated haemoglobin, insulin, and urine albumin-to-creatinine ratio. Subjects were segregated based upon presence (Group1) or absence (Group2) of metabolic syndrome based upon criteria of National Cholesterol Education Programme and the International Diabetes Federation. Differences in high and low density lipoprotein cholesterol were calculated between the groups.
Results: Of the 229 subjects, 120(52.4%) were women and 109(47.6%) were men. Overall, there were 107(46.7%) subjects in Group 1, and 122(53.3%) in Group 2. Non-high-density lipoprotein cholesterol was significantly different between subjects with and without metabolic syndrome as per both the study criteria (p<0.05 each).
Conclusion: Non-high-density lipoprotein cholesterol levels were higher in subjects with metabolic syndrome.
Keywords: Non-HDL-cholesterol, LDL-cholesterol, Glycated haemoglobin, Homeostasis Model Assessment for Insulin Resistance, HOMA-IR, Fasting plasma glucose, FPG, Urine albumin creatinine ratio, UACR. (JPMA 68: 554; 2018)

Introduction
Cardiovascular diseases (CVD) have become one of the leading causes of morbidity and mortality in the world.1 Insulin resistance (IR) or metabolic syndrome (MS) has emerged to have a very strong association with CVDs.2 The various component included in the definition of MS include measures of obesity (like waist circumference), high density lipoprotein cholesterol (HDL-c), triglycerides (TG), systolic or diastolic hypertension and fasting hyperglycaemia.3 The CVD mortality and morbidity associated with each of these criteria components in isolation or as MS need no further introduction.4 Moreover, hyperlipidaemia is also a recognised risk factor for CVD. Traditionally low density lipoprotein cholesterol (LDL-c) and very recently the non-HDL-care mainly being employed to depict risk in all categories of patients and for both primary and secondary CVD and Ischaemic Heart Disease (IHD) risk prevention.5,6 However, these later measures of risk depiction i.e., LDL-c and non-HDL-c are not included or related with components of MS or underlying IR.

The obvious questions include what role or association LDL-c and non-HDL-c have with IR and with components of MS. Secondly, markers like non-HDL-c contain information from both TG and LDL-c excluding the positive impact of HDL-c,7 thus theoretically implying multi-component information. With the emergence of the concept of ‘atherogenic dyslipidemia’ and ‘residual risk’ non-HDL-c have been proven to perform better in terms of risk prediction for CVD.8,9 Moreover, some evidence is also available where correlation between LDL-c and non-HDL-c was observed to be less in MS.10 Lastly, non-HDL-c, unlike TG and LDL-c, needs prior fasting while non-HDL-c has been recommended in non-fasting status thus implying its possible application more feasible and cost-effective.11

The current study was planned to compare non-HDL-c and LDL-c among subjects with or without MS, glycation status and nephropathic changes as determined by urine albumin creatinine ratio (UACR).

Patients and Methods
This cross-sectional study was carried out from Jan 15 to Sep 15, 2016, at the department of pathology and medicine PNS HAFEEZ and department of chemical pathology and clinical endocrinology (Armed Forces Institute of Pathology), Rawalpindi, after being approved by the institutional ethical committee. The target population was asymptomatic subjects referred from
medical outpatient department (OPD) for CVD risk evaluation in exact medical fasting status. Sampling methodology was non-probability convenience method. Subjects who were pregnant, having some acute infectious proves/disease exacerbations, having some chronic ailment, indoor patients, children and those found not observing appropriate medical fasting were excluded from the study. After formally signing the consent forms, the subjects were clinically evaluated and their various anthropometric indices, including body mass index (BMI), waist, height and hip circumference were measured as per World Health Organisation (WHO) recommendations.12

Up to 10ml of blood was collected in ethylenediamine tetra acetic acid (EDTA) bottles, plain tubes and sodium fluoride bottles for estimation of glycated haemoglobin (HbA1c), fasting plasma glucose (FPG), serum insulin and lipid parameters. A spot urine specimen was also collected for measurement of UACR, which was analysed using immunoturbidimetric method on ADVIA 1800. Glucose was analysed by glucose oxidase-phenol-aminophenazone (GOD-PAP) method. HbA1c was measured by fast ion-exchange resin separation method. Serum insulin was measured using chemiluminescence’s technique on Immulite® 1000. Total cholesterol and TG were measured by Cholesterol Oxidase (CHOD)-PAP and glycerol-3-Phosphate Oxidase (GPO)-PAP method on Selectra-ProM; while LDL-c and HDL-c were analysed by cholesterol esterase method on ADVIA 1800 Chemistry System respectively. The calculation for Homeostasis Model Assessment for Insulin Resistance (HOMA-IR) was done as per the method of Mathew's et al.13 Non-HDL-c was calculated by subtracting total cholesterol from HDL-c.

Both International Diabetes Federation (IDF) and National Cholesterol Education Programme (NCEP) criteria were used to segregate our subjects into 2 groups: subjects with MS in Group 1, and subjects not positive for MS in Group 2.14,15

Data was entered into Excel (Microsoft Office-2007) and later transferred into SPSS 15. Descriptive statistics in terms of mean±standard deviation (SD) were calculated for age. Frequency and percentage were calculated for gender. Independent sample-t test was used to compare the differences LDL-c and non-HDL-c in both groups. Correlation between various evaluated parameters, including LDL-c, non-HDL-c, HbA1c, blood pressures, FPG and HOMA-IR and HOMA beta cell function (%B) were also sought by Pearson’s correlation. Finally, LDL-c and non-HDL-c was evaluated by one-way analysis of variance (ANOVA) for cluster wise increase in MS.

Results

Of the 229 subjects, 120(52.4%) were women and 109(47.6%) were men. Overall, there were 107(46.7%)

Table: Correlation values for non-high density lipoprotein (HDL) cholesterol and low density lipoprotein (LDL) cholesterol for various biochemical parameters including HOMA-IR, A1c and UACR.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>LDL-cholesterol</th>
<th>Non-HDL-cholesterol</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI (Kg/m²)</td>
<td>Pearson Correlation (r)</td>
<td>0.032</td>
</tr>
<tr>
<td></td>
<td>2-tailed sig. (p-value)</td>
<td>0.626</td>
</tr>
<tr>
<td>Age (Years)</td>
<td>Pearson Correlation (r)</td>
<td>0.082</td>
</tr>
<tr>
<td></td>
<td>2-tailed sig. (p-value)</td>
<td>0.216</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>Pearson Correlation (r)</td>
<td>0.020</td>
</tr>
<tr>
<td></td>
<td>2-tailed sig. (p-value)</td>
<td>0.758</td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg)</td>
<td>Pearson Correlation (r)</td>
<td>0.006</td>
</tr>
<tr>
<td></td>
<td>2-tailed sig. (p-value)</td>
<td>0.934</td>
</tr>
<tr>
<td>WHgP</td>
<td>Pearson Correlation (r)</td>
<td>0.169*</td>
</tr>
<tr>
<td></td>
<td>2-tailed sig. (p-value)</td>
<td>0.010</td>
</tr>
<tr>
<td>Fasting plasma glucose (mmol/L)</td>
<td>Pearson Correlation (r)</td>
<td>-0.025</td>
</tr>
<tr>
<td></td>
<td>2-tailed sig. (p-value)</td>
<td>0.711</td>
</tr>
<tr>
<td>A1c (%)</td>
<td>Pearson Correlation (r)</td>
<td>-0.011</td>
</tr>
<tr>
<td></td>
<td>2-tailed sig. (p-value)</td>
<td>0.864</td>
</tr>
<tr>
<td>Insulin (uU/ml)</td>
<td>Pearson Correlation (r)</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td>2-tailed sig. (p-value)</td>
<td>0.989</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>Pearson Correlation (r)</td>
<td>-0.035</td>
</tr>
<tr>
<td></td>
<td>2-tailed sig. (p-value)</td>
<td>0.598</td>
</tr>
<tr>
<td>Urine Albumin Creatinine Ratio (mg/mmol)</td>
<td>Pearson Correlation (r)</td>
<td>0.098</td>
</tr>
<tr>
<td></td>
<td>2-tailed sig. (p-value)</td>
<td>0.197</td>
</tr>
</tbody>
</table>

HOMA-IR: Homeostasis Model Assessment for Insulin Resistance
HbA1c: Glycated haemoglobin. UACR: Urine albumin creatinine ratio.
subjects in Group 1, and 122 (53.3%) in Group 2. Mean age of the male participants was 47.98±11.30 years and that of the females was 45.27±12.42 years (p=0.085). As per the IDF criteria 121 (53%) subjects had MS while 108 (47%) did not have it. Non-HDL-c was found to be significantly different between subjects with and without MS as per both NCEP and IDF criteria (p<0.05 each), while NCEP criteria did not show the differences for LDL-c to be different between subjects diagnosed with or without MS (Figure 1-4). Non-HDL-c showed higher and significant correlation with anthropometric indices, IR as measured by HOMA-IR and nephropathy marker UACR (Table). There was a step-wise increase in non-HDL-c which was not visible for LDL-c (Figure 5-6).
**Discussion**

The study has demonstrated a consistently higher non-HDL-c against LDL-c as per both NCEP and IDF criteria. Non-HDL-c depicted a staircase rise from subjects having no component association of MS to the ones having all five components present. LDL-c levels in contrast did not show a persistent increase between various clusters of MS. Moreover, non-HDL-c correlated better than LDL-c for IR and UACR. The supporting evidence in this regard comes from studies that identified the better risk prediction performance by non-HDL-c than LDL-c in various categories.\(^7,16,17\) The concept is important as the current reliance on LDL-c in clinical practices depicts CVD in a one-dimensional view. What about patients with normal LDL-c, but low HDL-c and raised TG which is the biochemical phenotype linked with underlying IR, diabetes mellitus, hypertension, obesity and CVD? Non-HDL-c has been shown to indicate the presence of atherogenic lipids for the patient which not only includes in the risk incurred by metabolic risk clustering but also includes the measures of previously termed independent risk factors like LDL-c and lipoprotein(a)\(^9\). \(^5\) Moreover, the non-HDL-c has also been more associated with residual CVD risk and depicts more clearly the atherogenic LDL-pattern B profile.\(^18\)

Provided that most literature review and clinical practice in general incorporates mostly LDL-c based targets for diagnosis and clinical decision making,\(^19,5,20,21\) still the evidence is fast emerging to provide equivalent non-HDL-c references.\(^16,22,17,23\) In our view, reliance solely on LDL-c will underscore CVD risk and thus may be replaced by non-HDL-c which can conglomerate the risk information from all lipid parameters.

Certain limitations to our findings must be acknowledged: Firstly, It is believed\(^24\) those future technologies segregating LDL and HDL cholesterol fractions and with clinically applicable methodologies to specifically target LDL-particle number may again need the re-assessment of CVD. Secondly, it must be acknowledged that the study was a cross-sectional design and further work may be required for broader application of non-HDL-c in Asian population which we believe may have a higher degree of CVD risk.

The study is considered clinically important as it highlighted the application of one marker i.e., non-HDL-c to be incorporated in CVD risk calculation for all categories, including MS, which may be not only cost-effective but will also make the approach clinically more applicable. Moreover, it will also address the underlying CVD risk concepts of atherogenic dyslipidaemia and CVD risk persisting after anti-cholesterol treatments.

**Conclusion**

Non-HDL-c levels were higher in subjects with MS, subjects having nephropathic changes as depicted by UACR and IR in comparison to LDL-c. Clinical decisions...
pertaining to CVD risks must incorporate the useful information provided by calculating non-HDL-c.

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**Conflict of Interest:** None.

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**References**


