Discordance between non-HDL cholesterol and LDL cholesterol levels in patients with diabetes without previous cardiovascular events

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Abstract

Objectives. – Despite achieving desirable LDL cholesterol levels, the residual cardiovascular (CV) risk remains high among patients with diabetes. This is partly due to the increased number of atherogenic LDL particles and apoB levels, despite optimal LDL levels. As correlation studies have shown that non-HDL cholesterol is an acceptable surrogate marker for apoB, this study aimed to determine the concordance between non-HDL and LDL cholesterol in diabetic patients with different triglyceride and HbA1c levels and metabolic syndrome (MS) status.

Methods and results. – Data from 11,005 diabetes patients from a large UK primary-care electronic database, with no previous CV events and not taking lipid-lowering therapy, were analyzed. Of the patients with LDL cholesterol < 1.8 mmol/L, only 58.6% had correspondingly low levels of non-HDL cholesterol (< 2.6 mmol/L). Concordance between very low LDL and very low non-HDL values was significantly less among patients with high triglycerides (25.5%) compared with those with low triglycerides (76.2%) (Pearson’s \( \chi^2 \) test = 177.6; \( P < 0.001 \)). However, greater concordance between very low LDL and very low non-HDL cholesterol levels was seen in patients without (77.9%), compared with those with (50.3%), the MS (Pearson’s \( \chi^2 \) test = 59.7; \( P < 0.001 \)). This persisted even after adjusting for hypertriglyceridaemia. Concordance was similar at different levels of glycaemia.

Conclusion. – There was a significant discordance between LDL and non-HDL cholesterol levels in diabetes patients with high triglycerides or the MS. This might explain patients’ high residual CV risk despite having achieved their desirable LDL cholesterol levels. Thus, treating both non-HDL and LDL cholesterol to achieve target values should be considered to reduce residual CV risk in patients with diabetes.

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Keywords: Diabetes; Discordance; Non-HDL cholesterol; Residual risk; Cardiovascular disease

Résumé

Discordance entre les concentrations de cholestérol non HDL et de cholestérol LDL chez des patients diabétiques indemnes d’antécédents cardiovasculaires.

Objectifs. – En dépit de l’obtention de concentrations plasmatiques de cholestérol LDL (LDLc) satisfaisantes, le risque cardiovasculaire résiduel reste élevé chez les patients diabétiques. Cela peut être expliqué en partie par l’augmentation du nombre de particules athérogènes LDL et des concentrations plasmatiques d’apoB, malgré un LDLc optimal. Des études de corrélation ont montré que le cholestérol non-HDL (non-HDLc) était un marqueur acceptable de substitution pour l’apoB, nous avons étudié la corrélation entre non-HDLc et LDLc chez des patients diabétiques pour différents niveaux de triglycérides, statut de syndrome métabolique (MS) et taux d’HbA1c.

Méthodes et résultats. – L’analyse a été réalisée à partir d’un échantillon de 11,005 patients diabétiques sans antécédents cardiovasculaires et sans traitement hypolipémiant à partir du registre électronique des médecins généralistes du Royaume-Uni. Parmi les patients avec LDLc < 1.8 mmol/L, seuls 58.6% avaient un non-HDLc correspondant bas (<2.6 mmol/L). La corrélation entre les valeurs très basses de LDLc et non-HDLc était un marqueur acceptable de substitution pour l’apoB, nous avons étudié la corrélation entre non-HDLc et LDLc chez des patients diabétiques pour différents niveaux de triglycérides, statut de syndrome métabolique (MS) et taux d’HbA1c.

Conclusion. – Il y a une discordance significative entre LDL et non-HDL cholesterol levels in diabetes patients with high triglycerides or the MS. This might explain patients’ high residual CV risk despite having achieved their desirable LDL cholesterol levels. Thus, treating both non-HDL and LDL cholesterol to achieve target values should be considered to reduce residual CV risk in patients with diabetes.

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1. Introduction

There is significant evidence to suggest that the risk of atherosclerotic vascular disease is directly related to plasma low-density lipoprotein (LDL) cholesterol levels [1]. However, despite having achieved their desirable LDL cholesterol levels, cardiovascular events remain high in patients with diabetes [2]. This residual risk may reflect the large quantity of circulating atherogenic LDL particles that come into contact with and enter the arterial wall rather than the measured concentrations of these lipoprotein cholesterol fractions. One study has shown a significant discordance between LDL cholesterol levels and LDL particles (measured using nuclear magnetic resonance techniques) in patients with diabetes [3]. As each of the atherogenic lipoprotein particles contains a single molecule of apolipoprotein B (apoB) [4], the latter provides a direct measure of the number of circulating atherogenic LDL particles, and is a better marker of LDL particle levels than the calculated LDL cholesterol values.

Although apolipoproteins can be precisely measured using World Health Organization standardized methods and reference intervals [5], these methods are not as readily available as are those for cholesterol, triglycerides (Tg) and calculated LDL in many clinical laboratories. It is, therefore, important to recognize that epidemiological evidence has shown that both apoB and non-HDL cholesterol are better predictors of cardiovascular events than is LDL cholesterol [6–8]. In a post-hoc analysis of the Treating to New Targets (TNT) and the Incremental Decrease in End Points Through Aggressive Lipid-Lowering (IDEAL) studies [9], levels of both non-HDL cholesterol and apoB were shown to be more closely associated with cardiovascular outcomes than were levels of LDL cholesterol. Furthermore, on the basis of correlation studies [10], the Adult Treatment Panel III (ATP III) concluded that non-HDL cholesterol was an acceptable surrogate marker for apoB and, thus, was included as a therapeutic target for hypertriglyceridaemic patients in the most recent National Cholesterol Education Program (NCEP–ATP III) guidelines [11] on the basis that the non-HDL cholesterol fraction would also represent cholesterol from triglyceride-rich lipoproteins.

The present study aimed to examine further the relationships between LDL and non-HDL cholesterol levels in a large number of diabetic patients with no previous cardiovascular events (primary cardiovascular prevention) and not taking any lipid-lowering therapy, using data from a large UK primary-care electronic database. The study also aimed to examine the relationship between the two cholesterol indices based on different Tg levels, glycaemic control and metabolic syndrome (MS) status.

2. Methods

2.1. Patients

This cross-sectional cohort study used The Health Improvement Network (THIN) database, which contains anonymous patients’ data from 304 general practitioner (GP) practices throughout England and Wales. The information obtained from the database was validated against UK patients’ characteristics by comparing the demographics, morbidity, mortality, prevalence and geographical rates with various national data sources [12,13].

A total of 60,258 patients with diabetes were identified, and their biochemical and demographic profiles as of 31 December 2005 were taken. Patients had to have been registered by their clinics for the whole of the preceding 12 months in order to be included in the analysis. The result was that 11,005 patients with diabetes aged 30 to 74 years, and not prescribed any lipid-lowering drug therapy and with no arterial disease (no history of ischaemic heart disease, cerebrovascular disease or peripheral vascular disease) were suitable for analysis. This large patient cohort reflects the clinical and biochemical parameters of patients prior to the full implementation of the new Joint British Societies (JBS 2), National Institute for Clinical Excellence (NICE) and General Medical Services Contract guidelines. Also, the present study was approved by the appropriate UK multicentre research ethics committee.

To explore the question of concordance/discordance, the cohort was divided into corresponding ranges in the two cholesterol indices in question: very low (<1.8 mmol/L), low (1.8–2.6 mmol/L) and high (>2.6 mmol/L) for LDL cholesterol; and <2.6 mmol/L, 2.6–3.37 mmol/L and >3.37 mmol/L, respectively, for non-HDL cholesterol measures. These corresponding ranges of LDL and non-HDL cholesterol were based on equivalent values of apoB levels among patients in the Collaborative Atorvastatin Diabetes Study (CARDS) [14]. Concordance was defined as when the two indices placed a subject within the same corresponding ranges. On the other hand, if the LDL and non-HDL cholesterol levels for a subject did not fall within corresponding ranges, the values were deemed discordant. Concordance/discordance between LDL and non-HDL cholesterol was also determined separately as a function of: (i) fasting Tg levels (low < 2.2 mmol/L, high 2.2–4.0 mmol/L); (ii) glycaemic control (good HbA1c levels <7%, poor 7–9% and very poor >9%); and (iii) MS status based on NCEP–ATP III criteria.

Not included in the present analyses were patients with fasting Tg > 4.0 mmol/L. All samples were taken from patients seen in routine clinical practice. Non-HDL cholesterol was calculated...
Table 1
Clinical and biochemical characteristics of the study population.

<table>
<thead>
<tr>
<th></th>
<th>Men (n=6134)</th>
<th>Women (n=4871)</th>
<th>Total (n=11,005)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>55.9 (12.1)</td>
<td>53.5 (12.9)</td>
<td>54.8 (12.6)</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>135.0 (16.0)</td>
<td>132.8 (17.3)</td>
<td>133.8 (16.8)</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>79.5 (9.6)</td>
<td>78.5 (9.9)</td>
<td>78.9 (9.8)</td>
</tr>
<tr>
<td>HDL cholesterol (mmol/L)</td>
<td>1.2 (0.4)</td>
<td>1.4 (0.4)</td>
<td>1.3 (0.4)</td>
</tr>
<tr>
<td>Total cholesterol (mmol/L)</td>
<td>4.7 (0.9)</td>
<td>4.9 (0.9)</td>
<td>4.8 (0.9)</td>
</tr>
<tr>
<td>LDL cholesterol (mmol/L)</td>
<td>2.8 (0.8)</td>
<td>2.8 (0.8)</td>
<td>2.8 (0.8)</td>
</tr>
<tr>
<td>Triglycerides (mmol/L)</td>
<td>1.8 (1.4)</td>
<td>1.7 (1.2)</td>
<td>1.7 (1.3)</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>29.8 (6.1)</td>
<td>31.3 (7.6)</td>
<td>30.3 (6.9)</td>
</tr>
<tr>
<td>Framingham 10-year CVD risk (%)</td>
<td>23.1 (13.0)</td>
<td>17.8 (11.3)</td>
<td>20.7 (12.5)</td>
</tr>
</tbody>
</table>

Data are presented as means (SEM).

as total cholesterol minus HDL cholesterol, and the 10-year cardiovascular disease (CVD) risk was calculated using the JBS risk calculator, derived from the Framingham algorithm, which uses eight risk factors [age, gender, systolic or diastolic blood pressure, smoking status, diabetes status, left ventricular hypertrophy (LHV; based on electrocardiography criteria), and total and HDL cholesterol]. Comparisons between categorical variables were made using Pearson’s χ² test.

3. Results

Out of a total of 60,258 patients with diabetes aged 30 to 74 years, 11,005 patients had a complete dataset, were not taking any lipid-lowering agent and had no history of atherosclerotic arterial disease and, therefore, were eligible for primary CVD prevention. Table 1 shows the baseline characteristics of the present study patients. Men (n=6134) outnumbered women (n=4871), the mean age was 53.7 years (55.9 years for men and 53.4 years for women) and the mean 10-year CVD risk for the total population was 20.7% (21.3% and 17.8% for men and women, respectively).

Concordance/discordance between LDL and non-HDL cholesterol levels for the whole cohort are shown in Table 2. Of the 939 patients with very low LDL cholesterol (< 1.8 mmol/L), 550 (58.6%) had correspondingly very low levels of non-HDL cholesterol (< 2.6 mmol/L) and 126 (13.4%) had high levels of non-HDL cholesterol (> 3.37 mmol/L). Of the 3116 patients with low LDL cholesterol levels (1.8–2.59 mmol/L), 1691 (54.3%) had correspondingly low levels of non-HDL cholesterol (2.59–3.37 mmol/L) and 846 (27.1%) had high non-HDL cholesterol levels.

As for those with high Tg (2.2–4.0 mmol/L), of the 235 patients with very low LDL cholesterol (< 1.8 mmol/L) and of the 654 patients with low LDL cholesterol (1.8–2.59 mmol/L), only 25.5% and 27.8%, respectively, had corresponding values of non-HDL cholesterol (< 2.6 mmol/L and 2.6–3.37 mmol/L, respectively). As regards the patients with low Tg (<2.2 mmol/L), of the 550 patients with very low LDL cholesterol (< 1.8 mmol/L), 419 (76.2%) had correspondingly very low non-HDL cholesterol levels (< 2.6 mmol/L) and 46 (8.4%) had high non-HDL cholesterol levels (> 3.37 mmol/L; Table 2).

As regards the patients with very low LDL cholesterol (< 1.8 mmol/L) and of the 3116 patients with low LDL cholesterol (1.8–2.59 mmol/L), the 235 patients with very low LDL cholesterol (< 1.8 mmol/L) and of the 654 patients with low LDL cholesterol (1.8–2.59 mmol/L), only 25.5% and 27.8%, respectively, had corresponding values of non-HDL cholesterol (< 2.6 mmol/L and 2.6–3.37 mmol/L, respectively). As regards the patients with low Tg (< 2.2 mmol/L), of the 550 patients with very low LDL cholesterol (< 1.8 mmol/L), 419 (76.2%) had correspondingly very low non-HDL cholesterol levels (< 2.6 mmol/L) and 46 (8.4%) had high non-HDL cholesterol levels (> 3.37 mmol/L; Table 2).

When stratified according to MS status, there was greater concordance between very low LDL and very low non-HDL cholesterol levels in patients without (77.9%) compared with patients with (50.3%) the MS (Pearson’s χ² test = 59.7; P < 0.001). Of the 303 patients with no MS and very low LDL cholesterol, only 19 (6.3%) had high non-HDL cholesterol values. In contrast, of the 489 patients with the MS and very low LDL cholesterol, only 1691 (54.3%) had correspondingly low levels of non-HDL cholesterol (2.59–3.37 mmol/L) and 846 (27.1%) had high non-HDL cholesterol levels.

Table 2
Patients according to LDL cholesterol categories corresponding to non-HDL cholesterol levels and stratified by serum triglycerides.

<table>
<thead>
<tr>
<th></th>
<th>&lt; 1.8</th>
<th>1.8–2.59</th>
<th>&gt; 2.59</th>
<th>&lt; 1.8</th>
<th>1.8–2.59</th>
<th>&gt; 2.59</th>
<th>&lt; 1.8</th>
<th>1.8–2.59</th>
<th>&gt; 2.59</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients (mmol/L)</td>
<td>939</td>
<td>3116</td>
<td>6950</td>
<td>550</td>
<td>2557</td>
<td>5310</td>
<td>235</td>
<td>654</td>
<td>1386</td>
</tr>
<tr>
<td>n</td>
<td>550 (58.6)</td>
<td>579 (18.6)</td>
<td>470 (6.8)</td>
<td>419 (76.2)</td>
<td>570 (22.3)</td>
<td>391 (7.4)</td>
<td>60 (25.5)</td>
<td>27 (4.1)</td>
<td>61 (4.4)</td>
</tr>
<tr>
<td>&lt; 2.6 mmol/L [n (%)]</td>
<td>263 (28.0)</td>
<td>1691 (54.3)</td>
<td>1524 (59.6)</td>
<td>84 (15.3)</td>
<td>1528 (28.8)</td>
<td>119 (50.6)</td>
<td>119 (50.6)</td>
<td>182 (27.8)</td>
<td>171 (12.3)</td>
</tr>
<tr>
<td>&gt; 3.37 mmol/L [n (%)]</td>
<td>126 (13.4)</td>
<td>846 (27.1)</td>
<td>461 (18.0)</td>
<td>46 (8.4)</td>
<td>3388 (63.8)</td>
<td>54 (23.0)</td>
<td>444 (67.9)</td>
<td>444 (67.9)</td>
<td>1152 (83.1)</td>
</tr>
</tbody>
</table>

Table 3
Patients according to LDL cholesterol categories corresponding to non-HDL cholesterol levels, and stratified by the presence and absence of the metabolic syndrome (MS).

<table>
<thead>
<tr>
<th>Patients (n)</th>
<th>&lt;2.6 mmol/L [n (%)]</th>
<th>2.6–3.37 mmol/L [n (%)]</th>
<th>&gt;3.37 mmol/L [n (%)]</th>
</tr>
</thead>
<tbody>
<tr>
<td>With the MS (mmol/L)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1.8</td>
<td>489</td>
<td>246 (50.3)</td>
<td>158 (32.3)</td>
</tr>
<tr>
<td>1.8–2.59</td>
<td>1958</td>
<td>231 (11.8)</td>
<td>1004 (51.3)</td>
</tr>
<tr>
<td>&gt;2.59</td>
<td>4253</td>
<td>209 (4.9)</td>
<td>837 (19.7)</td>
</tr>
<tr>
<td>Without the MS (mmol/L)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1.8</td>
<td>303</td>
<td>236 (77.9)</td>
<td>47 (15.5)</td>
</tr>
<tr>
<td>1.8–2.59</td>
<td>1295</td>
<td>373 (28.8)</td>
<td>719 (55.5)</td>
</tr>
<tr>
<td>&gt;2.59</td>
<td>2707</td>
<td>261 (9.6)</td>
<td>912 (33.7)</td>
</tr>
</tbody>
</table>

246 (50.3%) had corresponding values of non-HDL cholesterol and 85 (17.4%) had high non-HDL cholesterol (> 3.37 mmol/L) values (Table 3). As Tg is an important component of the MS, further concordance analyses were performed between patients with and without the MS, excluding those with Tg > 1.7 mmol/L. As with previous findings, greater concordance was noted between very low LDL and very low non-HDL cholesterol levels in patients without (77.3%) compared with those with (30.1%) the MS (Pearson’s $\chi^2$ test = 100.2; $P < 0.001$). This suggests that the association between LDL/non-HDL cholesterol discordance and the MS is not driven by hypertriglyceridaemia. However, it is worth noting that, by excluding patients with Tg > 1.7 mmol/L, the number of patients suitable for analysis was significantly reduced.

The prevalence of concordance/discordance between the two cholesterol indices stratified for different levels of HbA1c (< 7%, 7–9% and > 9%) was similar (Table 4). Of the patients with very low LDL cholesterol levels (< 1.8 mmol/L), the prevalence of patients with correspondingly very low non-HDL cholesterol levels (< 2.6 mmol/L) was 60.4%, 59.8% and 59.8% for the different levels of HbA1c, respectively (HbA1c < 7% vs. 7–9%, Pearson’s $\chi^2$ test = 0.019; $P < 0.90$; HbA1c < 7% vs. > 9%, Pearson’s $\chi^2$ test = 0.01; $P < 0.92$; and HbA1c 7–9% vs. > 9%, Pearson’s $\chi^2$ test = 0.0; $P < 0.99$).

4. Discussion

The results of the present study show discordance between non-HDL cholesterol, used as a surrogate marker of apoB level, and LDL cholesterol in a large cohort of diabetic patients who were not taking any lipid-lowering therapy and who had no previous CVD events. Of the patients with very low LDL cholesterol, only 58.6% had correspondingly very low levels of non-HDL cholesterol, while 13.4% had high levels of non-HDL cholesterol. Thus, having LDL cholesterol within normal levels in this large population cohort did not necessarily guarantee corresponding low non-HDL cholesterol levels. The degree of discordance appeared to be higher in patients with high Tg levels and in those with the MS, although concordance/discordance was not affected by glycaemic control. In addition, the findings in patients with the MS were not driven by raised Tg levels. We postulate that the observed discordance could explain the widely reported high residual risk of CVD among patients with diabetes despite having achieved their desirable LDL cholesterol levels.

Several studies have shown that both apoB and non-HDL cholesterol are better predictors of CVD risk than is LDL cholesterol [7,8,14]. On the basis of correlation studies, the ATP III concluded that non-HDL cholesterol is an acceptable surrogate marker for apoB [10,11]. Furthermore, the rationale for including non-HDL cholesterol as a therapeutic target is based on the evidence that LDL cholesterol fails to include the ‘atherogenic cholesterol’ carried by LDL remnants, including oxidized and modified LDL particle concentrations. Non-HDL cholesterol comprises LDL cholesterol plus very low-density lipoprotein (VLDL) cholesterol and the cholesterol from remnants of Tg-rich lipoprotein metabolism. Both VLDL and remnant cholesterol are known to be atherogenic and to increase when Tg concentrations are increased. Patients with type 2 diabetes who...
achieved non-HDL cholesterol targets were previously shown to have a lower prevalence of increased LDL particle concentrations compared with those who achieved corresponding LDL cholesterol targets [3]. The use of non-HDL cholesterol as a therapeutic target becomes even more important in diabetic patients with elevated Tg levels or the MS. In such cases, non-HDL cholesterol appears to take into account the under-representation of LDL particle concentrations in patients with high Tg, as the non-HDL cholesterol fraction reflects cholesterol from Tg-rich lipoproteins [VLDL and intermediate-level lipoprotein (IDL)] and represents the presence of smaller dense LDL particles depleted of cholesterol esters, but with a central core enriched with Tg [15]. Likewise, the MS, by virtue of its central aetiogenic mechanism of insulin resistance, exhibits a similar drive towards discordance between non-HDL and LDL cholesterol levels. Such discordance in patients with the MS has already been reported in the Framingham Heart Study [16]. More important, the role of insulin resistance as a pathogenic factor for discordance between non-HDL and LDL cholesterol has been previously shown to apply equally to patients with or without diabetes [17]. The present study also suggests that the discordance between the two cholesterol indices is not a function of glycaemic control.

The present study included patients who were not under any lipid-lowering treatment. Whether or not the concordance/discordance between non-HDL and LDL cholesterol reported here is the same during treatment of hyperlipidaemia is not known. This is because LDL cholesterol measurements during treatment for hyperlipidaemia have proved to be poor predictors of CVD outcomes due to the wide variability of treatment effects on LDL composition [18]. Also, sub-analyses from the Air Force/Texas Coronary Atherosclerosis Prevention Studies (AFCAPS/TexCAPS), Scandinavian Simvastatin Survival Study (4S), LIPID Trials and Leiden Heart Study have all found that ‘on treatment’ apoB values are better predictors of major coronary events than ‘on treatment’ LDL cholesterol levels [19–22]. Thus, abnormal apoB values can reveal a residual risk for future CVD events in patients despite desirable LDL cholesterol levels with treatment. More important, in contrast to the AFCAPS/TexCAPS in which statins were used, the Veterans Affairs High-Density Lipoprotein Intervention Trial (VA-HIT) found that levels of ‘on treatment’ apoB with gemfibrozil were not predictive of future CHD events [23].

The present study has some significant limitations that should be mentioned. The study analyzed cholesterol levels from a large number of patients across England and Wales, but could not take into account the different cholesterol assays used in different centres nor the timing of these cholesterol values in not predictive of future CHD events [23]. Finally, although the evidence and guidelines suggest that non-HDL cholesterol is an acceptable surrogate marker for apoB and LDL particle concentrations, the correlation between the two cholesterol indices is not perfect. However, apoB levels are not routinely available in primary-care practices. Nevertheless, and despite these limitations, the study objective was to highlight the potential discordance between the two cholesterol indices, and to provide a platform for discussion of the importance of non-HDL cholesterol and the limitations of LDL cholesterol as a therapeutic target for patients with diabetes in the context of primary CVD prevention.

In summary, the present study findings suggest significant discordance between non-HDL and LDL cholesterol in diabetic patients who are not under any lipid-lowering treatment and especially in those with high Tg levels or the MS. This may partly explain the high residual risk of CVD among patients with diabetes despite having achieved their desirable LDL cholesterol levels. While other factors may also contribute towards such high residual risks, the use of non-HDL cholesterol as a therapeutic target should be encouraged in patients with diabetes, the MS and high Tg levels, although further validation is required to refine its use in routine clinical practice.

Conflict of interest statement

Nothing to declare.

References


