Impact of interpretative commenting on lipid profiles in people at high risk of familial hypercholesterolaemia

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Abstract

Background: Familial hypercholesterolaemia (FH) is an autosomal dominant condition characterised by increased low density lipoprotein cholesterol (LDL-c), xanthomata and premature cardiovascular disease. However, it is currently underdiagnosed and undertreated in Australasia. We sought to investigate whether interpretative commenting on lipid profiles could improve FH detection and treatment.

Methods: A case–historical control study of individuals with serum LDL-c concentrations ≥6.5 mmol/L: 96 cases receiving an interpretative comment suggesting FH compared with 100 controls not receiving a comment.

Results: Serum LDL-c was repeated in 63 (66%) cases and 70 (70%) controls within 12 months. LDL-c decreased in 59 (94%) cases and in 61 (87%) controls. In individuals with a repeat LDL-c, a mean LDL-c reduction of 2.3 mmol/L (32%; p < 0.0001) was demonstrated in controls, compared with 3.0 mmol/L (42%; p < 0.0001) in cases; significantly greater than that of controls (p < 0.0005). Interpretative comments suggesting specialist review were associated with a higher referral rate compared with controls (11.5% vs 1%, p < 0.05).

Conclusion: Interpretative commenting was associated with a significant additional LDL-c reduction and increased specialist referrals compared with controls. However, only a minority of individuals received a specialist referral. Interpretative commenting may play an important role in the detection and management of FH.

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1. Introduction

Interpretative commenting involves applying additional information to a report to assist the clinician interpreting the results and is typically performed by the duty biochemist, a pathologist or, less frequently in Australia, a professionally qualified scientist [1]. Interpretative commenting is employed in the vast majority laboratories in the UK, despite debate over the influence this has on patient management and outcomes [2].

Interpretative comments are well received, especially by general practitioners (GPs), with 78% stating that they influenced patient management [3,4]. Interpretative commenting on large volume tests such as lipid profiles often necessitates the use of sophisticated computer software [2]. Given the multifactorial nature of absolute cardiovascular risk, interpretation of lipid profiles should occur within the broader concept of cardiovascular disease prevention [5–8].

Familial hypercholesterolaemia (FH) is an autosomal dominant condition characterised by increased LDL-c, xanthomata and premature cardiovascular disease [9]. Currently, the vast majority (~80%) of patients with FH are undiagnosed, and those who are diagnosed with FH, are often undertreated despite FH meeting the World Health Organization criteria for screening [9,10]. Detecting the first individual (index case) in a kindred with FH is a major challenge in FH management. Screening the first-degree family members of FH index cases (cascade screening) has been demonstrated to be cost effective and is recommended for adults and children [10–13].

We have previously demonstrated that community laboratories have the potential to detect FH, as they perform large numbers of LDL-c measurements with the vast majority requested by GPs [14]. People with an LDL-c ≥6.5 mmol/L are at high risk of having FH [15,16]. We now sought to determine the impact of adding interpretative comments highlighting the possibility of FH to lipid profiles of these people. We assessed the impact of interpretative commenting...
on: referral for specialist FH assessment, rates of LDL-c re-measurement and the subsequent LDL-c concentrations to determine if lipid lowering therapy was added.

2. Methods

This case–historical control study used serum lipid profiles measured at St John of God Pathology (SJGP) between the 1st of January 2008 and the 19th of October 2011. SJGP is private not-for-profit organisation providing clinical laboratory services to patients in primary care and private hospitals. In Western Australia, SJGP performs ~100,000 LDL-cholesterol measurements per year, 92% of which are requested by GPs [14].

Individuals in the intervention group were selected on the basis of an LDL-c concentration ≥ 6.5 mmol/L on a lipid profile requested by a GP between the 23rd of June and the 19th of October 2010. The control group, consisting of the first 100 individuals was selected retrospectively by reviewing the LDL-c results from the 1st of May 2009. Individuals in both groups were excluded if there was an identifiable potential secondary cause for the hypercholesterolaemia [hypothyroidism (TSH > 4.0 mU/L), mixed hyperlipidaemia (triglyceride > 4.0 mmol/L), nephrotic syndrome (proteinuria > 3 g/L and serum albumin < 30 g/L), and cholestasis (alkaline phosphatase (ALP) > 135 U/L and γ-glutamyltransferase (GGT) > 55 U/L in males or > 38 U/L in females) within ± 30 days of the LDL-c result.

Interpretative comments were added to the lipid results with the assistance of an expert system, Lab Wizard® (Pacific Knowledge Systems, Sydney, Australia) [17], with all comments reviewed by a chemical pathologist. Four different comments were used, all raising FH as a consideration, but with increasing content and specificity. The comments were as follows:

1. FH is an important consideration when LDL-cholesterol ≥ 6.5 mmol/L.
2. FH is an important consideration when LDL-cholesterol ≥ 6.5 mmol/L. Suggest review of clinical stigmata of FH (tendon xanthomata, corneal arcus), review family history and repeat full lipid profile.
3. FH is an important consideration when LDL-cholesterol ≥ 6.5 mmol/L. Suggest review of clinical stigmata of FH (tendon xanthomata, corneal arcus) and consider specialist referral.
4. FH is very likely when LDL-cholesterol > 8.4 mmol/L.

The expert system assisted in the selection of these comments; comment 3 could only be applied if there was a previous LDL-c of ≥ 6.5 mmol/L after reviewing LDL-cholesterol results back to the 1st of January 2008, whereas comment 4 could only be applied when the LDL-c was > 8.4 mmol/L.

Total cholesterol, triglyceride, and high density lipoprotein (HDL)-cholesterol analyses were performed with enzymatic, colorimetric assays using Siemens reagents on a Siemens Dimension RXL chemistry analyser (Siemens Healthcare Diagnostics, Tarrytown, NY, USA). LDL-c was calculated according to the Friedewald equation [18]. The coefficient of variation for total cholesterol was 1.8%.

The community laboratory database was searched with Crystal Reports software version 11.0.0.1282, SAP AG, Business Objects (Walldorf, Germany) and Microsoft Access 2003. Referral to and the outcome of review by the regional Lipid Disorders Clinic was determined by manual comparison of the case with the clinical databases. In order to capture patients who may have been reviewed by a private specialist, the regional Cardiovascular Genetics Laboratory database was reviewed to determine if genetic testing had been ordered on any of these individuals.

Statistical analysis was performed using Microsoft Excel 2003, STATA, StataCorp. 2011, Stata Statistical Software: release 12 and Simple Interactive Statistical Analysis [19]. A repeated measure, random effect, linear regression model was used to investigate the changes in LDL-c over time between the interpretative comment and control groups via an interaction term. Baseline characteristics were included as covariates to investigate any possible effect on the interaction term. Bootstrapped standard errors were employed in this analysis. Chi-squared or Fisher’s exact tests were used to compare the specialist referral rates.

This study was approved by the Royal Perth Hospital Human Research Ethics Committee (EC 2011/069).

3. Results

During the case selection period, 30,336 LDL-cholesterol results were issued, with 109 individuals identified with an LDL-c ≥ 6.5 mmol/L. Two individuals were excluded due to a potential secondary cause of hypercholesterolaemia (TSH > 4.0 mU/L). Eleven individuals did not have FH raised in the interpretative comments after review by the chemical pathologist; seven were aged ≥ 75 years, one had the result copied to a cardiologist, and one had recent hypothyroidism. The reason for exclusion by the chemical pathologist was not stated in the remaining two individuals. The subject characteristics for the 96 individuals remaining in the intervention group are described in Table 1 with a mean LDL-c of 7.1 ± 0.8 mmol/L (range, 6.5–11.2) and 83 different GP requestors.

The first one hundred individuals who met the same inclusion and exclusion criteria were selected from the 153 individuals in the control selection period with an LDL-c ≥ 6.5 mmol/L; their mean LDL-c was also 7.1 ± 0.8 mmol/L (range, 6.5–9.9) (Table 1) with 88 different GP requestors. There were no statistically significant differences in the demographics between the cases and controls.

A subsequent LDL-c was recorded in 63 individuals in the intervention group in the 12 months following their LDL-c selection. If more than one LDL-c was performed in the follow-up period, the first was selected. Fifty nine (89%) individuals from the intervention group demonstrated a reduction in their LDL-c, whereas four showed an increase. The mean follow-up LDL-c was 4.1 ± 1.6 mmol/L, demonstrating a significant 3.0 ± 1.7 mmol/L reduction (p < 0.0001; Fig. 1).

A subsequent LDL-c was recorded in 70 controls in the 12 months following their LDL-c selection. Sixty one (87%) controls demonstrated a reduction in their LDL-c, one remained the same and eight showed an increase. The mean follow-up LDL-cholesterol was 4.7 ± 1.7 mmol/L demonstrating a mean reduction of 2.3 ± 1.8 mmol/L (p < 0.0001; Fig. 2). The additional 0.7 mmol/L reduction in LDL-c in the intervention group when compared with controls was statistically significant (p < 0.005).

Adjusting for the patient demographics and characteristics including the presence of a clinical history provided on the request form (statin use, history of ischaemic heart disease (IHD) and diabetes) had no impact on the difference between the LDL-c reduction between the interpretative comment group and controls. Although less males had a repeat LDL-c when compared with females (p = 0.02), there was no effect seen for age, statin use, history of IHD, or diabetes. Interestingly, there was a trend towards a higher LDL-c repeat rate in individuals without any clinical history provided (36%) compared with individuals with a clinical history provided (19%), although this failed to reach statistical significance.

Table 1

<table>
<thead>
<tr>
<th>Subject characteristics.</th>
<th>Cases</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>96</td>
<td>100</td>
</tr>
<tr>
<td>Females</td>
<td>68</td>
<td>68</td>
</tr>
<tr>
<td>Age (years) mean ± SD [range]</td>
<td>53.7 ± 10.7 [26–74]</td>
<td>53.8 ± 14.8 [16–92]</td>
</tr>
<tr>
<td>LDL-c (mmol/L) mean ± SD [range]</td>
<td>7.1 ± 0.8 [6.5–11.2]</td>
<td>7.1 ± 0.8 [6.5–9.9]</td>
</tr>
<tr>
<td>No history provided (%)</td>
<td>36 (37.5)</td>
<td>31 (31)</td>
</tr>
<tr>
<td>Clinical history provided:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>8 (8.3)</td>
<td>9 (9)</td>
</tr>
<tr>
<td>Ischaemic heart disease (%)</td>
<td>2 (2.1)</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Statin (%)</td>
<td>5 (5.2)</td>
<td>7 (7)</td>
</tr>
</tbody>
</table>
Four individuals from the intervention group were referred to the regional Lipid Disorders Clinic compared with one control, although this was not statistically significant (p = 0.20). However, when specialist referral was stated in the interpretative comment, three (11.5%) of the 26 individuals were referred to a specialist, which was significantly greater than the one (1%) referred from the controls (p < 0.05). The mean time to referral was 229 days (range, 169–311).

The specific interpretative comments added to the individual cases and their outcomes are shown in Table 2. There were no statistically significant differences in the LDL-c reduction between the comment groups.

All four individuals were diagnosed with FH clinically after specialist review using the Dutch Lipid Clinic Network criteria; two had ‘definite’ FH and two had ‘probable’ FH. Both individuals with ‘definite’ FH had an identifiable LDL receptor (LDLR) gene mutation. The control individual was not clinically diagnosed with FH and did not have genetic testing after specialist review.

4. Discussion

This is the first study to investigate the impact of adding an interpretative comment to the lipid profile of individuals at high risk for FH on their subsequent management. Interpretative commenting was associated with a significant additional reduction in LDL-c compared with controls with no added comment. The significant reductions in LDL-c seen in both interpretative comment and control groups would be consistent with the initiation of HMG-CoA reductase inhibitor (statin) therapy [20]. However, the additional LDL-c reduction demonstrated in the interpretative comment group would be consistent with approximately double the dose of statins used in the control group [20]. Statin therapy has been demonstrated to significantly reduce IHD and mortality in FH [21,22]. The additional LDL-c reduction seen in the interpretative comment group would be predicted to provide a clinically significant further reduction in cardiovascular risk. High intensity statin therapy has also been predicted to be cost effective in FH [23].

Although specifically suggesting specialist referral in the interpretative comment was associated with a 10-fold increase in referrals, only the minority (11.5%) of these individuals were referred for specialist assessment. A possible explanation for the relatively low referral rates is the observation by some GPs that FH was just synonymous with a family history of raised cholesterol, and thus, the benefit of formal diagnosis of FH was not felt to be important [24].
is required to guide further measures to increase the identification and treatment of individuals with FH. The LDL-c selection criteria designed to identify individuals at very high risk for FH are one of the strengths of this study, as reflected by four of the five individuals referred for specialist assessment being clinically diagnosed with FH. The large sample size, relative to the specificity of the selection criteria, and the well matched cases and controls are the other strengths. However, there are some potential limitations of this study. Our study used historical controls, however, both the control and case periods occurred during a time of stable statin availability and FH case detection, as the FH Western Australia programme had been active since 2007. Furthermore, the majority of the study occurred when government regulations stated that a patient had to attend the laboratory named on the request form, and an individual’s GP tended to remain with a single pathology provider during this time. Although we may have missed individuals who had subsequent LDL-c measurements performed at a different laboratory, this was a constant for both the interpretative comment group and controls.

The improvement in clinical outcome with interpretative commenting encourages and highlights the role that clinical biochemists have in the detection and management of FH [25]. However, due to the observational nature of this study, we were unable to elucidate if the greater LDL-c reductions in the interpretative comment group were due to increased dose, compliance or use of more potent statin therapy. The clinical biochemists’ role in FH detection could be further advanced by investigating the reasons why specialist referral rates were low compared with lipid-lowering treatment rates.

5. Conclusion

Interpretative commenting was associated with a significantly greater reduction in LDL-c concentrations and an increase in specialist referrals compared with controls. However, interpretative commenting did not increase the LDL-c re-measurement rates, and even specifically suggesting specialist referral resulted in only a minority of individuals being referred. Thus while the potential role that interpretative commenting may have in individuals at risk for FH is encouraging, further investigation is required to optimise FH detection.

Conflict of interest

DAB, RB, AJH, JM, FMvB, GFW and JRB have no competing interests to declare. GE is a former employee of, and has previously held shares in, Pacific Knowledge Systems Pty Ltd. (PKS). He currently has no financial or other interest in PKS.

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References