Cases in primary care laboratory medicine

Testing pitfalls and summary of guidance in lipid management

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One of the difficulties in addressing the large differences in use of laboratory tests¹ is to produce robust protocols, supported by high level evidence, for the use of these tests. A working group has been established to improve the knowledge base in laboratory medicine and is working with Sir Muir Gray, director of clinical knowledge, process and patient safety for the National Programme for Information Technology.² The initiative has brought together contributions from a range of professional associations and clinical authors to improve knowledge in the use of laboratory testing. It is collating answers to about 100 frequently asked questions in primary care on the use of laboratory tests and is presenting these through a range of media, using a standardised literature search targeted towards clinical guidelines and evidence based reviews. The complete question-answer sets are being developed into prompts, reminders, and alerts to help doctors and nurses while they are treating patients. This series of articles has been constructed around relevant clinical cases which illustrate some of the problems that can arise in using, or not using, laboratory tests, linked to the guidance points obtained from these answers.

The key points are a synthesis of existing guidelines on the subjects concerned, and in most cases originate from the consensus of national or international experts. They are “the best we can get” at present, although the answering process has revealed questions that justify further research and could have a large impact on policies for use of tests. To enrich this debate, guidance is accompanied by evidence notes highlighting the strengths or weaknesses of the evidence base supporting the guidance.

This article presents and discusses two typical cases seen in a district hospital lipid clinic. Laboratories differ in the profiles of tests they offer, and some will add tests where considered appropriate. However, most laboratory testing is driven by the request which arrives on the laboratory form. In the case of lipid disorders, this process can lead to delayed or missed diagnosis and inappropriate or even potentially dangerous treatment.

Case 1

A 64 year old man was referred by his general practitioner to the local hospital lipid clinic because of

Summary points

Consensus guidelines exist for lipid management

Differences in use of tests between doctors are large

Secondary causes for lipid disorders are not uncommon and are easily diagnosed

Predisposing factors for adverse reaction to lipid lowering drugs can be identified

The evidence base for the guidance is still limited

This is the first article in the series

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hyperlipidaemia resistant to treatment with atorvastatin 40 mg. He had had a myocardial infarction in 2002 and had started taking the statin six months before referral on atorvastatin 10 mg. Before this, his total cholesterol concentration was 8.1 mmol/l, triglycerides 1.5 mmol/l, and high density lipoprotein (HDL) cholesterol 1.4 mmol/l. At referral his total cholesterol was 6.8 mmol/l, triglycerides 1.3 mmol/l, and HDL cholesterol 1.4 mmol/l. He seemed healthy and reported no specific complaints. He was slightly overweight (body mass index 28).

Liver enzymes three months before had been within the normal range, and no creatine kinase measurement was available. Retesting confirmed the previous lipid results but showed a creatine kinase activity of 3460 IU/l, alanine aminotransferase activity of 30 IU/l, and that aspartate aminotransferase was raised at 108 IU/l. Urea and creatinine were within normal limits and a subsequent urine screen for myoglobinuria was negative. Random blood glucose was 5.8 mmol/l.

The atorvastatin was stopped and the patient's renal function and creatine kinase were monitored every three days for two weeks, after which the creatine kinase had fallen to 2400 IU/l; it was the same a week later. When he returned to the clinic after this three week period the creatine kinase activity had not fallen further and a simple battery of tests was organised to exclude other causes for his myopathy (autoantibodies, erythrocyte sedimentation rate, thyroid function).

Although he was clinically euthyroid, his thyroid stimulating hormone concentration was 52 mIU/l, free T4 was 4 pmol/l, and he was started on thyroxine. Two months later he reported feeling generally fitter; his cholesterol was 5.4 mmol/l and creatine kinase was within the normal range, and he was restarted uneventfully on a statin.

Case 2

A 45 year old man was referred to the local lipid clinic with raised cholesterol which had not responded to treatment with 40 mg of simvastatin. At the time of referral he had a total cholesterol concentration of 8.3 (other lipid results not stated) and an alanine aminotransferase concentration of 176 IU/l (five times the upper limit of normal), normal renal function, fasting glucose of 4.7 mmol/l.

The patient was a non-smoker with no history of hypertension or family history of diabetes, but a strong family history of ischaemic heart disease, two brothers having died in their early 50s from documented "heart attacks." The patient's alcohol consumption was around 20 units weekly (approximately two bottles of red wine, half of which was drunk at weekends). He was of normal build (body mass index 26) and had no clinical signs of hyperlipidaemia or evidence of peripheral vascular disease.

His total cholesterol concentration was 7.2 mmol/l and triglycerides 9.6 mmol/l. Renal function was normal and alanine aminotransferase was 162 IU/l. Thyroid stimulating hormone was 3.5 mIU/l.

The simvastatin was stopped and fenofibrate 267 mg/day started. Eight weeks later his cholesterol was 5.0 mmol/l and triglycerides 3.1 mmol/l. His alanine aminotransferase had fallen to 117 IU/l.

Discussion

These two cases illustrate two simple pitfalls in lipid management: missed secondary hyperlipidaemia with

Testing lipids

How often should patients' lipids be tested after starting lipid lowering treatment?

- 8 ($\pm$ 4) weeks after starting drug treatment
- 8 ($\pm$ 4) weekly after adjustments to treatment until within the target range

How often should cholesterol or lipids be tested once a patient has reached target or optimal cholesterol?

- Annually (unless there is a specific reason for more frequent reviews)

How often should cholesterol or lipids be tested when assessing a patient's coronary risk?

Before starting lipid lowering drug treatment:

- At least two measurements taken 1-12 weeks before starting drug treatment

In patients taking lipid lowering drugs:

- In secondary prevention not at treatment threshold: annually
- Higher risk primary prevention not at treatment threshold: every 1 or 2 years
- In lower risk primary prevention: every 5 years

Liver enzymes and statins

How often should liver enzymes be routinely measured in patients taking statins?

Measure alanine aminotransferase:

- Before treatment with a statin
- 8 weeks after starting a statin or after any dose increase
- Annually thereafter if liver enzymes are $<3\times$ upper limit of normal

What if liver enzymes become raised in a person taking a statin?

If $\leq 3\times$ upper limit of normal:

- Continue statin
 - Recheck liver enzymes in 4-6 weeks
 - No extra monitoring required unless values rising
- If $\geq 3\times$ upper limit of normal (depending on magnitude of rise):
- Stop statin or reduce dose, recheck liver enzymes within 4-6 weeks
 - Cautious reintroduction of statin may be considered (eg, lower dose)

How often should creatine kinase be measured in patients taking statins?

Pre-treatment

- Before starting treatment with a statin
- If baseline creatine kinase level >5 times ULN, do not start statin

Monitoring

Risk factors for myopathy absent:

- Routine monitoring of creatine kinase is not necessary
- Check creatine kinase if patient develops myalgia

Risk factors for myopathy present:

- Balance risk/benefit of treatment with a statin
- If a statin is prescribed: check creatine kinase within 8 weeks of commencing statin, after any dosage increase or if patient develops myalgia

What if creatine kinase becomes raised in a person taking a statin?

If $\geq 5\times$ upper limit of normal:

- Stop treatment, check renal function and monitor creatine kinase fortnightly
- Consider secondary causes of myopathy if creatine kinase remains elevated

If $\leq 5\times$ upper limit of normal:

- If no muscle symptoms, continue statin (patients should be alerted to report symptoms; consider further checks of creatine kinase)
- If muscle symptoms, monitor symptoms and creatine kinase regularly if creatine kinase continues to rise

a secondary cause of myopathy in case 1, and failure to diagnose and therefore correctly treat a mixed hyperlipidaemia in case 2. In both cases, following the consensus guidelines on testing in lipid disorders and coronary prevention would have identified the problems and led more quickly to a correct diagnosis and treatment, and could have avoided outpatient referral.

Undiagnosed and clinically unapparent hypothyroidism is not uncommon in patients presenting with hypercholesterolaemia.³ Serum thyroid stimulating hormone rises with increasing serum cholesterol

Secondary hyperlipidaemia and hypertriglyceridaemia

When should I screen for secondary hyperlipidaemia and what investigations are required?

In all patients in whom lipid lowering therapy is being considered. The investigations are:

- Dietary, alcohol, and drug history
- Urine dipstick testing for protein
- Laboratory or point of care blood glucose
- Renal function
- Liver enzymes (transaminase)
- Thyroid stimulating hormone (if the total cholesterol is >8 mmol/l, unless thyroid disease is suspected clinically)

When should I measure triglycerides at the same time as I measure cholesterol?

- In all people being assessed for risk of cardiovascular disease
- In all people being considered for lipid lowering treatment
- In monitoring, if the first triglyceride level was >2 mmol/l

What triglyceride levels are associated with a risk of pancreatitis and require treatment on this basis?

Serum triglycerides of:

- 5 mmol/l carry a probable increased risk of pancreatitis
- 10 mmol/l carry a high risk of pancreatitis
- 20 mmol/l carry a very high risk of pancreatitis

Persistent values over 5 mmol/l justify treatment

concentration⁴ and can be associated with myopathy which may be incorrectly attributed to treatment of the hypercholesterolaemia with a statin. In this case the thyroid function testing (in an apparently euthyroid patient) was triggered by the failure of the creatine kinase to fall more rapidly. The raised aspartate aminotransferase is of assumed muscle origin in view of the normal alanine aminotransferase. Treatment of the hypothyroidism corrects the lipid disorder, although in this case of secondary prevention, statins were restarted to achieve current treatment goals in this patient group. As thyroid myopathy is a predisposing factor for statin induced muscle disorders,⁵ it is important also to identify these patients in view of the potential risk of rhabdomyolysis, which is extremely rare and may be avoidable in patients with predisposing factors (for example, alcoholic or thyroid myopathy, myositis).⁶ Measurement of creatine kinase before starting statin or fibrate treatment is therefore recommended.

Case 2 highlights the limited benefit of statins in treating severe mixed hyperlipidaemia and the fact that, by definition, these diagnoses can be missed if full lipid profile is not requested before deciding on lipid lowering treatment. As the national service framework for coronary heart disease recommends use of risk calculation instruments,⁷ this patient should, in principle, have had HDL cholesterol measured during his risk assessment, although it has not been uncommon for some practitioners to manage lipid disorders on the basis of a total cholesterol measurement alone and to

refer patients whose total cholesterol fails to fall when they take statins. Some laboratories will also measure total and HDL cholesterol without measuring triglycerides. Although some statins are licensed for use in mixed hyperlipidaemia, they primarily reduce low density lipoprotein (LDL) cholesterol and may have limited effect on hypertriglyceridaemia.

The second case also highlights the fact that transaminases are not infrequently raised in patients with mixed hyperlipidaemia, often as a result of non-alcoholic steatohepatitis associated with the raised triglycerides.⁸ This can be incorrectly attributed to alcohol excess. The biochemical findings can be improved by effectively treating the hypertriglyceridaemia. Both statins and fibrates are contraindicated to varying degrees in liver disease and are reported to cause occasional cases of hepatotoxicity, but successful treatment of hypertriglyceridaemia will often greatly improve liver enzyme results if this is the cause of the anomaly.

In neither of these cases can conventional risk calculation instruments be used to reliably guide lipid lowering treatment. The first patient is by definition a candidate for secondary prevention, and in the second patient the raised triglycerides preclude the use of conventional risk calculators. Population based risk calculators do not apply to patients with severe hypercholesterolaemia (>7.8 mmol/l), who potentially justify treatment based on the cholesterol level alone.⁷ As HDL cholesterol may be raised in severe hypercholesterolaemia, the ratio of total to HDL cholesterol may be within the population range when LDL cholesterol is greatly raised.

Questions and answers: learning points

The series of questions and answers summarised in the boxes may be found in the first two reviews in best practice in primary care pathology published in the *Journal of Clinical Pathology*.^{9 10} In this article we present the key recommendations from these reviews. This guidance contains recommendations backed up by varying degrees of evidence and raise a number of questions for future research into the use of laboratory investigations in diagnosis and monitoring. They are designed to summarise existing consensus guidance on the subject.

Evidence note

The guidance points are based on a review of national and international guidelines, which have mostly been established by expert consensus. Observational studies in relevant population groups have found identifiable risk factors for rhabdomyolysis,^{5 6} although there is no clear evidence that moderately raised creatine kinase concentrations constitute such a risk factor and no clear evidence that this prevents rhabdomyolysis.

Thyroid disease is not uncommon in patients with severe hypercholesterolaemia (12% in people with total cholesterol >8 mmol/l in one observational study³). The effectiveness of screening for hypothyroidism at lower cholesterol concentrations is unclear, but screening would seem justifiable in patients with more severe disease. Secondary conditions associated with hyperlipidaemia seem to be rare

Useful websites

Lab Tests Online (UK) (www.labtestsonline.org)—a comprehensive guide to laboratory tests and their use for patients

Cochrane Library (www.nelh.nhs.uk/cochrane.asp)—information and systematic reviews on evidence based medicine. The Cochrane collaboration is beginning reviews on laboratory diagnostic testing

Journal of Clinical Pathology (www.jclinpath.com)—subscription website containing electronic access to the *Journal of Clinical Pathology*, with full content of the questions and answers examined in this article

Clinical evidence (www.clinicalevidence.com)—summaries of current evidence based management guidelines

PRODIGY (www.prodigy.nhs.uk)—clinical decision making guidelines principally for general practitioners

in general practice populations¹¹ but more common in hospital clinics. The tests recommended for patients whose lipids are within the population reference range are justified in patients who are being assessed for lipid lowering treatment on the basis of having additional coronary risk factors and risk factors. Both of these recommendations have a strong evidence base.

The use of (at least) two tests before treatment with a cholesterol lowering drug is started is justified physiologically by the intra-individual variability of cholesterol measurements.^{7 12 13} The monitoring intervals are arbitrary and are based on the assumption that treatment should be titrated to a target.

The evidence for monitoring cholesterol concentrations and alanine aminotransferase activity is weak. The incidence of true drug induced hepatotoxicity in patients taking lipid lowering drugs is unknown, and few cases have occurred in large scale randomised trials.¹⁴ Post-marketing surveillance data indicate that one case of liver failure occurs in a million person years of use,¹⁴ but this assumes accurate disease reporting and correct attribution of a causal relation with drug treatment.

The incidence of raised transaminases (>3 times upper limit of normal) was greater in the placebo arms of the randomised clinical trials than in the treatment arms, and further examination of reported cases is needed to identify the true incidence of hepatotoxicity and the merits of alanine aminotransferase monitoring. Similarly, it is not possible to conclude whether the thresholds of three times upper limit of normal (alanine aminotransferase) or five times upper limit of normal (creatinine kinase) constitute adequate evidence based thresholds for discontinuing lipid lowering treatment and whether stopping lipid lowering treatment in some of these patients may cause more harm than good.

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Corrections and clarifications

Achieving the millennium development goals for health: Cost effectiveness analysis of strategies to combat malaria in developing countries

The authors of this paper, by Chantal M Morel and colleagues (*BMJ* 2005;331:1299-302), have advised us that they made an error in the cost calculations for malaria treatment, resulting in an underestimate of the costs of treatment interventions. A corrected version of table 6 in the full version of this paper (the table in the print version) is now posted on bmj.com (<http://bmj.bmjournals.com/cgi/content/full/bmj.38639.702384.AE/DC2>) giving the costs, effectiveness, and cost effectiveness of the health maximising set of interventions.

All interventions studied remain highly cost effective in both African regions. The principal change is that in the Afri-D region insecticide treated bed nets are now the most cost effective intervention overall, followed by the combination of insecticide treated bed nets, indoor residual spraying, case management with artemisinin based combination therapy, and intermittent presumptive treatment with sulfadoxine-pyrimethamine in pregnancy. In Afri-E, however, artemisinin based combination therapy remains the most cost effective intervention overall, followed by the combination of case management with artemisinin based combination therapy and insecticide treated bed nets; then the combination of case management with artemisinin based combination therapy, insecticide treated bed nets, and indoor residual spraying; and, finally, the combination of case management with artemisinin based combination therapy, insecticide treated bed nets, indoor residual spraying, and intermittent presumptive treatment with sulfadoxine-pyrimethamine in pregnancy. Full details are available from the authors.