RATIONAL TESTING

# Investigating mildly abnormal serum aminotransferase values

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Cite this as: *BMJ* 2010;341:c4039
doi: 10.1136/bmj.c4039

This series of occasional articles provides an update on the best use of key diagnostic tests in the initial investigation of common or important clinical presentations. The series advisers are Steve Atkin, professor, head of department of academic endocrinology, diabetes, and metabolism, Hull York Medical School; and Eric Kilpatrick, honorary professor, department of clinical biochemistry, Hull Royal Infirmary, Hull York Medical School."

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How do you approach the investigation of a patient with mildly abnormal aminotransferase tests? This article will guide you through diagnosis and assessment of severity

A 43 year old man of South Asian origin, working as a software engineer, was found to have a serum alanine aminotransferase value of 64 (normal range 0-40) U/l at a routine health check arranged by his company. He had an unremarkable medical history and took no regular medications. Of note, his father had died of ischaemic heart disease at the age of 67 years. Clinical examination was unremarkable. His height was 1.7 m and weight 79 kg (body mass index 27). The results of the remaining basic liver blood tests were normal (bilirubin 12 (0-20) µmol/l; alkaline phosphatase 105 (30-150) U/l; albumin 38 (35-50) g/l). Full blood count and serum urea, creatinine, and electrolytes were also within normal limits.

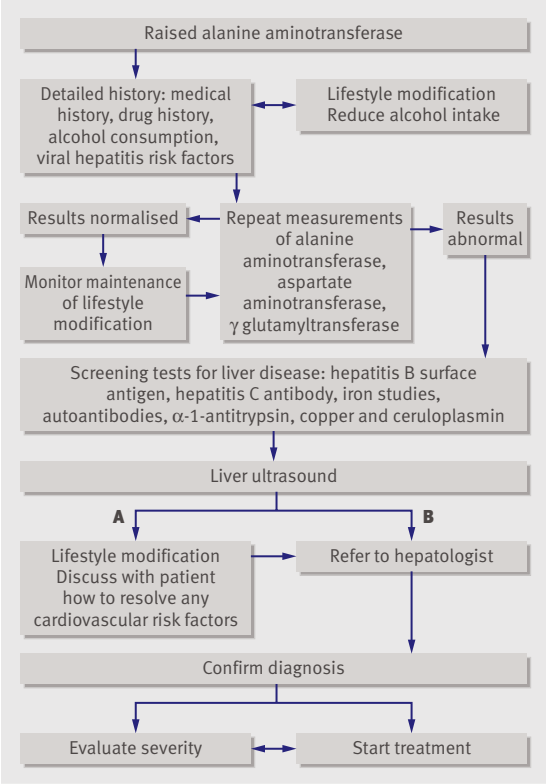
## What is the next investigation?

An initial history and clinical examination are necessary for determining the likely aetiology of the raised alanine aminotransferase value, the presence of any comorbidity that may accelerate disease progression, and the presence of stigmata of chronic liver disease. History should include details of alcohol intake, risk factors for chronic viral hepatitis, use of prescription medication, and over the counter or herbal remedies.

### Liver biochemistry

The general practitioner requested a repeat serum alanine aminotransferase value (which was 58 U/l) and serum aspartate aminotransferase and γ glutamyltransferase values (52 (0-40) U/l and 55 (11-51) U/l respectively).

Raised serum alanine aminotransferase values usually indicate hepatocellular damage. Aminotransferase values of less than five times the upper limit of normal are often considered mild, while those more than five times the upper limit of normal are severe, representing more extensive hepatocellular injury. Mildly raised values do not exclude severe chronic liver disease; indeed evidence exists that substantial liver damage may be present even with relatively mild biochemical derangements.[1] Therefore we recommend that even mild derangements of aminotransferase values that persist on retesting over a three month period should be investigated further (figure). If clinical features suggest a more pressing need for investigation (such as jaundice or raised bilirubin, deranged clotting, or hepatic decompensation) investigation should be expedited.




**Suggested pathway for investigating mild to moderately raised aminotransferase values (<5 times the upper limit of normal). Branch A is recommended if investigations suggest non-alcoholic fatty liver disease without comorbidity. Branch B is recommended if a case is atypical, if liver comorbidity is discovered, or if aminotransferase values do not settle after lifestyle modification. Referrals should be considered on a case by case basis**

All patients found to have raised serum alanine aminotransferase should have serum aspartate aminotransferase and γ glutamyltransferase measured. The ratio of aspartate aminotransferase to alanine aminotransferase may provide information about the likely aetiology of the liver disease[2]; a ratio >2 is suggestive but not diagnostic of alcohol related liver disease, a ratio of <1 typically suggests hepatic steatosis or chronic viral hepatitis. Raised γ

glutamyltransferase values and increased mean cell volume are also associated with alcoholic liver disease.

### Full blood count, serum albumin, and prothrombin time/coagulation tests

Low serum albumin and raised prothrombin time are indicative of impaired hepatic synthetic function, and along with low platelet count they suggest hypersplenism and portal hypertension resulting from cirrhosis.

### Additional tests if liver biochemistry is persistently abnormal

There are numerous causes of mildly raised aminotransferases. The most common are excessive alcohol intake (>14 units for females and >21 units for males) and obesity leading to type 2 diabetes mellitus. Singly or in combination, these may lead to cirrhosis, often without physical signs being present until late in the natural course of the disease. No clear evidence exists to guide the timing of testing for persistently abnormal liver biochemistry. We suggest waiting three months before doing screening tests to exclude less common diagnoses, although this will also clearly depend on the clinical context and on availability of testing services. These tests include:

- For viral hepatitis: hepatitis B surface antigen, and hepatitis C antibody
- For metabolic disease: ferritin and iron studies to exclude haemochromatosis; fasting glucose for evidence of diabetes mellitus that may be associated with non-alcoholic fatty liver disease.

If the abnormal aminotransferase values persist and the initial screening panel is negative, the following investigations should be undertaken (in practice, these are often performed simultaneously):

- For autoimmune liver disease: antinuclear, smooth muscle, liver-kidney microsomal-1 and mitochondrial antibodies
- For α-1 antitrypsin deficiency: serum alpha1-antitrypsin levels
- For Wilson's disease: serum copper and ceruloplasmin concentrations.

If screening tests for these conditions are positive, referral to a hepatologist is advised for confirmatory testing, staging, and treatment. The prevalence of chronic hepatitis B and C in first generation immigrants of South Asian origin in England has been estimated to be 3% and 1.6% respectively but varies by country of birth.[3] In this patient, however, the screening for liver disease did not provide any positive results.

### Ultrasound scanning

Often liver ultrasonography is arranged in parallel as part of the routine assessment of deranged liver function tests. Ultrasound scanning is a widespread and economical test that enables examination of the liver parenchyma, particularly for hepatic fat accumulation (steatosis) and exclusion of coincidental common "comorbidities" including cholelithiasis. However, it is operator dependent and may be technically limited by obesity. Increased echogenicity commonly reflects hepatic steatosis, with a sensitivity of 60%-94% and specificity of 66%-95%; however, quantification of steatosis is considered unreliable.[4] An irregular liver border and lack of parenchymal homogeneity may indicate cirrhosis, and an enlarged spleen may indicate portal hypertension.

## Outcome

In this patient, the ultrasound scan showed diffusely increased echogenicity of the liver consistent with fatty infiltration. Given a history negative for high alcohol consumption, these results would be consistent with non-alcoholic fatty liver disease.

### Non-alcoholic fatty liver disease

Non-alcoholic fatty liver disease is best considered as the hepatic manifestation of the metabolic syndrome. The prevalence of non-alcoholic fatty liver disease is estimated to be 20-30% in Western populations.[5] Of the patients with the disease who have raised aminotransferase levels, 43-55% have histological steatohepatitis, and it is these patients who are at greatest risk of progressing to cirrhosis.[6]

With such a high proportion of the adult population having non-alcoholic fatty liver disease, the challenge facing clinicians both in primary and secondary care is to identify and target treatment at those at greatest risk of cirrhosis without the routine need for liver biopsy. Optimum management remains an area of active research but is probably best delivered as a partnership between general practice and hepatology services. Associated cardiovascular risk factors (obesity, hypertension, dyslipidaemia, insulin resistance, and diabetes mellitus) should be sought and tackled as these may represent a greater risk to the patient than the liver disease. Currently, specialist hepatology referral for additional investigation and risk stratification using non-invasive biochemical or imaging modalities[7 8] (and in selected cases liver biopsy) should be considered on a case by case basis.[6] In patients in whom the results of investigations are consistent with non-alcoholic fatty liver disease and aminotransferase values return persistently to within normal ranges on adoption of sustained lifestyle changes, onward referral may not be required.

This patient was referred to a hepatologist and seen in a subspecialist non-alcoholic steatohepatitis clinic with a multidisciplinary team comprising a diabetologist, dietitian, and psychologist to support lifestyle modification strategies and compliance. Additionally, he was found to have dyslipidaemia, and an oral glucose tolerance test showed raised fasting glucose and impaired glucose tolerance; he was treated with drugs combined with dietary and lifestyle modification. The prevalence of non-alcoholic steatohepatitis with advanced fibrosis is higher among patients with a raised alanine aminotransferase value and insulin resistance. The "NAFLD (non-alcoholic fatty liver disease) fibrosis score"[7] based on readily available anthropometric and biochemical indices suggested an indeterminate risk for advanced fibrosis, and so a liver biopsy was performed that confirmed the presence of steatohepatitis with moderate fibrosis, indicating the patient to be of higher risk of future liver related morbidity.[9] During follow-up the patient's weight reduced to 73 kg and his serum alanine aminotransferase value improved, suggesting amelioration of the steatohepatitis.

**Contributors:** JFLC, QMA and HCT devised, wrote, and edited the manuscript.

**Competing interests:** All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare that (1) none have support from commercial organisations for the submitted work; (2) none have relationships with companies that might have an interest in the submitted work in the previous 3 years; (3) their spouses, partners, or children have no financial relationships that may be relevant to the submitted work; and (4) none have non-financial interests that may be relevant to the submitted work.

**Provenance and peer review:** Commissioned; externally peer reviewed.

**Patient consent not required (patient anonymised, dead, or hypothetical).**

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## A PATIENT'S JOURNEY

# Two hip replacements

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Cite this as: *BMJ* 2010;340:c1502
doi: 10.1136/bmj.c1502

This is one of a series of occasional articles by patients about their experiences that offer lessons to doctors. The *BMJ* welcomes contributions to the series. Please contact Peter Lapsley (plapsley@bmj.com) for guidance.

A retired general practitioner had hip replacements in 1997 and 2009. Here she describes the improvements made in surgical techniques and case management between her two operations

In 2009 I had a left hip replacement, having had a new right hip in 1997. Both operations took place in the same hospital and were carried out by different surgeons, and both have been very successful.

I have nothing but praise for the surgeons and staff who cared for me on both occasions. However, the 12 years between the operations saw substantial improvements in surgical techniques and postoperative case management, making the second operation a much more pleasant experience. This was partly because the orthopaedic technique had been improved and refined and is now less invasive and so reduces damage to the surrounding muscles. After the first operation it was more than a week before I could raise the operated leg from the bed, whereas in 2009 I could do so on the same day as the operation. For the second operation I had a spinal anaesthetic, which made the immediate pain control and recovery much better.

However, the most important difference was that in 2009 the preparation and recovery of hip replacement patients were in the hands of a multidisciplinary team of specialist orthopaedic nurses, physiotherapists, and occupational therapists, rather than only in the hands of the surgeon. Specialist orthopaedic nurses had initiated the team approach, and the consultant surgeons had agreed to such delegation and compromised on a uniform policy of postoperative management. The team members shared their different expertise to achieve a united aim of quality of care and rapid recovery for patients.

### The team approach

After the first consultation with the surgeon I attended a "hip school" with several other patients. It lasted about an hour, and one of the hip team members explained what to expect when coming in to hospital. We were shown x ray films of damaged hips and were able to handle examples of the different types of hip prosthesis. We were each measured for crutches and a stick and shown how to use them. We were able to borrow the crutches and sticks from the hospital, returning them postoperatively when the team deemed they were no longer needed. They also lent each of us a DVD demonstrating advised exercises for before and after the operation. The same information was provided in booklet form, along with an invaluable list of "dos" and "don'ts" for after the operation. My fellow patients and I found the knowledge offered by the hip school empowering. It raised our morale and confidence and increased our determination to cooperate with each other and with the team.

### USEFUL RESOURCES

Rapid Recovery Hip Replacement Programme (www.hampshire-hip.co.uk)—A video guide to rapid recovery after the operation, provided by Basingstoke and North Hampshire NHS Foundation Trust

The British Orthopaedic Association (www.boa.ac.uk/en/patient-liaison/elderlyhip)—Guidance for elderly patients with hip fractures

National Joint Registry (www.njrcentre.org.uk)—Information on hip and knee replacement operations

British Hip Society (www.britishhipsociety.com)—Homepage of the British Hip Society, including a link to download the *BHS Hip Replacement Booklet - A Guide For Patients*

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