Biochemistry results
- and what to do with them
or
The right test, the right time & the right result!

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The right test

I MAY NOT KNOW WHAT I'M DOING
BUT AT LEAST IT LOOKS IMPRESSIVE
The ICE effect!

Rolling annual complement tests on PCT patients 2004-2009

Tumour markers

• Use with caution!

• NONE are proven to have value in screening and are often entirely normal in the early stages of disease (and sometimes in quite advanced malignancy)

• ‘Patient pressure’ may be an issue, but patients should have it explained to them that these are not designed as screening tests and that a ‘normal’ result does not exclude cancer
Tumour marker requestes

Rolling annual total CA-125 & CEA tests on PCT patients 2004-2009

CA-125

• A marker for ovarian cancer – but NOT specific
  • Levels are raised in endometriosis and other benign gynaecological conditions
  • High levels in ascites and other intra-abdominal malignancies
• Proven value in follow-up of cases
• No role in screening at present
  • Recent trials have increased demand
  • Random tests of no value
  • Serial tests may have a role in the future, in combination with ultrasound and examination
PSA

• Value in screening is not proven
• Care must be taken when collecting samples
  • Do NOT collect:
    • For 48 hours after sexual intercourse
    • For 48 hours after rectal examination
    • For 48 hours after vigorous physical exercise (especially bicycle riding!)
    • For at least 6 weeks after a prostatic biopsy or prostate surgery
Iron, ferritin, transferrin…..

• Serum iron is NOT a good measure of iron status:
  • Levels fall in acute illness (to very low levels)
  • Serum levels are related to intake – sample collected a few hours after iron tablet or multivitamin tablet are misleadingly high
• Best measure is ferritin combined with haematological indices
• Serum iron mainly useful in iron overload

Please…..please…….please……..

• Don’t look for ‘transferrin’ on ICE and then ask for every test with the word transferrin in it……
  • They’re not all relevant!
    • Soluble transferrin receptors are a specialist (& restricted) haematology test
    • Carbohydrate-deficient transferrin is also a specialist & restricted test for monitoring alcohol intake
    • Transferrin glycoforms are a specialist & restricted paediatric test for a specific inborn error of metabolism
    • Asialotransferrin (Tau protein) is found in CSF
• If you don’t know what the test is, please don’t ask for it!
Allergy testing

• There are over 1,000 specific allergy tests available (& they are all expensive!)
  • Don’t ask for ‘allergic ?to what’
  • Take a careful history
    • Is it seasonal or all year round? (pollen?)
    • Is it worse indoors or out? (HDM, moulds?)
    • Is it related to specific foods? (nuts? Fish?)
    • Is it worse when exposed to someone’s pets?
  • Please ... give us this information on the request form so we can do the right tests!
  • Use the lab handbook!
… the right time….

- LH & FSH
  - Results are only interpretable if collected between days 1-5 of cycle
  - Results at mid-cycle peak can’t be interpreted
- Progesterone
  - ONLY useful to see if ovulation has occurred
  - NOT useful in menopause
  - MUST be collected between days 20-22
- No point in measuring vitamin B12 levels for at least 3 months after B12 injection
- Thyroid hormones
  - Takes 6 weeks to stabilise TSH after starting TSH or a dose change
  - No point in re-requesting during this time

What’s new?

- HbA1c reporting
- CKD guidelines
  - IN: Urine albumin/creatinine ratio
  - OUT: urine protein creatinine ratio
  - OUT: urine protein dipsticks
New CKD guidelines

• Patients found to have eGFR below 60 (CKD Stage 3 or worse) should have a urine albumin:creatinine ratio measured (instead of a protein:creatinine ratio)

• Urine ‘dipstick’ testing is NOT adequate

• 24 hour protein measurement is NOT recommended
3.1 Key priorities for implementation

• To detect and identify proteinuria, use urine albumin:creatinine ratio (ACR) in preference, as it has greater sensitivity than protein:creatinine ratio (PCR) for low levels of proteinuria.

• For quantification and monitoring of proteinuria, PCR can be used as an alternative.

• ACR is the recommended method for people with diabetes (“microalbumin”).

What does this mean?

• Instead of requesting a protein:creatinine ratio (UPCR), an albumin:creatinine ratio (UACR) should be requested.

• This is what is already measured in diabetics (when it’s called microalbumin!)
  • this leads to challenges (problems?)!
UACR

- Early morning urine preferred
- A positive result must be confirmed
- Advise patients NOT to collect samples
  - Within 48 hrs of sexual intercourse
  - If they have a urinary infection
  - If they are menstruating
- If gross proteinuria is detected (>200 mg protein/mmol creatinine) it is inappropriate to measure the albumin:creatinine ratio and patients should be monitored using a protein:creatinine ratio
- The albumin:creatinine ratio is significantly more expensive than a protein:creatinine ratio
  - Approx £8 instead of £3 (!)

Confounding factors

- Timing of urine
  - First void urine samples provide lower variability than random samples
- Effects of exercise, posture, fever, diet
- Timing of medication (e.g. diuretics)
- Inappropriately collected sample (intercourse, UTI, menstruation, etc)
- Concentration of urine
- Method variation:
  - creatinine assay
  - protein method
**CKD guideline (2)**

- Offer ACEI/ARBs to non-diabetic people with CKD and hypertension and ACR ≥30 mg/mmol (approximately equivalent to PCR ≥50 mg/mmol, or urinary protein of ≥0.5 g/day)
  
  - **NOTE**
  - CKD treatment level >30 mg/mmol
  - **BUT**
  - Diabetes monitoring
    - Males abnormal >2.5 mg/mmol
    - Females abnormal >3.5 mg/mmol

**So.........**

- We need to report the appropriate reference range or interpretive text

- **SO**

- We need to know whether the albumin:creatinine ratio is being requested as part of diabetes monitoring or as part of CKD investigation......
Urine ACR

- As this is effectively the same test as a ‘microalbumin’ so the lab has to make some changes:
  - A request for ‘microalbumin’ will be reported as an albumin:creatinine ratio with the comments appropriate to diabetics
  - All microalbumin/albumin:creatinine ratio requests will also have a protein:creatinine ratio measured to detect gross proteinuria
  - ICE will be changed to reflect these changes

So: ICE

- Will offer three tests:
  - Urine albumin:creatinine ratio (diabetes monitoring)
  - Urine albumin:creatinine ratio (CKD monitoring)
  - Urine protein:creatinine ratio (proteinuria monitoring)

- Urine microalbumin requests will be assumed to be for the monitoring of diabetes and the cut-offs appropriate to diabetes will be reported
CKD guideline (3)

• Stage 3 CKD should be split into two subcategories defined by:
  • GFR 45–59 ml/min/1.73 m² (stage 3A)
  • GFR 30–44 ml/min/1.73 m² (stage 3B)

• The lab will make this change on its reports

CKD guideline (4)

• People with CKD should usually be referred for specialist assessment if any of the following apply:
  • heavy proteinuria i.e. ACR ≥70 mg/mmol, (approximately equivalent to PCR ≥100 mg/mmol or urinary protein excretion ≥1 g/24 h) unless known to be due to diabetes and already appropriately treated
  • proteinuria i.e. ACR ≥30 mg/mmol, (approximately equivalent to equivalent to PCR ≥50 mg/mmol, or urinary protein excretion ≥0.5 g/24 h) together with haematuria
Oh! By the way…..

- Eating meat raises the serum creatinine and lowers the apparent eGFR
- If a new patient has a low eGFR (between 40-60) and a second sample is to be collected to confirm this
  - Advise them to refrain from eating meat for 24 hrs before the test

Urine microalbumin

- Local PCT policy is:
  - Do a single microalbumin
  - If normal, re-test in 6 months
  - If abnormal re-test as soon as possible
    - Remind patients not to collect samples if they have a urine infection and not for 48 hours after sexual intercourse or during menstruation
  - Patients should no longer collect 3 samples and bring to the laboratory at the same time
    - PCT policy has changed
    - If a sample is contaminated from infection, intercourse likelihood is that all samples will be affected and cause false positive
    - Many patients misunderstand the instructions and collect one sample and divide into 3 pots and bring them up together!
HbA1c reporting changes

- At present, HbA1c is reported as a % of the total Hb which is glycated
- Different methods give different results for HbA1c
- In future, all assays will be calibrated against an international reference method
- Results will be reported as a ratio: mmol glycated Hb: mol of non-glycated Hb
‘Off with the old and on with the new’

<table>
<thead>
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<th>IFCC HbA1c (mmol/mol)</th>
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Ranges

- **Target range:**
  - Was 6.5 – 7.5%: now 48 – 59 mmol/mol

- **Non-diabetic range:**
  - 4.0 – 6.0%: now 20 – 42 mmol/mol

- **‘Estimated average glucose’**
  - One study has reported on the value of reporting an eAG result but this may be misleading and will NOT be reported in the UK
When results are misleading….

- Patients with some abnormal haemoglobins
  - We will advise you and suggest that fructosamine is measured instead
- Any condition with increased red cell turnover
  - Anaemia
  - Haemolysis
  - Acute inflammatory conditions (e.g. RA)
  - Drugs
  - Uraemia
  - Alcoholism

Timescale

- Laboratories will start to report in the new units, alongside the old ones, from 1st June 2009
- From 1 Jun 2011 results will ONLY be reported in new units
- The lab will issue BOTH results and BOTH will appear on ICE
  - You will need to check how these appear on your local GP system!
HbA$_{1c}$ Standardisation
For Clinical Health Care Professionals

**Change to reporting of HbA$_{1c}$**
From 1 June 2009, the way in which HbA$_{1c}$ results are reported in the UK is changing. This leaflet explains why and how this will happen.

**What is HbA$_{1c}$?**
Glucose in the blood binds irreversibly to a specific part of haemoglobin in red blood cells, forming HbA$_{1c}$. The higher the glucose, the higher the HbA$_{1c}$. HbA$_{1c}$ circulates for the lifespan of the red blood cell, so reflects the prevailing blood glucose levels over the preceding 2-3 months.

**What does it tell us?**
The Diabetes Control and Complications Trial (DCCT) in Type 1 diabetes and the UK Prospective Diabetes Study (UKPDS) in Type 2 diabetes both showed that the risk of microvascular and macrovascular complications of diabetes increases as HbA$_{1c}$ increases. HbA$_{1c}$ thus gives a measure of an individual's risk of the long-term complications of diabetes.

**Why measure it?**
Serial measurements of HbA$_{1c}$ show how an individual's glucose control, and thus risk of complications, changes in response to alterations in management. HbA$_{1c}$ should be measured 2-6 monthly. Target HbA$_{1c}$ levels can be set for individual patients and therapy adjusted accordingly.

**How is HbA$_{1c}$ reported currently?**
Current HbA$_{1c}$ assays in the UK and other parts of the world are aligned to the assay used in the DCCT, so that an individual's risk of complications can be inferred from the result.

**What are the current targets?**
General targets for HbA$_{1c}$ of 6.5 - 7.5% should be set for an individual, taking into consideration their risk of severe hypoglycaemia, cardiovascular status and co-morbidities.

**Why Change?**
After the DCCT, a new standard specific for HbA$_{1c}$ was prepared by the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC). In future, manufacturers will supply IFCC standardised values for their calibrators as well as DCCT-aligned values. The units for reporting HbA$_{1c}$ will also be changed so that HbA$_{1c}$ reported by laboratories is traceable to the IFCC reference method. Global comparison of HbA$_{1c}$ results will therefore be possible.

**What are the new units?**
HbA$_{1c}$ results traceable to the IFCC reference method will be expressed as mmol per mol of haemoglobin without glucose attached.
How do old and new relate?
A guide to the new values expressed as mmol/mol is:

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What are the targets in new units?
The equivalent of the current DCCT HbA_1c targets of 6.5% and 7.5% are 48 mmol/mol and 59 mmol/mol in the new units, with the non-diabetic reference range of 4.0% to 6.0% being 20 mmol/mol to 42 mmol/mol.

When is the changeover to new units?
HbA_1c results expressed in the new units are obviously very different to those currently in use. From 1 June 2009, results will be provided in the UK as both IFCC-standardised units (mmol/mol) and DCCT-aligned units (%). This will give everyone time to become familiar with the new units and how they relate to DCCT numbers, and thus to the risk of complications.

From 1 June 2011, results will be reported only in the new IFCC units.

What are the limitations of HbA_1c measurement?
HbA_1c results (DCCT or IFCC) will be misleading in certain situations eg a variety of haematological conditions where there is abnormal red cell turnover, where there is an abnormal haemoglobin, and in some patients with renal or liver disease. In pregnancy, HbA_1c falls by around 0.5% due to haemodilution and other factors.

In the presence of abnormal haemoglobin, HbA_1c results can vary depending on the method used to measure HbA_1c and the particular haemoglobinopathy involved. For these reasons, such HbA_1c results should be used to detect trends in a patient’s glycaemic control rather than for target setting.

If any condition leads to a change in red cell survival, then HbA_1c measurement by any means can, at best, be used to track changes in glycaemia. Other measures of glycaemia may then be required, such as more reliance on self monitored blood glucose values or the use of a serum fructosamine assay, if available.

Why not report eAG?
Conceptually, converting the HbA_1c result to an equivalent “average glucose” level might help our understanding and interpretation of HbA_1c. A recent large study reported on how to calculate an estimated average glucose (eAG) from an HbA1c result. However, the study was carried out in a restricted population; issues have been raised about the study design; and an eAG will have limited applicability to the majority of patients who do not measure their own blood glucose levels. In some patients, the estimate may also prove inaccurate enough to be misleading. It has been agreed that in the UK, eAG results will not be reported the moment. Further research into the applicability and utility of eAG to the wide range of people with diabetes is on-going and eagerly awaited.
I haven’t had the result back….

- A doctor requests some tests
- 10 days later he has no results, so the doctor / receptionist phones the lab
  - I saw Mrs Z two weeks ago and asked for a serum rhubarb but I haven’t got the answer back yet…..
  - We look on the computer – there are records of Mrs Z but nothing for the last year
  - It’s suggested that we must have lost the sample as Mrs Z insists that she had her blood taken
- So --------
What might have happened?

• Did she really have the blood taken?
• Did she come to Southend?
  • You’d be surprised how many patients go to another hospital that’s more convenient or perceived as better
  • If she did go to another hospital your practice probably isn’t on their computer system, so you don’t get results back …. and we don’t have access to the results
  • Up to 1/200 of our requests are not from local GPs / Southend hospital!

• If we make a mistake (wrong sample collected or tests missed) we try to contact you or the patient
  • If you’re a GP in Chelmsford we may have no way of getting a report to you…..
  • If you’re a Southend GP and the patient went to Basildon you may not get a report back……..

• PLEASE ask patients not to go to other hospitals to be bled!
Patients who bring up samples

• If you ask a patient to collect a sample and bring up to the lab (e.g. urine sample)
  • PLEASE ask them to label it with their
    • Full name
    • Date of birth
    • Date and time of sample
  • Patients often leave samples with no information on the sample bottle – we can’t accept these and this inconveniences everyone!

User handbook

• There is a Pathology user handbook available on the Southend Hospital website:
  • www.southend.nhs.uk/GPs
Any questions?