RATIONAL TESTING

Investigating an incidental finding of thrombocytopenia

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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. To suggest a topic for this series, please email us at practice@bmj.com.

This article discusses the most common causes of incidental thrombocytopenia and provides advice on the relevant investigations

An asymptomatic 64 year old woman presented to her general practitioner with fatigue and weight gain. Full blood count indices were haemoglobin 125 g/L (reference range 115-165), mean cell volume 90 fL (80-99; 1fL=1 μm^3), platelets 54×10^9/L (150-400), white cell count 6.3×10^9/L (4-11), and neutrophils 4.8×10^9/L (2-7.5). A blood film confirmed the low platelet count but was otherwise normal.

What is the next investigation?

Thrombocytopenia may result from impaired production of platelets (for example, as a result of marrow dysfunction), increased destruction (immune or non-immune), abnormal distribution, or a combination thereof. Table 1 lists common causes and examples.

If isolated thrombocytopenia is picked up incidentally in an apparently asymptomatic patient with no relevant drug treatment and a normal blood film, the diagnosis is usually immune thrombocytopenia (ITP).[1 2] No accurate data on the relative frequencies of different causes of thrombocytopenia are available in the literature, although there is now an international paediatric and adult registry.[3] ITP is an acquired disorder characterised by an isolated thrombocytopenia of less than 100×10^9/L, and new evidence shows that this is the result of both increased platelet destruction and impaired production.[4] Adult chronic ITP has an incidence of about 6 per 100 000 per year in the developed world, with an equal sex ratio, although it is more common in women in the age range 30-60 years. In children the incidence has been estimated at 2-6 per 100 000 per year. It is a diagnosis of exclusion, with no specific tests that can positively diagnose it. ITP may be primary or secondary to other conditions (such as systemic lupus erythematosus, lymphoproliferative disorders, HIV, and hepatitis C). Although the evidence base to guide investigation is limited, international consensus reports on the investigation and management of primary ITP have recently been published.[1 2 5]

History and clinical examination can point to the underlying cause.

LEARNING POINTS

When thrombocytopenia is found, repeat the blood count and request a blood film. This will confirm whether thrombocytopenia is genuine and will help direct subsequent investigations

Take a careful drug history, ask about risk factors for HIV and hepatitis C, and assess for features of liver disease

If the patient is well, has no abnormal clinical findings, and has isolated thrombocytopenia with no other abnormalities on blood count or film, immune thrombocytopenia is the most likely cause

The risk of bleeding is not based on the platelet count alone; also consider age, comorbidity, mandated anticoagulation, risk of trauma, and any need for surgery

Table 1 | Common causes of thrombocytopenia

Causes	Examples
Immune defects	Primary immune thrombocytopenia (ITP) or ITP secondary to conditions such as systemic lupus erythematosus, lymphoproliferative diseases (such as chronic lymphocytic leukaemia), HIV, or hepatitis C infection
Drugs and some vaccines	Alcohol, heparin, quinine, trimethoprim, thiazides, gold, valproate, phenytoin, carbamazepine,
Any acute or chronic infection (bacterial, viral, or protozoan)	Streptococcus, tuberculosis, mycoplasma, *Helicobacter pylori*, malaria, Epstein-Barr virus, varicella zoster virus, rubella, HIV, hepatitis C
Bone marrow dysfunction	Myelodysplasia, bone marrow infiltration (including leukaemia, lymphoma, myeloma, and metastases), aplastic anaemia, myelofibrosis
Liver disease	Any cause (with or without cirrhosis and hypersplenism)
Hypersplenism	Any cause of splenomegaly
Haematinic deficiency	Vitamin B_{12} deficiency, folate deficiency
Microangiopathic haemolysis	Such as disseminated intravascular coagulopathy, thrombotic thrombocytopenic purpura, haemolytic uraemic syndrome
Pregnancy specific	Gestational thrombocytopenia, HELLP (haemolysis, elevated liver enzymes and low platelets) syndrome, disseminated intravascular coagulopathy

History

Age

Myelodysplasia is more common in older patients and an important differential diagnosis in younger patients is congenital thrombocytopenia (for example, May-Hegglin anomaly and Bernard-Soulier syndrome). Incidental thrombocytopenia is also more likely to be immune than inherited in children, and ITP is usually short lived after a viral infection, with most children recovering spontaneously. By contrast, in adults it tends to develop insidiously and follow a more chronic course.

Bruising or bleeding

If present, these symptoms suggest that the thrombocytopenia is genuine and should prompt screening for a more generalised coagulopathy. Specifically ask about epistaxis, haematuria, menorrhagia, and excessive bleeding with previous haemostatic challenges (such as surgery, dental extraction, and childbirth). A recent history (especially if previously normal counts are documented) suggests an acquired cause, whereas a lifelong history (with or without a family history) suggests a mild inherited cause.

Constitutional symptoms

Symptoms such as fevers, night sweats, and weight loss should prompt investigation for lymphoma, infection, or cancer. Patients with ITP are usually well and have no specific symptoms.

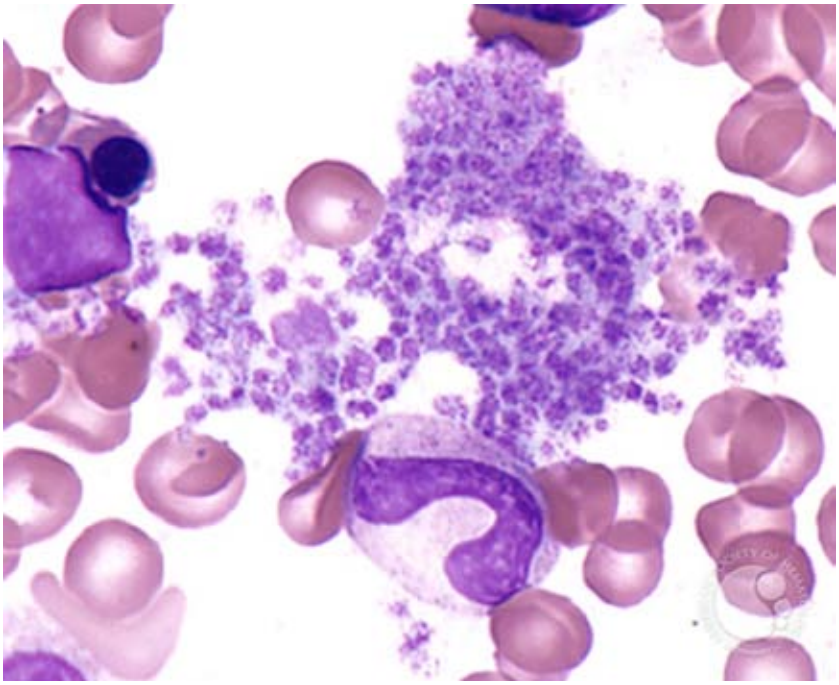
Infection and immune history

Occasionally, thrombocytopenia is the first manifestation of HIV or hepatitis C infection in an otherwise well patient, and it is important to assess risk factors and not to overlook screening.[6] *Helicobacter pylori* infection has

also been associated with ITP and should be considered in patients with dyspepsia. The response to eradication treatment is variable.[7] Other recent acute or chronic infections (viral, bacterial, or protozoan), some vaccinations (with live attenuated viruses), or a history of autoimmunity (for example, rashes or arthralgia) may also be relevant.

Drug and alcohol history

Consider all recently started drugs (prescription or non-prescription) as potential causes. Some (such as cytotoxics) result in a predictable thrombocytopenia, whereas others result in idiosyncratic thrombocytopenia. Quinine consumption (tonic water) can result in profound thrombocytopenia through an immune mediated mechanism.[8]



Blood film showing artefactual clumping of platelets

Table 2 | Suggested investigations in patients with thrombocytopenia

Investigation	Relevance
Full blood count	Previous counts and indices may be helpful
Blood film	Can confirm genuine thrombocytopenia, and other abnormalities may offer clues to cause
Liver function tests and measurement of γ-glutamyl transferase	Liver dysfunction is a common cause of low platelet numbers; γ-glutamyl transferase may be increased in alcohol excess
Renal function	Abnormalities may suggest systemic illness (such as thrombotic thrombocytopenic purpura, haemolytic uraemic syndrome, systemic lupus erythematosus
Lactate dehydrogenase	Increased in associated haemolysis (for example, disseminated intravascular coagulopathy, thrombotic thrombocytopenic purpura, autoimmune haemolysis) and some lymphoproliferative disorders
C reactive protein	If increased may suggest infection, autoimmune disease, or cancer
Immunoglobulins	Polyclonal increase often seen in HIV; paraproteins are found in some lymphoproliferative disorders; common variable immunodeficiency is associated with immune thrombocytopenia
HIV and hepatitis C serology	Check serology if risk factors for these infections are present (because thrombocytopenia may be their first presentation; some advocate checking serology regardless of risk factors) or liver function tests are abnormal
Prothrombin time/partial thromboplastin time/fibrinogen/D-dimers	Useful if the patient is unwell or a generalised coagulopathy is suspected (bruising or bleeding); abnormal in disseminated intravascular coagulopathy
Serum B_{12} and red cell folate	Macrocytosis as a result of B_{12} deficiency can be a cause of thrombocytopenia; the mean cell volume is usually but not always increased

An increasing number of patients are being discharged into the community with thromboprophylaxis. Consider heparin induced thrombocytopenia in patients recently started (<14 days) on heparin; these patients may or may not have thrombotic manifestations. Low molecular weight heparin is about 10 times less likely than unfractionated heparin to have this effect.[9] Excessive alcohol intake is a common cause of modest thrombocytopenia (often with macrocytosis), with the platelet count usually at 75-100×10^9/L.

Cancer

A history of cancer may cause thrombocytopenia by many mechanisms, including bone marrow infiltration and chronic microangiopathic haemolysis.

Pregnancy

Pregnancy broadens the differential diagnosis and should be considered in women of child bearing age. Gestational thrombocytopenia is mild (>80×10^9/L), common, occurs in the third trimester, and has no adverse clinical consequences. However, the hypertensive disorders (pre-eclampsia and HELLP (haemolysis, elevated liver enzymes, and low platelets) syndrome) may also occur in the third trimester and need urgent obstetric review. Disseminated intravascular coagulation may be precipitated by obstetric emergencies such as placental abruption, postpartum haemorrhage, amniotic fluid embolism, or sepsis. ITP may first present incidentally in pregnancy because women of this age group are commonly affected. The serious and rare associated condition, thrombotic thrombocytopenic purpura, can occur during any trimester.

Clinical examination

Clinical inspection for petechiae, bruising, mucosal bleeding, and fundal bleeding may help define the severity of thrombocytopenia and risk of bleeding.

Lymphadenopathy or hepatosplenomegaly should prompt concern about lymphoproliferative disease, autoimmune disease, cancer, or infection.

Features of chronic liver disease are relevant. Even in the absence of hypersplenism, liver disease can cause thrombocytopenia by many mechanisms, including impaired production of thrombopoietin.[10]

Investigations in primary care

When a low platelet count is picked up incidentally, the full blood count must be repeated and a blood smear performed. Comparison with previous results may show changes over time. Timing, degree of thrombocytopenia, clinical context, and the presence or absence of bleeding will help direct investigations and the need for referral.[11]

In all patients, a blood film is important to confirm whether thrombocytopenia is genuine or factitious (platelet clumping owing to EDTA antibodies or giant platelets failing to be counted by automated analysers; figure). In the presence of platelet clumping, the full blood count will be more accurate if performed on a citrated sample. In ITP, red and white cells have normal morphology and platelets may be large but otherwise normal. Other abnormalities in the film may offer clues to the underlying cause of throm-

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- Interpreting arterial blood gas results (*BMJ* 2013;346:f16)
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- Investigating asthma symptoms in primary care (*BMJ* 2012;344:e2734)
- Interpreting and investigating proteinuria (*BMJ* 2012;344:e2339)

bocytopenia. Features of other conditions include dysplastic changes (in myelodysplasia), abnormal circulating cells (such as leukaemic blasts), and red cell fragments (suggesting microangiopathic haemolysis in cancer, disseminated intravascular coagulopathy, or thrombotic thrombocytopenic purpura). Red cell fragments and a raised lactate dehydrogenase should prompt urgent referral to haematology to exclude the potentially fatal diagnosis of thrombotic thrombocytopenic purpura, which requires prompt plasmapheresis. The other classic features of thrombotic thrombocytopenic purpura (neurological symptoms, fever, and renal dysfunction) are not always present.[12] Table 2 lists other suggested investigations.

When to refer?

Patients with modest isolated thrombocytopenia (platelet count 100-150×10^9/L) without atypical features (such as lymphadenopathy or fever) do not require referral to hospital, particularly if the counts are stable. It is prudent to occasionally recheck the full blood count in primary care to ensure that counts do not deteriorate or another condition become evident. For example, rarely, isolated thrombocytopenia with no circulating blasts in the peripheral blood is the initial presentation of acute leukaemia. If the results of the full blood count are unchanged when repeated six weeks later, it is usually safe to extend the follow-up interval to several months. Patients must be aware that they should re-present if new symptoms such as bruising or bleeding occur.

Indications for urgent referral include severe thrombocytopenia (<20×10^9/L), severe bleeding, and red cell fragments or blasts on the blood film. Referral is also warranted if the patient has constitutional symptoms, bruising, minor bleeding, or abnormalities on examination (such as lymph nodes or splenomegaly) or the blood film (such as dysplastic changes). Referral to or discussion with a haematologist is reasonable if the platelet count is less than 100×10^9/L or the patient also has anaemia, neutropenia, or other changes in the blood count, such as macrocytosis. Many such situations can be discussed on an advisory basis without formal review in a hospital clinic.

Consensus guidelines recommend bone marrow examination (after referral) in patients over 60 years of age (mainly to exclude dysplasia) and in those with systemic symptoms or signs suggestive of haematological cancer.[1 2]

Outcome

After referral to haematology and a period of careful observation, the patient's platelet count dropped further (<30×10^9/L). Subsequent investigations included a bone marrow examination, which confirmed the presence of megakaryocytes with no abnormal features, therefore supporting the diagnosis of ITP.

The decision to start treatment should balance the individual patient's bleeding risk against the side effects of treatment. Bleeding risk is influenced not only by platelet count, but also by age and comorbidity, such as liver or renal dysfunction. Platelet counts greater than 30×10^9/L rarely require treatment in the absence of bleeding, trauma, surgery, or mandated anticoagulation.[1 2] If the platelet count is less than 50×10^9/L, avoid antiplatelet agents such as aspirin and non-steroidal anti-inflammatory drugs if possible.

If the decision is to treat (as in this case), the mainstay of treatment for ITP is immunosuppressive therapy, usually starting with corticosteroids.[1 2 13] Tranexamic acid can be useful for the management of mucosal bleeding but must be avoided if haematuria is present because of the risk of clot retention.

Our patient initially responded well to steroid treatment but repeatedly relapsed on steroid withdrawal. Second line treatment options include rituximab, which has good evidence of efficacy although it is not licensed for this condition,[14] or laparoscopic splenectomy for long term remission. Other agents with good quality data on effectiveness from randomised controlled trials include the thrombopoietin receptor agonists, romiplostim or eltrombopag, although cost is a problem.[15 16] Romiplostim is now approved by NICE for patients with ITP that is severely symptomatic and refractory to standard treatment.

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

1 Neunert C, Lim W, Crowther M, Cohen A, Solberg L Jr, Crowther MA; American Society of Hematology. The American Society of Hematology 2011 evidence-based practice guideline for immune thrombocytopenia. *Blood* 2011;117:4190-207.
2 Provan D, Stasi R, Newland AC, Blanchette VS, Bolton-Maggs P, Bussel JB, et al. International consensus report on the investigation and management of primary immune thrombocytopenia. *Blood* 2010;115:168-86.
3 Kühne T, Berchtold W, Michaels LA, Wu R, Donato H, Espina B, et al; on behalf of the Intercontinental Cooperative ITP Study Group. Newly diagnosed immune thrombocytopenia in children and adults: a comparative prospective observational registry of the Intercontinental Cooperative Immune Thrombocytopenia Study Group. *Haematologica* 2011;96:1831-7.
4 Bromberg ME. Immune thrombocytopenic purpura—the changing therapeutic landscape. *N Engl J Med* 2006;355:1643-5.
5 Rodeghiero F, Stasi R, Gernsheimer T, Michel M, Provan D, Arnold DM, et al. Standardisation of terminology, definitions and outcome criteria in immune thrombocytopenic purpura of adults and children: report from an international working group. *Blood* 2009;113:2386-93.
6 Liebman HA. Viral-associated immune thrombocytopenic purpura. *ASH Education Book* 2008;1:212-8.
7 Howard A, Liebman HA, Stasi R, Provan D. Helicobacter pylori and chronic ITP. *ASH Education Book* 2008;1:206-11.
8 Quinine induced thrombocytopenia. *Medicines safety update* 2010, Vol 2, No 4.
9 Martel N, Lee J, Wells PS. Risk for heparin-induced thrombocytopenia with unfractionated and low-molecular-weight heparin thromboprophylaxis: a meta-analysis. *Blood* 2005;106:2710-5.
10 Pradella P, Bonetto S, Turchetto S, Uxa L, Comar C, Zorat F, et al. Platelet production and destruction in liver cirrhosis. *Hepatology* 2011;54:894-900.
11 Arnold DM, Lim W. A rational approach to the diagnosis and management of thrombocytopenia in the hospitalized patient. *Semin Hematol* 2011;48:251-8.
12 Scully M, Hunt B, Benjamin S, Liesner R, Rose P. Guidelines on the diagnosis and management of thrombotic thrombocytopenic purpura and other thrombotic microangiopathies. *Br J Haematol* 2012;158:323-35.
13 Godeau B, Chevret S, Varet B, Lefrère F, Zini JM, Bassompierre F, et al. Intravenous immunoglobulin or high dose methylprednisolone, with or without oral prednisone, for adults with untreated severe autoimmune thrombocytopenic purpura: a randomised, multicentre trial. *Lancet* 2002;359:23-9.
14 Auger S, Duny Y, Rossi JF, Quittet P. Rituximab before splenectomy in adults with primary idiopathic thrombocytopenic purpura: a meta-analysis. *Br J Haematol* 2012;158:386-98.
15 Kuter DJ, Rummel M, Boccia R, Macik BG, Pabinger I, Selleslag D, et al. Romiplostim or standard of care in patients with immune thrombocytopenia. *N Engl J Med* 2010;363:1889-99.
16 Cheng G, Saleh MN, Marcher C, Vasey S, Mayer B, Aivado M, et al. Eltrombopag for management of chronic immune thrombocytopenia (RAISE): a 6-month, randomised, phase 3 study. *Lancet* 2011;377:393-402.

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UNCERTAINTIES

Should inpatient hyperglycaemia be treated?

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This is one of a series of occasional articles that highlight areas of practice where management lacks convincing supporting evidence. The series adviser is David Tovey, editor in chief, the *Cochrane Library*. To suggest a topic for this series, please email us at uncertainties@bmj.com.

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- Does routine oxygen supplementation in patients with acute stroke improve outcome? (*BMJ* 2012; 345:e6976)
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- Should selective digestive decontamination be used in critically ill patients? (*BMJ* 2012;345:e6697)
- What factors influence prognosis in children with acute cough and respiratory tract infection in primary care? (*BMJ* 2012;345:e6212)

Two large scale randomised controlled trials in the 1990s were the first such trials to show that the control of blood glucose helped to prevent long term complications in people with types 1 and 2 diabetes.[1 2] Glucose concentrations can rise not only in people with pre-existing diabetes, but also, for short periods, in people without the condition—in particular, during times of acute illness, when it is called stress hyperglycaemia.[3] As discussed below, data show that raised blood glucose concentrations in people with and without a previous diagnosis of diabetes are associated with short term harm. However, whereas the benefits of good glycaemic control over a long period in people with diabetes are well established, uncertainty remains about whether treating transient hyperglycaemia, in particular in hospital inpatients, makes any difference to short term outcomes.

Sometimes the question is moot and treating hyperglycaemia is crucial—for example, in diabetic ketoacidosis or hyperosmolar hyperglycaemic states[4] or in patients who are symptomatic from their hyperglycaemia. This article does not discuss these states.

What is the evidence of the uncertainty?

I searched PubMed, the Cochrane Library, and Clinical Evidence to identify publications that concerned the outcomes of hyperglycaemia in hospital inpatients and those that dealt with treating the hyperglycaemia. Since the two trials in the 1990s,[1 2] other studies have also shown that hyperglycaemia in inpatients with and without pre-existing diabetes is associated with poor outcomes. However, most trials were observational, with only a few randomised controlled trials. A meta-analysis of 34 randomised control trials assessing perioperative insulin infusion in 2192 surgical patients concluded that "perioperative insulin infusion may reduce mortality but increases hypoglycaemia in patients who are undergoing surgery."[5] However, only 14 of these studies included patients with diabetes, with 13 studies excluding them and the rest not reporting whether patients with diabetes were included.

Observational data from an unselected cohort of over 1500 acute general medical admissions with and without diabetes showed that length of stay, readmission rates, and 30 day mortality rates rose with higher blood glucose concentrations.[6] Other observational evidence from hospital episode statistics based on discharge coding of over four million patients showed that those who also had diabetes stayed in hospital the longest, regardless of the specialty.[7] There is also a wealth of observational data to show that elective or emergency surgical patients with or without pre-existing diabetes also have poorer outcomes when they have high preoperative glycated haemoglobin concentrations (reflecting poor preadmission glycaemic control) or high perioperative blood glucose concentrations.[8 9]

People with stress hyperglycaemia may be at risk of developing type 2 diabetes in the long term. However, evidence from intervention studies is sparse or conflicting on whether aggressive treatment of the hyperglycaemia during a patient's hospital stay makes a difference to short or long term outcomes or even affects outcomes related to their cause for admission. Indeed, data from well conducted large randomised controlled trials and observational studies show that the use of glucose lowering agents—in particular, insulin—are associated with increased levels of harm, in the form of severe hypoglycaemia.[10 11]

A few randomised controlled trials show that short term, tight glycaemic control using insulin therapy in intensive care seemed to reduce mortality, infection rate, and length of hospital stay.[12 13] Other well conducted randomised controlled trials in intensive care patients have been either equivocal[14 15] or associated with harm, with the largest such study of over 6000 patients showing that tight glycaemic control was associated with higher incidence of severe hypoglycaemia and increased mortality.[16] Randomised controlled trials have shown that short term tight glycaemic control can also help patients who have cardiac surgery—benefits included fewer sternal wound infections.[5] However, patients in intensive care or having cardiac surgery are a minority. Furthermore, the data from randomised controlled trials for patients presenting with acute coronary syndromes remain conflicting,[17 18] although this is probably because of poor study design and recruitment. The data for acute coronary syndrome seem so contradictory that the American Heart Association avoided the topic of hyperglycaemia in its 2008 position paper on the management of acute coronary syndrome, despite a substantial proportion of patients presenting with concurrent hyperglycaemia, and hyperglycaemia being associated with poor outcomes.[19]

There are good theoretical reasons why glucose reduction with insulin should be beneficial, with reductions in endothelial dysfunction, immune dysfunction, and the maintenance of adequate vasodilatation.[20] But insulin use in any patient with hyperglycaemia is fraught with problems and is often used incorrectly or ineffectively—the use of subcutaneous "sliding scales" being one such problem.[21] Precipitating severe hypoglycaemia by aggressive glucose lowering with insulin is a major concern, as is the lack of confidence among junior doctors in managing the condition.[22] However, recently published documents and education packages (available at www.diabetes.nhs.uk/safety) have sought to reduce these errors.[23] Uncertainty also remains about the glucose targets that should be aimed for and the best agents to achieve these.

The data presented show that high glucose concentration in people with and without diabetes is associated with poor outcomes. However, as I found no directly relevant systematic reviews it remains to be determined if the raised blood glucose is the cause of the poor outcomes or if it is just an epiphenomenon.

RECOMMENDATION FOR FURTHER RESEARCH

Population

All adult hospital inpatients, including elective and emergency patients, from all medical and surgical specialties, and with or without a previous diagnosis of diabetes

Intervention and comparisons

Initial phase: observational data to assess the relation between blood glucose and glycated haemoglobin concentrations on admission, and outcomes

Next phase: randomised controlled trials to compare good glycaemic control (such as target blood glucose concentrations of 4-12 mmol/L) with usual standard of care, taking into account multiple confounders in these groups, such as age, comorbidities, pre-existing diabetes, medication use

Outcomes

To include in-hospital mortality, 30 day mortality, length of stay, 30 day hospital readmission rates, and postoperative complication rates for surgical patients. Other outcomes would depend on the specialty.

Is ongoing research likely to provide relevant evidence?

Large, well conducted randomised controlled trials are needed in several patient populations to establish whether glycaemic control reduces or prevents the harms associated with hyperglycaemia.

All of the factors discussed here mean that very large numbers of patients would be needed over many sites for a long time. A search on www.clinicaltrials.gov shows that several studies of glycaemic control in hospital inpatients are ongoing, but most are studying small numbers of patients in specialised populations. Although these smaller scale studies help greatly, it is important that the methods used in these smaller studies are adequate to allow rigorous and meaningful meta-analyses to be conducted to help resolve the uncertainties raised in this article. Definitive, large studies are likely to be very expensive, and therefore in the current economic environment are unlikely to be conducted in the size needed to answer such questions.

What should we do in light of the uncertainty?

Given the data showing that hyperglycaemia in hospital inpatients is detrimental, all adult patients with or without a pre-existing diagnosis of diabetes should have their blood glucose measured on admission. If they are found to be hyperglycaemic then efforts should be made to control their glucose concentrations on the basis of pragmatic consensus documents drawing largely on the best available observational data previously described. For example, the guidelines commissioned by England's NHS Diabetes on the perioperative management of patients with diabetes having surgery recommend that for inpatients needing a prolonged starvation time (that is, more than one missed meal) a variable rate intravenous insulin infusion should be used, with the aim of keeping their blood glucose concentrations ideally between 6 mmol/L and 10 mmol/L (with a range of 4 mmol/L to 12 mmol/L being considered "acceptable").[24] For those whose diabetes status is not known, no accepted guidelines exist; however, the recommendation is to have the same glycaemic targets as for people with diabetes.[3]

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1 Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med* 1993;329:977-86.
2 UK Prospective Diabetes Study Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* 1998;352:837-53.
3 Dungan KM, Braithwaite SS, Preiser J-C. Stress hyperglycaemia. *Lancet* 2009;373:1798-807.
4 Joint British Diabetes Societies Inpatient Care Group. The management of the hyperosmolar hyperglycaemic state (HHS) in adults with diabetes. 2012 www.diabetes.nhs.uk/document.php?o=3778.
5 Gandhi GY, Murad HM, Lynn DN, Erwin PJ, Cavalcante AB, Nielsen HB, et al. Effect of perioperative insulin infusion on surgical morbidity and mortality: systematic review and meta-analysis of randomized trials. *Mayo Clin Proc* 2008;83:418-30.
6 Evans NR, Dhatariya KK. Assessing the relationship between admission glucose levels, subsequent length of hospital stay, readmission and mortality. *Clin Med* 2012;12:137-9.
7 Sampson MJ, Dozio N, Ferguson B, Dhatariya K. Total and excess bed occupancy by age, speciality and insulin use for nearly one million diabetes patients discharged from all English acute hospitals. *Diabetes Res Clin Pract* 2007;77(1):92-8.
8 Walid MS, Newman BF, Yelverton JC, Nutter JP, Ajjan M, Robinson JS. Prevalence of previously unknown elevation of glycosylated hemoglobin in spine surgery patients and impact on length of stay and total cost. *J Hosp Med* 2010;5(1):E10-4.
9 Frisch A, Chandra P, Smiley D, Peng L, Rizzo M, Gatcliffe C, et al. Prevalence and clinical outcome of hyperglycemia in the perioperative period in noncardiac surgery. *Diabetes Care* 2010;33:1783-8.
10 NHS Information Centre. National Diabetes Inpatient Audit. 2012. www.ic.nhs.uk/diabetesinpatientaudit.
11 NICE-SUGAR Study Investigators. Hypoglycemia and risk of death in critically ill patients. *N Engl J Med* 2012;367:1108-18.
12 Van den Berghe G, Wouters P, Weekers F, Verwaest C, Bruyninckx F, Schetz M, et al. Intensive insulin therapy in the surgical intensive care unit. *N Engl J Med* 2001;345:1359-67.
13 Van den Berghe G, Wilmer A, Hermans G, Meersseman W, Wouters PJ, Milants I, et al. Intensive insulin therapy in the medical ICU. *N Engl J Med* 2006;354:449-61.
14 Brunkhorst FM, Engel C, Bloos F, Meier-Hellmann A, Ragaller M, Weiler N, et al. Intensive insulin therapy and pentastarch resuscitation in severe sepsis. *N Engl J Med* 2008;358:125-39.
15 Preiser J-C, Devos P, Ruiz-Santana S, Melot C, Annane D, Groeneveld J, et al. A prospective randomised multi-centre controlled trial on tight glucose control by intensive insulin therapy in adult intensive care units: the Glucontrol study. *Intensive Care Med* 2009;35:1738-48.
16 NICE-SUGAR Study Investigators. Intensive versus conventional glucose control in critically ill patients. *N Engl J Med* 2009;360:1283-97.
17 Malmberg K, Ryden L, Efendic S, Herlitz J, Nicol P, Waldenstrom A, et al. Randomized trial of insulin-glucose infusion followed by subcutaneous insulin treatment in diabetic patients with acute myocardial infarction (DIGAMI study): effects on mortality at 1 year. *J Am Coll Cardiol* 1995;26(1):57-65.
18 Malmberg K, Ryden L, Wedel H, Birkeland K, Bootsma A, Dickstein K, et al. Intense metabolic control by means of insulin in patients with diabetes mellitus and acute myocardial infarction (DIGAMI 2): effects on mortality and morbidity. *Eur Heart J* 2005;26:650-61.
19 Antman EM, Hand M, Armstrong PW, Bates ER, Green LA, Halasyamani LK, et al. 2007 focused update of the ACC/AHA 2004 guidelines for the management of patients with ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines: developed in collaboration with the Canadian Cardiovascular Society endorsed by the American Academy of Family Physicians: 2007 writing group to review new evidence and update the ACC/AHA 2004 guidelines for the management of patients with ST-elevation myocardial infarction, writing on behalf of the 2004 writing committee. *Circulation* 2008;117:296-329.
20 Chaudhuri A, Dandona P, Fonseca V. Cardiovascular benefits of exogenous insulin. *J Clin Endocrinol Metab* 2012;97:3079-91.
21 Hirsch IB. Sliding scale insulin—time to stop sliding. *JAMA* 2009;301:213-4.
22 George JT, Warriner D, McGrane DJ, Rozario KS, Price HC, Wilmot EG, et al. Lack of confidence among trainee doctors in the management of diabetes: the Trainees Own Perception of Delivery of Care (TOPDOC) Diabetes Study. *QJM* 2011;104:761-6.
23 Fowler D, Rayman G, NHS Diabetes. Safe and effective use of insulin in hospitalised patients. 2010. www.diabetes.nhs.uk/our_publications/reports_and_guidance/inpatient_and_emergency/.
24 Dhatariya K, Flanagan D, Hilton L, Kilvert A, Levy N, Rayman G, et al. Management of adults with diabetes undergoing surgery and elective procedures: improving standards. 2011. www.diabetes.nhs.uk/our_publications/reports_and_guidance/inpatient_and_emergency/.

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