PRACTICE

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.

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

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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.

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]

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.

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.

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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