Diabetic ketoacidosis at the onset of type 1 diabetes

Is still common, despite the consistency of predictive factors worldwide

DR P MARAZZI/SPL

RESEARCH, p 137

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Despite major advances in the care of diabetes, diabetic ketoacidosis remains a leading cause of morbidity, mortality, and hospital admission in children and adolescents with type 1 diabetes.[1] Deaths are mainly caused by cerebral oedema, which is more common in patients who are younger, have new onset diabetes, or have a longer duration of symptoms.[1 2] Other possible causes of morbidity and mortality associated with diabetic ketoacidosis include hypokalaemia, pulmonary oedema, cerebral thrombosis or infarction, and rhabdomyolysis.[1-3] Given these life threatening complications and the healthcare costs associated with hospital admission, prevention of diabetic ketoacidosis should be the primary goal for clinicians.

In the linked systematic review, Usher-Smith and colleagues looked at 46 studies of more than 24 000 children from 31 countries to identify factors associated with the presence of diabetic ketoacidosis at diagnosis of diabetes in children and adolescents.[4] The studies span the late 1980s to 2008. The authors report a high prevalence of diabetic ketoacidosis—between 21.6% and 53.8% in Europe and North America, and 68.2% in Saudi Arabia—similar to that seen in the mid-1990s.[1] In some countries, such as the United Kingdom, the prevalence of diabetic ketoacidosis remained the same—at 27%—before (1985-96) and after (2004-7) the turn of the 21st century.[4] In a study from Germany and Austria, the prevalence of ketoacidosis at the onset of diabetes also stayed the same throughout the 13 year study period (1995 to 2007).[5] This is surprising because, with the rising incidence of type 1 diabetes (mean increase of 3-5% a year), especially in young children,[6] greater awareness of the disease should have resulted in a decrease in the prevalence of ketoacidosis at the onset of diabetes.

The review also shows similarities in predictors of diabetic ketoacidosis across nations and cultures: younger age, misdiagnosis, delayed diagnosis, certain minority ethnic groups, and lack of health insurance were consistently associated with diabetic ketoacidosis. Protective factors that decreased the risk of diabetic ketoacidosis include having a first degree relative with type 1 diabetes, higher parental education, and higher background incidence of type 1 diabetes, all of which are explained by education, recognition, or having experience with diabetes.

Improvements in public and professional awareness of risk factors for and symptoms of diabetes could help prevent diabetic ketoacidosis. This is achievable, as shown by the community and physician awareness campaign in Italy, which reduced the rates of diabetic ketoacidosis from 78% to almost zero two years after the campaign began,[7] and remained effective eight years later.[8]

The findings from this study should heighten the awareness of clinicians caring for children and adolescents. Continuing education should be provided on the presentation of diabetes. Questions about polyuria and enuresis should always be part of the review of systems during history taking in visits to primary care. Dipstick testing of urine for glucose and ketones should be done routinely in any sick child, especially those under 6 years, whether or not the cause of sickness is known. Blood ketones can be measured at the point of care in clinics or urgent care settings to detect ketonaemia when patients cannot provide urine specimens. To increase public awareness, information about diabetes in children should be given to teachers and to the public, possibly using poster displays at schools and paediatricians' offices, as was done in the Italian campaign,[7] or electronically through social media networks.

Other benefits of avoiding ketoacidosis at diagnosis should be emphasised to reinforce preventive efforts. Compared with children with ketoacidosis at diagnosis, those without it have significantly better residual β cell function, which results in better glycaemic control and a higher rate of partial remission.[9-11] Several studies have reported an association between more severe ketoacidosis at diagnosis, greater loss of β cell function, and younger age at diagnosis.[9 11] Delayed diagnosis or difficulty in recognising diabetes in this age group therefore is not the only challenge—it also seems that a more aggressive form of the disease occurs in younger children, whereby rapid β cell destruction speeds up the progression to diabetic ketoacidosis. The higher titres of insulin autoantibodies and islet cell antibodies seen in younger children support the concept of a more aggressive form of diabetes.[11 12] These differences in pathogenesis of type 1 diabetes in different age groups warrant future study and may provide insights on age specific interventions to decrease the prevalence of ketoacidosis at diagnosis and to preserve residual β cell function.

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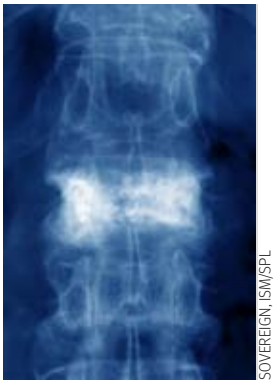
Vertebroplasty for vertebral fracture

On the basis of current evidence, cannot be recommended as the first line treatment



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In the linked meta-analysis of individual patient data, Staples and colleagues assess whether vertebroplasty for vertebral fracture is more effective than placebo in certain subgroups of people.[1]

Insufficiency fractures of the vertebra are a major cause of morbidity and are estimated to affect about one in four adults over the age of 50 years. Risk factors include age, low body mass index, smoking, alcohol misuse, family history, use of corticosteroids, and chronic illness. Although these associations may be used to predict the incidence of disease,[2] this remains a substantial problem in later life, and preventive treatment has yet to reduce the incidence.

Medical interventions, such as lifestyle changes, hormone replacement, and bisphosphonates, have been used to treat vertebral fractures. However, it is unclear how best to manage the fracture, to alleviate pain, and to reduce long term disability. Since the original description of vertebroplasty in 1987,[3] percutaneous cement augmentation has been widely advocated for pain management. Such procedures are normally performed on a day case basis and are undertaken using heavy sedation with fluoroscopy to guide an injection of cement into the fractured vertebra.

Many large unblinded trials have shown that cement augmentation results in a 70-90% improvement in symptoms within a few weeks.[4 5] However, imaging of acute fractures often shows multiple healed injuries even though patients have no recollection of the event, so spontaneous resolution must be common. Current guidance from the National Institute for Health and Clinical Excellence is that all patients with a symptomatic vertebral fracture confirmed by imaging should be treated conservatively for at least four weeks before considering spine augmentation.[6]

The first two randomised controlled trials comparing vertebroplasty with a control procedure were published in 2009.[7 8] The studies found startlingly similar results, with almost identical improvement in symptoms in patients treated by percutaneous augmentation of spinal fractures and those in whom local anaesthetic was infiltrated into the region of the fracture. The findings raised concerns among clinicians and patients that vertebroplasty is ineffective, although it has perhaps been overlooked that both studies gave over 85% recovery in a group of patients who had been in pain for many months. Some professional groups, such as the American Academy of Orthopaedic Surgeons, have recommended against vertebroplasty as a primary treatment for insufficiency fracture due to osteoporosis, whereas others have considered restricting spinal augmentation to subsets of patients, such as those who do not respond to anaesthetic injection. There is vigorous debate in the UK and Europe with no current consensus.

Given that many studies have shown lower success rates with simple conservative management than with vertebroplasty, something must have worked, the question is how? There are three possible reasons that the two trials found no benefit of vertebroplasty over the control procedure. Firstly, there may have been a high placebo response to any interventional procedure. Secondly, patients may have spontaneously recovered in both groups. Thirdly, the pain may have had more than one cause, one of which responded to the control intervention and the other to vertebroplasty.

The randomised controlled trials have been criticised for potential flaws, including the possibility that the patients were unblinded to the intervention, but this has been refuted by review of the data.[9] The authors of one of the trials also considered the possibility that the local anaesthetic injection was therapeutic, and in 19 patients they injected local anaesthetic at the site of the fracture before considering cement augmentation; they found little benefit.[10] They also suggest that vertebroplasty is essentially a potent placebo.[11] However, a recent prospective audit reviewed patients who were first treated by injecting local anaesthetic and steroid in the paraspinal region at the level of pain, sometimes two or three segments below the fracture.[12] About 34% of patients had immediate pain relief, which lasted at least two months. Therefore in a subgroup of about a third of patients, pain may come from other spinal structures as a result of loss of sagittal balance—the consequence of spinal deformity secondary to the fracture—rather than from motion at unhealed fractures. The patients who failed to respond were treated with cement augmentation, with success in 23 of 24 cases (94%), which suggests a role for vertebroplasty when other causes of pain are excluded. These findings may explain the difference in results between the two randomised studies and what is seen in clinical practice.

An alternative explanation for the findings of the randomised trials is that the different durations or severity of the pain might result in a different response to treatment. Staples and colleagues' meta-analysis of data from both papers analyses subgroups of patients to see whether the results would have been different if the selection criteria were more rigorous. Their analysis suggests that this is not the case and that the results stand.

Given that the prospective audit found that facet infiltration with cement augmentation in selected cases can relieve symptoms in more than 90% of cases [12] it would be hard to argue that we should revert to the old treatment of long term opiate analgesia with its associated morbidity in this age group. Should cement augmentation be abandoned or perhaps confined to subgroups of patients? [9]

What should clinicians do in the light of current evidence? It is sensible to use safer and less invasive techniques initially—infiltration of local anaesthetic, and perhaps steroids in the region of the pain, may alleviate symptoms sufficiently in a third of patients to break the pain cycle or potentially cover the period before spontaneous recovery. Cement augmentation may have a role in those who fail to respond.

Currently, there is probably insufficient evidence to reach a firm conclusion. A study to repeat the randomised trials using a more tightly controlled patient selection is under way. It may also be prudent to investigate further the mechanism of pain in vertebral fractures because it is likely to be multifactorial.

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Safety of adjuvanted pandemic influenza A (H1N1) 2009 vaccines

Risk of Guillain-Barré syndrome, if any, is smaller than for 1976 swine flu vaccines

RESEARCH, p 141

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Guillain-Barré syndrome has been a focus of safety monitoring since the report in 1976 of an increased risk of almost one extra case per 100 000 influenza vaccinations of swine origin.[1] Subsequent studies have shown either no increased risk or a slightly increased risk (1-2 per million vaccinees) after vaccination for seasonal flu.[2] The spread of the 2009 pandemic influenza A (H1N1) virus, which contained genes of swine origin, resulted in the development and widespread use of influenza A (H1N1) monovalent vaccines (2009 H1N1 vaccines).[3] These included formulations containing oil in water adjuvants that had not previously been widely used in flu vaccines in Europe. Although available evidence suggested that the adjuvanted vaccines had acceptable safety profiles,[3] data on the risk of rare adverse events, such as Guillain-Barré syndrome, were limited.

In the linked study, Dieleman and colleagues report the first data on adjuvanted 2009 H1N1 vaccines and the risk of Guillain-Barré syndrome from a case-control study conducted in five European countries.[4] Overall, the results suggest that if there was an increased risk associated with the adjuvanted 2009 H1N1 vaccines studied, it was considerably smaller than that seen with the 1976 swine flu vaccines. Whether there was an increased risk, however, is not clear.

Although the study used a common protocol and data collection instruments, countries differed substantially in case ascertainment, subject enrollment, and sources of data on vaccinations and other potential risk factors, as well as specific vaccine brands. The results varied considerably by country—the unadjusted odds ratios from four countries ranged from 1.3 to 9.5 (data from one country were limited and not included in the analysis).

Adjustment for influenza-like illness or upper respiratory tract infection strongly influenced the results, although these data were available for only three of the countries. Adjustment for both of these respiratory illnesses decreased all the odds ratios (range 1.1-1.8) and all 95% confidence intervals overlapped 1.0 in the individual country analyses, as well as the pooled analyses. Further adjustment for receipt of seasonal flu vaccine either did not change or further decreased (to less than 1.0 in some analyses) the odds ratio estimates. In sub-analyses restricted to people without preceding respiratory illnesses the unadjusted odds ratios were between 1.9 and 2.5 (with 95% confidence intervals that overlapped 1.0) but decreased to 1.2 after adjustment for preceding seasonal flu vaccination.

Although respiratory (and other) infections have often been associated with Guillain-Barré syndrome, respiratory

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illnesses have not previously been identified as strong confounding factors for the association between seasonal flu vaccines and the syndrome. Perhaps confounding by these respiratory illnesses was more apparent for the 2009 H1N1 vaccines in Dieleman and colleagues' study because vaccination occurred concurrently with circulation of pandemic H1N1 virus, whereas in typical flu seasons vaccination occurs before widespread circulation of the virus. The study also had some puzzling findings on seasonal flu vaccine. In the data from the United Kingdom, the 2009-10 seasonal flu vaccine (unadjuvanted) was associated with an increased risk of Guillain-Barré syndrome. This is surprising given that a previous analysis using the same UK database found no evidence of an increased risk associated with seasonal flu vaccines administered from 1990 to 2005.[5]

The finding that adjuvanted 2009 H1N1 vaccines were not associated with a substantially increased risk of Guillain-Barré syndrome is consistent with the results published to date on unadjuvanted 2009 H1N1 vaccines. These include studies from spontaneous reporting systems in the United States and China,[6 7] in which reported rates of the syndrome after receipt of unadjuvanted H1N1 vaccines were lower than the expected background rates. Although spontaneous reporting systems are subject to under-reporting, these results suggest that there was not a large increased risk of the syndrome. A large epidemiological study of unadjuvanted H1N1 vaccine in the US found a small increased risk of less than one excess case per million vaccinations, although respiratory illnesses were not controlled for.[8] Other studies of H1N1 vaccines and risk of the syndrome have been conducted in the US and internationally,[4 9] but their results have not yet been published.

Although pandemic influenza A (H1N1) 2009 monovalent vaccines are no longer being used, data on their safety are relevant to current clinical practice because the H1N1 strain in the pandemic vaccine has been incorporated into the currently recommended trivalent seasonal vaccine. Most of the trivalent seasonal flu vaccines currently used in Europe do not contain an adjuvant, and no adjuvanted flu vaccines are used in the US. Nonetheless, the safety findings on adjuvanted flu vaccines will be important if such vaccines become more common in the future, whether in seasonal flu vaccines or for the next pandemic.

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How to improve surgical research

A change in attitudes, training, and infrastructure, and much lobbying, are needed

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On 15 June the Royal College of Surgeons published its report *From Theory to Theatre: Overcoming Barriers to Innovation in Surgery*,[1] which outlined the problems that surgical research faces and how they might be solved. Surgery has advanced spectacularly in the past 50 years, but many advances have not come from carefully planned research using valid study designs. Consequently, neither the public nor the surgical community seems convinced that we need scientific research into surgery, as opposed to research into diseases that surgeons can treat. That this perception is dangerously wrong is one of the key messages of the college's report.

The report highlights past surgical achievements to a degree that might lead the naive observer to ask why—if surgeons are doing so well—they need to change anything. However, it also cites the decline of academic surgery in universities, the disappearance of meaningful contact with research from surgical training programmes, and the enormous practical difficulties caused by past failure to build a robust research infrastructure or an intellectual support network within surgery. The most telling fact in the document is that although the Medical Research Council and National Institute for Health Research spent £1.53bn (€1.71bn; $2.45bn) in 2008-9 on research, only £25.5m went to surgical research. This is not a uniquely British problem—figures on National Institutes of Health support in the United States are only slightly better[2]—but it is shocking considering the contribution of surgery to effective treatment.

The report is honest about how the social culture of surgeons has contributed to this failure. Their implicit model of professionalism makes surgeons reluctant to randomise or to cooperate in large groups—a toxic mix of attitudes that has proved near lethal in a modern research world where single pioneers can rarely hope to succeed. A substantial part of the report deals with the difficulties of implementation once a new technique is shown to be superior, although this is really a distinct (and equally important)

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problem that needs its own strategy. Setting it to one side might have allowed more in depth consideration of the problems of supporting research itself. The authors identify the lack of incentives and of training opportunities as two of the main reasons for such failures of dissemination. It is always easier to describe problems than to solve them, and current financial difficulties exacerbate this problem by inhibiting ideas that require new funding. Nevertheless, some of the authors' recommendations will inevitably cost money. They will also require several disparate stakeholders to be convinced by the college's message. Eight of the 15 recommendations require action by the Department of Health or by NHS senior management via the commissioning and regulatory infrastructures, whereas four will need movement from the Postgraduate Medical Education and Training Board and perhaps the General Medical Council. Getting major research funders to treat surgical research as a special case (recommendation 9) may well be the hardest trick, but one of the most important. The report recognises that many of the crucial levers for helping surgical research are to do with changing the environment within which it exists. There are excellent suggestions about possible incentives for surgeons and trusts. For example, appropriate recognition of research activity by schools of surgery, consultant appointment panels, and clinical excellence award boards would improve motivation within the profession, while the commissioning apparatus could reward trusts that support research via the commissioning for quality and innovation framework and through more rigorous requirements around audit.

The need to reintroduce research methodology to specialist training programmes is recognised, and, importantly, the report identifies a key structural barrier to the adoption of new techniques by calling for specific financial support mechanisms for mentoring and training consultants who wish to start using them. The NHS has never recognised the need for this, but in an increasingly risk averse environment it has become a major problem for surgeons who wish to develop their practice.

Much lobbying will be needed if the report is to achieve its aims. The problems may need to be outlined in starker terms to convince some key players of the need for action, and a compelling vision of the potential benefits of better quality surgical research needs to be presented. The harsh fact is that surgical research desperately needs help to improve its infrastructure and achievements. The report recognises that surgery faces special challenges in designing, conducting, and reporting research, but that an intellectual framework for this is now available.[3]

A national plan for building the infrastructure needs to be developed, including the development of surgical trials units specifically dedicated to developing and supporting high quality studies of surgical techniques, using appropriate methodology. Attitudes of course need to change: it has always been a puzzle that engineering research, for example, can be intensely practical and results oriented yet retain intellectual respectability, but that research into surgical techniques has sometimes been regarded by academics with disdain. However, a thriving surgical research enterprise that demonstrably benefits patients and society would soon earn respect.

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The decline in heart transplantation in the UK

Means that left ventricular assist devices should be considered for long term support in advanced heart failure

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Heart transplants have offered a second chance of life for patients with advanced heart failure who fail to respond to optimal medical treatment and other treatments for more than 30 years in the United Kingdom. These people form a very small proportion (about 200) of the total number of people in the UK with heart failure (estimated at 750 000 currently). In patients with refractory heart failure who are relatively free of comorbidities, transplantation is seen as a final treatment option by clinicians who regularly treat heart failure. Survival at 10 years after transplantation is about 50%,[1] and this is far better than for patients with advanced heart failure, whose survival is often less than 50% at one year.[2] However, despite the announcement of a record high number of UK donors available for organ transplants (which includes all organs, not just hearts), heart donation continues to decline.[3] Heart transplant rates (separated from rates for other organs) have consistently declined over the past 10 years, with a 46% reduction in that time period. Furthermore, this problem seems particular to the UK (figure).

Statistics available from the International Society of Heart and Lung Transplantation put this decline into an international perspective, and they show that in Europe and the United States rates are steady or are only marginally declining.[1] Several important questions need to be answered, such as why have the reported increases in donors not translated into more heart transplants?[4] One explanation is the relatively small number of intensive care unit beds in the UK.[5]

What are the consequences of the reduced number of heart transplants? The first is that the use of left ventricular assist devices as an alternative treatment for end stage heart failure needs to be increased. These devices are mechanical pumps that can restore the output of the left ventricle in patients with refractory heart failure. Newer generation devices produce survival rates comparable to transplant at one to two years, so could be considered as an alternative

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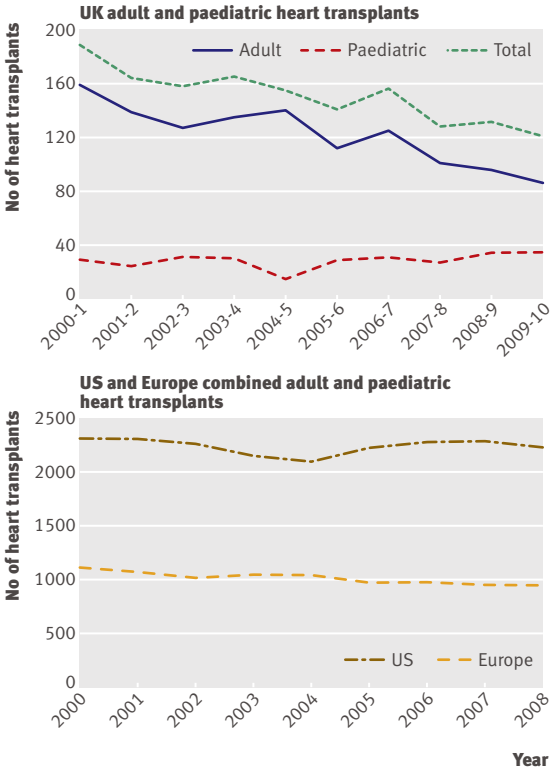

UK and international heart transplant numbers. Top: Data are courtesy of UK Transplant; bottom: adapted from Stehlik et al,[1] with permission from Elsevier

in some situations. These devices can be used as a "bridge to transplantation"—that is, supporting a patient until a suitable heart becomes available (currently funded in the UK)—or, as approved in some countries (such as the US and some European countries, but not currently in the UK), as "destination therapy," where the patient is not considered a suitable candidate for transplantation and receives long term support with the device.

Trials show that destination therapy can prolong survival in end stage heart failure. In the first Rematch trial the Heartmate XVE pulsatile device improved survival relative to medical treatment in patients with advanced heart failure not suitable for transplantation.[2] In this study, the risk of death from any cause was reduced by 48% in the patients receiving a left ventricular assist device compared with the medical treatment group (relative risk 0.52, 95% confidence interval 0.34 to 0.78; P=0.001). In Rematch 2 the Heartmate XVE device was compared with the newer continuous flow Heartmate 2 device.[6] Patients with continuous flow devices had better survival rates at two years (58% v 24%; P=0.008). Adverse events and device replacements were significantly less common in patients with the continuous flow device. Quality of life and functional capacity were not significantly different between the groups.

On the basis of these trials, left ventricular assist devices were recently recommended for destination therapy in guidelines from the European Society of Cardiology.[6] Although the long term outcomes with left ventricular assist devices are not as good as with transplantation, the lack of a "supply" problem with ventricular assist devices makes them an attractive alternative.

The second consequence of the reduced availability of heart transplants is that we need to reconsider which patients should be prioritised to have the few heart transplants that are performed. Patients with heart failure who are not suitable for left ventricular assist devices but might benefit from heart transplantation should be the focus of heart transplantation in the future. For example, patients with refractory right heart failure or restrictive cardiomyopathy may fare better with transplantation as a primary strategy because persistent right heart failure will remain after implantation of the left ventricular assist device.[7] People with ventricular assist devices who develop serious complications in some situations might also be best served with a transplant. In addition, adults with congenital heart disease who develop refractory heart failure are often not suitable for a left ventricular assist device given their complex anatomy, so transplantation is the only option. Although there is a perception that these are high risk patients for transplantation, a study found that with increasing experience in a single centre, five year survival can increase from 50% to 69%.[8] These complex patients are best managed in specialised centres with expertise in management of both congenital heart disease and transplantation.

The third consequence of the reduced number of heart transplants is that it is difficult for surgeons in the six UK units to maintain their expertise, so the number of units may need to be reduced. This has recently been accepted, and in the near future the Department of Health is going to conduct a review of cardiothoracic transplantation in the UK. This review must recognise that the use of long term ventricular assist devices for destination therapy is an essential service that needs to be developed in transplant centres as a consequence of the falling heart transplant numbers, and that there needs to be adequate provision of heart transplantation for adults with congenital heart disease and heart failure.

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