DM

Letters

Severe diabetic ketoacidosis

I would like to comment on both the Fiskin submission [1] and the Paton letter [2], which raise the issue of hyperchloraemia in diabetic ketoacidosis (DKA) and how this deserves to be addressed.

In Fiskin's case [1], although important elements are lacking in the report, the patient received 5925 ml normal saline plus KCl in the first 24 h. Since each litre of 0.9% NaCl contains 154 mEq Cl^-, this equates to at least 900 mEq Cl^- administered from saline alone in 24 h plus the additional Cl^- from KCl. In Paton's case [2] normal saline also appears to have been given with resultant hyperchloraemia and normalization of the anion gap.

This sequence is common during the treatment of DKA, especially when normal saline is used, although the arterial pH usually does not remain low [3–7]. Since ketones are threshold substances at the level of the kidney, once their serum concentration exceeds the kidneys reabsorptive capacity they are excreted in the urine and because they are anionic, even at maximally acid urine pH, they obligate the excretion of positively charged ions such as sodium and potassium. In turn, the kidney, in order to maintain the integrity of the intravascular volume, conserves sodium and, to maintain electroneutrality, the reabsorbable anion, chloride. This sequence is typically seen in young patients with DKA and normal renal function who have not been vomiting and therefore maintain a high fluid intake and large volume diuresis as their DKA evolves.

These patients present with what Androgue' and colleagues called a 'masked' hyperchloraemic acidosis or a mixed anion gap and mineral acid acidosis [3–5]. Clinicians will overlook this abnormality when patients with DKA present unless they calculate whether the fall in serum bicarbonate is fully matched by the rise in the anion gap. When the rise in anion gap is less than the reduction in bicarbonate, a hyperchloraemic acidosis is likely already present, albeit unrecognized. This hyperchloraemia becomes 'unmasked' when, with fluids and insulin, the ketones are further lost in the urine or metabolized to bicarbonate, leaving a persistent hyperchloraemia in their wake.

Regeneration of bicarbonate in DKA requires in part a metabolizable substrate – typically ketones – which, if fluid intake and diuresis were substantial, have been lost to the body [3–5]. In the absence of ketones or a comparable substrate capable of being metabolized, once insulin activity is restored, to bicarbonate, the ability of the kidney to regenerate bicarbonate is slow and hyperchloraemia may persist.

If to this sequence is added the traditional fluid therapy of DKA with normal saline containing 154 mEq each of Na^+ and Cl^- per litre plus KCl, the hyperchloraemia is compounded iatrogenically. Indeed, I have seen Cl^- levels exceeding 135 mEq/L with venous bicarbonates between 12 and 15 mEq/L for days after admission when this scenario is not recognized.

We have suggested that normal saline is an unphysiological and illogical replacement solution with which to challenge the ketoacidotic uncontrolled diabetic patient [6,7]. While the hyperchloraemia may only be 'cosmetic' in most cases and will be corrected in time by a normal kidney when saline is discontinued it is unnecessary and may result in acidosis, especially if the patient's kidney function is already impaired. Worsening or perpetuation of this hyperchloraemia is preventable by using a number of physiological multielectrolyte solutions which are commercially available (e.g. Plasmalyte, Isolyte, Normosol and Lactated Ringer's*). These preparations contain approximately 100 mEq/l of Cl^- with the remaining anions made up by acetate, gluconate, or lactate which can be metabolized to bicarbonate, thus replacing the lost bicarbonate precursor ketones. Further, the additional chloride traditionally administered with KCl can be avoided by using the phosphate or acetate salts of potassium.

The reason for not administering bicarbonate in DKA is too well known to require elaboration here.

R. Matz
Mount Sinai School of Medicine, New York, NY, USA

*Editor's note: Ringer's lactate solutions are rarely used in UK practice, partly because in other insulin infusion regimens they can support a rise in blood glucose, presumably as the lactate is a substrate for gluconeogenesis.

References

1 Fiskin R. Severe diabetic ketoacidosis: the need for large doses of insulin. *Diabetic Med* 1999; **16:** 347–350.
2 Paton RC, Sathiavageeswaran M. Severe diabetic ketoacidosis. *Diabetic Med* 1999; **16:** 884.
3 Androgue' HJ, Wilson H, Boyd AE, Suki WK, Eknoyan G. Plasma acid-base patterns in diabetic ketoacidosis. *N Engl J Med* 1982; **307:** 1603–1610.
4 Androgue' HJ, Eknoyan G, Suki WK. Diabetic ketoacidosis: role of the kidney in acid–base homeostasis re-evaluated. *Kidney Int* 1984; **25:** 591–598.
5 Androgue' HJ, Barrero J, Eknoyan G. Salutary effects of modest fluid replacement in the treatment of adults with diabetic ketoacidosis. Use inpatients without extreme Volume deficit. *JAMA* 1989; **262:** 2108–2113.
6 Carroll P, Matz R. Uncontrolled diabetes mellitus in adults: Experience in treating ketoacidosis and hyperosmolar non-ketotic coma with low-dose insulin and a uniform treatment regimen. *Diabetes Care* 1983; **6:** 579–585.
7 Matz R. Coping with electrolyte imbalances in uncontrolled diabetes. *J Crit Illness* 1997; **12:** 341–346.

Failure to reduce nicotine addiction in young adults with diabetes

Smoking is an independent risk factor for cardiovascular disease and diabetic patients who smoke have a 4–6 fold increase in ischaemic heart disease risk compared with non-smoking non-diabetic persons [1]. Smoking has also been implicated in the development of microvascular disease, particularly diabetic nephropathy [2]. Unfortunately, many young people with diabetes start smoking [3,4] and their smoking prevalence appears similar to the non-diabetic population [3,4]. We have audited the effect of regular standard anti-smoking counselling given during routine attendance at our diabetes centre.

Ninety-three patients who admitted smoking and were attending our Young Adult Diabetic Clinic were studied. Their mean age was 30 years (range 17–45), and 55 (59%) were male. Seventy-four (80%) had Type 1 diabetes and overall mean diabetes duration was 9.5 years (range 0.5–26). At our clinic, smoking is intermittently, though regularly, discussed with patients, and relevant posters are displayed in the waiting area. However, at the start of this study, the cohort was asked at each visit about smoking, and whether attempts to stop were being made, and if they were successful. Advice was given by a doctor reinforced by a specialist nurse and literature dealing with methods of stopping smoking was also offered. Smoking habits were assessed at the start of the study, 6–12 months later and finally after 18–24 months, all at routine appointments. Smoking load was assessed by direct questioning and by measurement of breath carbon monoxide (CO) and urinary cotinine (Cot)–creatinine (Cr) ratio (a ratio of over 1.0 μg/mg was used to suggest active smoking, based on previous studies [4–6]).

Data were available on 93 patients after 6–12 months (mean 10 months) and on 77 patients after 18–24 months (mean 20 months). The results are shown in Table 1. After 10 months the mean reported number of cigarettes smoked per day and urinary Cot–Cr ratios were unchanged, and remained unchanged in the 77 patients followed up to 20 months. Three patients claimed they had given up smoking by 10 months and remained stopped at 20 months. These claims were supported by urine Cot–Cr levels < 1 μg/mg. Mean breath CO levels were significantly lower at both 10 months and 20 months follow-up ($P < 0.05$ compared to baseline). No patient said they had used nicotine substitution therapy.

The data suggest that the counselling had very little effect on smoking habits. Previous studies suggest that even more intensive advice (including 'stop-smoking clinics') is also ineffective, and indeed can lead to patients falsely claiming to have stopped or cut down on cigarette consumption [7,8]. Our patients however, gave an honest smoking history as judged by urinary continine levels. The reduction in breath CO noted at follow-up probably reflects less cigarettes smoked in the hours prior to attending clinic.

Changing a behaviour pattern which relates to pharmacological dependence, and which is reinforced many times each day, is a major challenge. Most people with diabetes who smoke however do wish to stop and many have made several attempts, only to relapse back to the smoking habit. People with diabetes often feel restricted by treatment regimens, and many also fear weight gain. It may be that a combination of these factors counteract anti-smoking advice. A significant number of people with diabetes do eventually stop smoking, but unfortunately this is often after the development of serious microvascular or macrovascular complications [9].

This study demonstrates that patients with diabetes give an honest smoking history after 'non-threatening' stop-smoking counselling in routine clinics, although the effectiveness of the technique is poor. Nevertheless, it is obviously important to continue anti-smoking counselling, because of the major benefits to health that follow smoking cessation. Smoking remains worryingly common in the diabetic population [9,10], and there is no doubt that more effective stop-smoking strategies are urgently needed. These might include nicotine replacement therapy and/or behavioural techniques, which need to be objectively assessed.

Table 1 Claimed smoking habits and objective markers of smoking load in young diabetic smokers (mean and SD)

	Baseline (n = 93)	10 months (n = 93)	20 months (n = 77)
Smoking history (cigarettes/24 h)	17 ± 10	17 ± 10	17 ± 10
Breath carbon monoxide (p.p.m.)	18.0 ± 10.6	14.8 ± 10.1*	14.9 ± 7.6*
Urinary cotinine–creatinine ratio (μg/mg)	5.8 ± 5.1	5.6 ± 4.7	4.7 ± 4.2

*$P < 0.05$ compared to baseline (Student's paired t-test).

Acknowledgements

We are grateful to the staff of the Walton Hospital Diabetes Centre for their help and cooperation.

A. A. Ismail*, M. E. Wallymahmed†, G. V. Gill*† and I. A. MacFarlane†

*Division of Tropical Medicine, Liverpool School of Tropical Medicine, Liverpool, UK

†Walton Diabetes Centre, University Hospital Aintree, Liverpool, UK

References

1 Stamler J, Vaccaro O, Neaton J, Wentworth D for the MRFIT Research Group. Diabetes and other risk factors in 12-year

cardiovascular mortality for men screened in the Multiple Risk Factor Intervention Trial (MRFIT). *Diabetes Care* 1993; **16:** 434–444.
2 Muhlhauser I. Cigarette smoking and diabetes: an update. *Diabetic Med* 1994; **11:** 34.
3 Masson EA, MacFarlane IA, Priestley CJ, Wallymahmed ME, Flavell HD. Failure to prevent nicotine addiction in young people with diabetes. *Arch Dis Childhood* 1992; **67:** 100–102.
4 Shaw NJ, McClure RJ, Kerr S, Lawton K, Smith CS. Smoking in diabetic teenagers. *Diabetic Med* 1992; **10:** 275–277.
5 Peach B, Ellard GA, Jenner PJ, Morris RW. A simple inexpensive test for cigarette smoking. *Thorax* 1985; **40:** 351–357.
6 Jarvis MJ, Tunstall-Pedoe H, Feyerabend C, Vesey C, Saloojee Y. Comparison of tests used to distinguish smokers from non-smokers. *Am J Public Health* 1987; **77:** 1435–1438.
7 Ardron M, MacFarlane IA, Robinson C, Heyningen CV, Calverley PMA. Anti-smoking advice for young diabetic smokers: is it a waste of breath? *Diabetic Med* 1988; **5:** 667–670.
8 Bodmer CW, MacFarlane IA, Flavell H, Wallymahmed M, Calverley PMA. How accurate is the smoking history in newly diagnosed diabetic patients? *Diab Res Clin Pract* 1990; **10:** 215–220.
9 Sinah RN, Patrick AW, Richardson L, Wallymahmed M, MacFarlane IA. A six-year follow-up study of smoking habits and microvascular complications in young adults with Type 1 diabetes. *Postgrad Med J* 1997; **73:** 293–294.
10 Ismail AA, Gill GV, Houghton GM. Smoking habits of patients with type 2 diabetes. *Pract Diabetes Int* 1998; **15:** 197–199.

The use of lispro for high sugar content snacks between meals in intensive insulin regimens

Compliance with insulin treatment and diet reduces the long-term complications of diabetes [1,2] but conventionally imposes lifestyle restrictions. Typically intensive insulin regimens in the UK use three injections of soluble insulin pre-meal and isophane pre-bed with snacks of 'sensible' foods (e.g. a banana, apple, digestive biscuit, etc.) between meals to avoid hypoglycaemia. People without diabetes frequently eat snacks such as ice cream, chocolate bars and cakes. Use of lispro insulin in intensive insulin regimens can give good glycaemic control [3,4], even after carbohydrate rich meals [5] and supplemental lispro doses have been used for the successful correction of acute hyperglycaemia [6]. The consequence of injecting extra lispro deliberately before a sugary snack eaten mid-afternoon has not formally been investigated.

Patients with Type 1 diabetes mellitus (DM) were recruited. All had a dietary review with conventional snacks recommended routinely only before bed. They started to use lispro pre-meals and isophane insulin (Humulin I) pre-bed. Accutrend glucometers (Boehringer Mannheim, Mannheim, Germany) were used to test capillary glucose pre-meal, 2½ – 3 h after lunch (mid-afternoon) and pre-bed with a target of 4–10 mmol/l. Once suitable insulin doses for the desired level of glycaemic control had been achieved, patients chose a snack they wished they were 'allowed' to eat. This was eaten mid-afternoon on study days following an educated guess at an initial dose of supplemental lispro, and the dose adjusted to maintain glucose between 4 and 10 mmol/l through the period post-snack over the next few days (1–3). Capillary glucose was measured before all three meals of the day, pre-bed and at 30-min intervals from mid-afternoon until the evening meal. The final insulin doses, snack and similar meals were used on all subsequent study days, which proceeded only if pre-breakfast, lunch and mid afternoon glucose were between 4 and 10 mmol/l. Patients collected data when a mid-afternoon snack was eaten with extra lispro and when no snack or extra lispro injected. A maximum of six snack and six non-snack days were undertaken alternately. On one day only, patients ate the snack without the extra lispro. Any hypoglycaemic event occurring on study days was recorded.

The area under the glucose curve (AUC) from mid-afternoon to evening meal was calculated using the trapezoid rule and Student's *t*-tests used to compare the three different study days. Glucose data are expressed as means ± SEM.

Nine of the 20 patients enrolled managed to supply usable data for the study. Their mean age was 39.6 years (range 26–51), duration of diabetes 11.4 years (2–23), HbA_{1c} 8.9% (7.1–11.8) and body mass index 26.4 kg/m^2 (18.1–32.3). The other 11 did not achieve satisfactory glycaemic control prior to study days or failed to supply the necessary data within the allocated time. Finding a suitable lispro dose pre-snack took 1–3 attempts. The mean lispro dose pre-lunch was 11.9 and pre-snack 3.9 units. Lunch was typically sandwiches and the snack a chocolate bar. With the correct dose of pre-snack lispro hypoglycaemia did not occur on study days. The AUC for glucose on snack days with extra lispro and non-snack days was 1462.1 ± 42.1 vs. 1457.8 ± 40.4 l.mmol.min.l^{-1} (P = 0.94). When no pre-snack lispro was given, glucose surged, peaking at 5 mmol/l above the mid-afternoon level. The AUC (2168.8 ± 131.9) was also significant greater compared to the other two test days (P < 0.001) (Fig. 1).

Using supplemental insulin for snacks between meals is not common practice in the UK probably through fear of

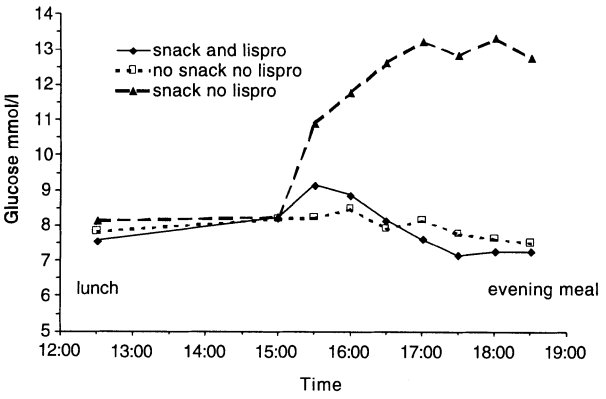

Figure 1 Mean afternoon glucose on all study days

hypoglycaemia. Our study demonstrates lispro safely pre-empted hyperglycaemia as a result of changes in dietary routine. Patients with Type 1 DM indulging in high sugar content snacks suffer unacceptable surges in glucose without extra insulin. With the correct lispro dose identified for a chosen snack, glucose excursion was attenuated and hypoglycaemia avoided despite injecting soon after the lunch time dose. We are not advocating routinely using lispro this way or abandoning sensible diets and healthy snacks. Abuse of snacking and extra lispro will inevitably cause weight gain. Careful selection of patients to recommend a regimen of occasional supplemental lispro is advisable. Further trials in a more controlled laboratory setting may be helpful. Patient glucometer data may not be reliable and a direct comparison with conventional soluble insulin would be useful to fully assess hypoglycaemia risk. However, assuming patients do not object to extra injections and extra glucose testing, this study highlights an area of improved flexibility and quality of life when using lispro.

N. Kong, M. M. Kitchen and R. E. J. Ryder
Department of Diabetes and Endocrinology, City Hospital NHS Trust, Dudley Road, Birmingham, UK

References

1 The 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. *New England J Med* 1993; **329:** 977–986.
2 Reichard P, Nilsson BY, Rosenqvist U. The effect of long-term intensified insulin treatment on the development of microvascular complications of diabetes mellitus. *New England J Med* 1993; **329:** 304–309.
3 Holleman F, Schmitt H, Rottiers R, Rees A, Symanowski S, Anderson JH. Reduced frequency of severe hypoglycemia and coma in well-controlled IDDM patients treated with insulin lispro. *Diabetes Care* 1997; **20:** 1827–1832.
4 Pfutzner A, Kustner E, Forst T, Schulze-Schleppinghoff B, Trautmann ME, Haslbeck M *et al.* Intensive insulin therapy with insulin lispro in patients with type 1 diabetes reduces the frequency of hypoglycemic episodes. *Exp Clin Endocrinol Diabetes* 1996; **104:** 25–30.
5 Heinemann L, Heise T, Wahl LC, Trautmann ME, Ampudia J, Starke AA *et al.* Prandial glycaemia after a carbohydrate-rich meal in type I diabetic patients: using the rapid acting insulin analogue [Lys (B28), Pro (B29)] human insulin. *Diabetic Med* 1996; **13:** 625–629.
6 Holleman F, van den Brand JJ, Hoven RA, vand der Linden JM, Van der Tweel B, Hoekstra JB *et al.* Comparison of LysB28, ProB29-human insulin analog and regular human insulin in the correction of incidental hyperglycemia. *Diabetes Care* 1996; **19:** 1426–1429.

Errata

Diabet Med 1999; 16: 755–761

Comparison of acarbose and metformin in patients with Type 2 diabetes insufficiently controlled with diet and sulphonylureas: a randomized, placebo-controlled study.

B. Willms and D. Ruge

On p759 of this article, in the section *Adverse events*, the last sentence of the first paragraph (which reads 'In total 35 of the patients reporting adverse events withdrew from the study: 18 from the acarbose group, 13 from the placebo group and four from the metformin group') should be deleted.

Thus, the first paragraph of this section should read:

> The number of adverse events reported was comparable for the three groups (total number of occurrences: acarbose 56; metformin 57; placebo 57). There were slightly more gastrointestinal events in the acarbose group (number of occurrences: acarbose 42; metformin 37; placebo 37) but this was balanced by fewer other events, including fewer incidents of hypoglycaemia (number of occurrences: acarbose: 3; metformin 5; placebo 3). Adverse events were generally mild, non-treatment limiting and confined to the gastrointestinal tract.

The true number of drop outs in this study can be found on p757 in the section *Results*, subsection *Patients*.

Diabet Med 2000; 17: 124–129

Correlations between insulin sensitivity and bone mineral density in non-diabetic men

B. Abrahamsen, A. Rohold, J. E. Henrikson and H. Beck-Nielson

A typographical error in the above article led to *hyperglycaemia* being mistakenly reproduced as *hypoglycaemia* in the first section of the abstract (p124). This section should read:

Aims To investigate relationships between bone mineral density (BMD), insulin secretion and insulin sensitivity, controlling for body composition, in view of data suggesting that hyperglycaemia leads to decreased osteoblast proliferation and a negative calcium balance and that insulin stimulates osteoblast differentiation and collagen synthesis, with no clear evidence if this response in impaired in insulin resistance.