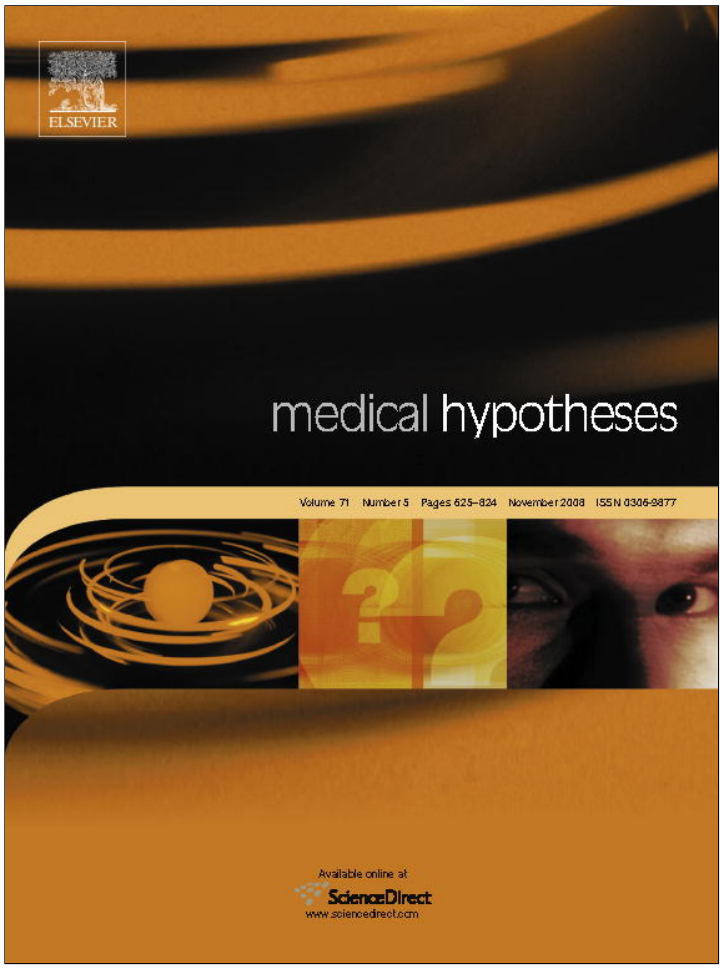

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People with type 1 diabetes using short acting analogue insulins are less dehydrated than those with using human soluble insulin prior to onset of diabetic ketoacidosis

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Summary Diabetic ketoacidosis (DKA) is associated with disturbances of acid base, fluid balance and electrolytes. Much of the established literature states that the fluid deficit in someone presenting with DKA is in the region of 6—8 l of fluid (about 100 ml/Kg), and this needs to be the fluid volume that is replaced in the first 24 h following admission to hospital.

The physiology of fluid loss in DKA is complex. In summary, however, as blood glucose levels rise, the renal threshold for active glucose reabsorbtion is exceeded leading to glucose loss in the urine. This leads to an osmotic diuresis, and thus dehydration if oral intake is insufficient. Further losses are accounted for by hyperventilation, sweating and vomiting.

With the older insulins — such as soluble human insulins, the duration of action was 8—10 h, with a peak of action at ~2—4 h after subcutaneous injection. Because very low insulin concentrations are sufficient to prevent ketone production, and because insulin concentrations would stay sufficiently high enough to do this, ketones would not be formed for up to 10 h after the last injection. Furthermore, concentrations of ketones sufficiently high enough to make a person unwell may take several more hours to develop. However, during this time, as insulin concentrations declined, blood glucose levels would increase, eventually overcoming the renal threshold, causing the renal diuresis and subsequent dehydration.

Thus, on human soluble insulin, there is the opportunity to become profoundly dehydrated prior to the onset of significant ketoacidosis.

The new rapid acting analogue insulins have durations of action of between 4 and 6 h. Thus the individual would become absolutely insulin deficient relatively quicker than with human soluble insulin. In this circumstance, the blood glucose would not have time to rise as high as with human soluble insulin deficiency before significant ketosis develops, thus leading to a lesser degree of dehydration.

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New rapid acting insulin analogues are becoming more widely used. This suggests that the volumes needed to replace those lost prior to the onset of significant DKA may be lower.

Diabetic ketoacidosis (DKA) is a potentially life threatening condition occurring usually in situations of insulin deprivation or inadequate insulinisation in people with type 1 diabetes mellitus. It may also very occasionally occur in people with ketosis prone type 2 diabetes [1].

There are several reasons why DKA occurs. These include deliberate insulin omission, intercurrent illness, surgery, trauma, alcohol, the late presentation of previously undetected type 1 diabetes, and the use of medication that alter carbohydrate metabolism [2].

DKA is associated with marked acid—base, fluid balance and electrolyte disturbances, from which there continues to be an appreciable mortality. The primary treatment for DKA is fluid replacement as well as insulin and correcting the electrolyte disturbances. The factors influencing fluid loss associated with DKA are complex and fluid replacement regime for DKA remains contentious [3].

The volume of fluid lost may be as much as 6—8 l. If insulin is omitted, then blood glucose begins to rise. This glucose is filtered out by the kidneys along with several waste products into the urine. However, because it is important not to lose glucose in the urine, the kidneys have a way of reabsorbing the glucose to prevent it being excreted. This reabsorbtion mechanism has a limit to its capabilities. If the amount of glucose filtered into the urine exceeds the reabsorbative capacity (''the renal threshold''), then glucose is lost in the urine. Because glucose needs to be dissolved in water, whenever glucose is lost in the urine, water must follow. The higher the blood glucose, the higher the urine glucose, and the higher the urinary water loss. This is the cause of the polyuria associated with high blood glucose levels.

People using animal insulin often suffered due to the immunogenicity of the protein. This led to the development of areas of lipohypertrophy at the sites of injection. As a result, in the 1980s recombinant human insulin was made available. This is identical to human insulin, and produces none of the immune reactions seen with the animal products. However, it became clear that despite the insulin being identical it continued to be given in a highly unphysiological fashion. In healthy individuals without diabetes, the insulin is delivered directly to the liver via the splanchnic circulation, whereas exogenous insulin still needs to be given as a subcutaneous injection. With this in mind, the analogue insulins were produced with minor amino acid changes to allow for rapid subcutaneous absorption to try and mimic more closely the concentrations of insulin in the splanchnic and systemic circulation seen in people without diabetes.

Older (human) soluble insulins worked slower than the newer, rapid acting analogue insulins [4]. They also are present in the blood for a long longer after a subcutaneous injection than the newer rapid acting (analogue) insulins.

Ketones are produced when there is almost no circulating insulin [5]. High levels of ketones are present in DKA. DKA is a medical emergency and is associated with a high complication rate, including death, with dehydration being a major component of the complications associated with DKA.

With older (human) soluble insulin, the levels were measurable in the blood for up to 12 h after a subcutaneous injection. This meant that there were unlikely to be ketones present until the person had almost no circulating insulin. However, when circulating insulin levels begin to drop, then blood glucose levels would begin to rise. After some time, blood glucose levels would rise high enough to overcome the renal threshold and then glucose and water would be lost, eventually leading to dehydration. The time taken to develop ketoacidosis could be very long, allowing a fluid deficit of 6 to 8 litres to develop.

With newer rapid acting (analogue) insulins, the levels are measurable in the blood for only up to 6 h after a subcutaneous injection. This means that ketones are much more likely to develop sooner after the last subcutaneous injection when compared with a similar dose of older (human) soluble insulin. This means that whilst insulin levels go down faster, and the degree of rise of blood glucose may be similar to that seen with a lack of older (human) soluble insulins, because the time taken to develop ketoacidosis is shorter, the likelihood that the person will become sicker sooner is higher. However, with the earlier presence of ketoacidosis, it is probable that there has not been sufficient time to develop the same degree of dehydration seen with the older (human) soluble insulins.

Thus the hypothesis is that the continued adherence to old guidelines suggesting that the volumes of fluid that need to be replaced in people presenting with DKA is no longer true. Indeed, continuing

to use inappropriately large volumes may be associated with fluid overload.

References

[1] Umpierrez GE, Smiley D, Kitabchi AE. Narrative review: ketosis-prone type 2 diabetes mellitus. Ann Intern Med 2006;144(5):350—7.

[2] Kitabchi AE, Umpierrez GE, Murphy MB, Kreisberg RA. Hyperglycemic crises in adult patients with diabetes: A consensus statement from the American Diabetes Association. Diabetes Care 2006;29(12):2739—48.

[3] Dhatariya KK. Diabetic ketoacidosis. BMJ 2007;334(7607): 1284—5.

[4] Hirsch IB. Insulin analogues. N Eng J Med 2005;352(2): 174—83.

[5] Wallace TM, Matthews DR. Recent advances in the monitoring and management of diabetic ketoacidosis. QJM 2004; 97(12):773—80.