The Relationship Between Kidney Size and Function in Short-Term Diabetic Patients

Dear Sir,

In a recent Letter to the Editor, Gundersen and Mogensen [1] presented a statistical evaluation of the available data from studies of glomerular filtration rate (GFR), renal plasma flow and kidney size in short-term Type 1 (insulin-dependent) diabetic patients. Their analysis led them to suggest that the major – perhaps even the sole – determinant of the increased GFR in short-term Type 1 diabetic patients is the increased kidney size. This suggestion may well be valid in clinically so-called well controlled diabetic patients, but it is certainly not so in poorly controlled subjects. Previous studies in poorly controlled Type 1 diabetic patients have demonstrated a 20% reduction in GFR during 1–2 weeks of improved metabolic control [2, 3]. Recently, we studied GFR and kidney size (by ultrasound) in newly diagnosed Type 1 diabetic patients without ketoacidosis, before and after 8 days of strict metabolic control [4]. GFR was elevated by 44% before insulin treatment and remained 20% above normal after 8 days of strict metabolic control. The size of the enlarged kidney remained unchanged after 8 days of strict metabolic control. These data suggest that the elevation of GFR in poorly controlled Type 1 diabetic patients consists of two parts: rapid and slow reversible components of approximately the same order of magnitude. The rapidly reversible part can hardly be explained by morphological changes alone since kidney size was unchanged. Furthermore, the demonstrated increase in the glomerular filtration surface area (partly constituting one of the three well-known determinants of GFR) in newly diagnosed Type 1 diabetic patients also remains unaltered after 3 months of insulin treatment [5], a time by which a substantial decline in GFR would be expected.

It is documented that GFR in Type 1 diabetic patients can be increased or decreased within minutes in response to physiological changes in plasma levels of insulin, glucose and glucagon [6–10]. It is extremely unlikely that changes in kidney size can account for these rapid changes in GFR.

Studies in poorly controlled insulin-treated streptozotocin diabetic rats have shown that the elevated GFR is due to increased renal plasma flow, raised transglomerular filtration pressure, and probably also enlarged ultrafiltration coefficient (i.e. the product of the glomerular water permeability and the surface area available for filtration) [11, 12].

We conclude that the elevation of GFR in poorly controlled Type 1 diabetic patients consists of both rapid and slow reversible components. The rapidly reversible part, accounting for approximately half of the elevation, cannot be explained by the demonstrated enlargement of the kidney or of the glomerular surface area, but is due to an increase in the remaining two GFR determinants: renal plasma flow and transglomerular pressure. We agree with Gundersen and Mogensen that the slowly reversible part of the GFR elevation is probably due to enlargement of the kidney.

Yours sincerely,

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Insulin Aggregation and the Use of Infusion Pumps

Dear Sir,

A recent article in *Diabetologia* [1] recommended the use of a phosphate buffered (pH 7.0) highly purified insulin preparation in conjunction with EDTA treatment of the reservoir and tubing (to minimize metal ion contamination of the delivery system) in order to avoid the problem of insulin aggregation in artificial infusion de-

vices. An earlier study [2] had shown that the ability of physiological fluids in vitro to dissolve crystals of insulin at a normal pH was dependent on the bicarbonate content. I wish to report a practical application of this latter observation to the problem of insulin aggregation in insulin infusion devices.

I use the Delta pump [3], an open loop insulin delivery system which utilizes U-100 regular insulin contained in a reservoir and propelled forward through the tubing by the repetitive action of a solenoid plunger pinching the area of tubing located between two check valves. The reservoir is usually refilled every 3–7 days depending on the patient's daily insulin requirement. Since the aggregation of insulin solutions had been described in implanted devices maintained at body temperature, I was surprised to meet this problem in the Delta open-loop pump. The precipitation seemed to start in either the tubing near the needle and/or in the tubing between the check valves. Since the tubing adjacent to the subcutaneously placed needle is pressed against the skin, aggregation here is consistent with the association of this problem with higher temperatures [4]. The insulin contained in the area between the valves is subjected to the repetitive action of the solenoid plunger. Aggregation here is consistent with the association of this problem with agitation of the insulin solution [4].

To circumvent this problem, I initially dissolved glutamic acid (50 mg/10 ml vial) into the insulin under sterile conditions [5]. Although this prevented the aggregation, dissolving the dicarboxylic amino acid was difficult and some patients complained of burning at the needle site, especially during the administration of the preprandial bolus. After publication of reference 2, I used a physiological concentration of NaHCO_3 (26 mmol/l) to achieve the same end. To obtain this concentration, which is equivalent to 0.26 mmol/10 ml vial, 0.3 ml of the commercially available (at least in the USA) bicarbonate solution (44.5 mmol/50 ml) is added under sterile conditions to a 10 ml vial of U-100 regular insulin. The addition of bicarbonate has been successful in preventing aggregation of the insulin solutions in the eight patients in whom this method has been used. The first patient was started nearly one year ago. Since aggregation seems to occur more readily when flow rates are low, it is particularly gratifying that this approach has been successful in a patient receiving 0.003 ml/h (0.3 U/h).

Insulin aggregation has not been reported to be a problem with other open-loop insulin delivery systems (Mill-Hill and Autosyr-

ringe), probably because they use less concentrated insulin solutions. However, Autosyringe have modified their device so that now U-100 insulin can be utilized. If insulin aggregation becomes a problem in the tubing near the patient's body, the addition of physiological concentrations of NaHCO_3 should be helpful.

Yours sincerely,
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Aspects of Non-Enzymatic Glycosylation of Serum Proteins in Relation to Different Glucose Loads

Dear Sir,

Svendsen et al. [1] and Bolli et al. [2], respectively, have shown rapid changes in the concentration of total stable and unstable glycosylated haemoglobin A_{1c} (HbA_{1c}) and HbA_1 to be dependent on short-term fluctuations in blood glucose levels. This phenomenon is regarded as representing the formation and dissociation of unstable HbA_1 (aldimine-linked adduct), which is correlated with significant increases or reductions in glycaemic values.

Recently, non-enzymatic glycosylation of total serum proteins has also been shown to be increased in diabetic patients [3–5]. However, it has not been proven whether rapid changes in glucose levels in vivo and in vitro affect the level of glycosylated serum proteins [5]. We have therefore measured glycosylated serum proteins in ten normal subjects (aged 40 ± 10 years; mean $\pm$ SD) and in 12 Type 1 (insulin-dependent) diabetic patients (aged 38 ± 9 years) after an overnight fast during an oral glucose tolerance test and several days later during a continuous 5 h IV infusion of glucose (0.33 g/kg body weight in a bolus + 0.9 g/min in normal subjects and 0.6 g/min in diabetic patients). Glycosylated serum proteins levels were determined by thiobarbituric acid reaction before and after dialysis of serum samples against 0.15 mol/l saline solution (1:350) at 4°C for 18 h [3]. In the diabetic patients, the fasting glucose levels were

higher (8.1 ± 3.1 mmol/l) than in the normal subjects (4.3 ± 0.3 mmol/l). Before dialysis, glycosylated serum proteins, expressed as nmol 5-hydroxymethylfurfural (5-HMF)/mg protein, showed values which were in parallel with the glycaemic values observed before and during the glucose loads. After dialysis, glucose was always < 0.2 mmol/l in samples from both groups, while 5-HMF gave values lower than those observed before removal of glucose ($p < 0.001$). The mean fall was proportionate to glycaemic levels ($p < 0.001$). However, in every assay, diabetic patients showed higher 5-HMF values than normal subjects ($p < 0.001$, Table 1). Moreover, after dialysis, 5-HMF levels were not significantly increased after different glucose loads. In normal and diabetic subjects, they ranged between 0.51 and 0.53 and between 0.93 and 0.97 nmol 5-HMF/mg protein, respectively, during the oral glucose tolerance test with similar values during IV glucose infusion.

In agreement with the findings in vitro of Kennedy et al. [4], our observations in vivo indicate that the determination of glycosylated serum protein levels is influenced by free glucose present in the sample. However, as the oxalic acid used in the thiobarbituric acid reaction test induces rearrangement of the Schiff base [6], it cannot be excluded that the decreases in 5-HMF found after dialysis could