No, the glycaemic target in the critically ill should not be ≤ 6.1 mmol/l

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Abbreviations

ICU intensive care unit
PN parenteral nutrition
TAG triacylglycerol

Over the past 10 years, a number of studies have been published suggesting that an intensified approach to glycaemic control in hospitalised patients, using intravenous insulin infusion, results in improved outcomes, including decreased mortality rate. These observations have resulted in dramatic changes in the management of hospital hyperglycaemia in Europe and in North America. In the present issue of *Diabetologia*, Van den Berghe recommends a blood glucose target of 4.4–6.1 mmol/l for patients in the intensive care unit (ICU) [1], a position endorsed at a consensus conference convened by the American College of Endocrinology and co-sponsored by the American Diabetes Association, the American Heart Association, the Endocrine Society, the Society of Critical Care Medicine and several other organisations [2]. For reasons outlined in this paper, we believe that the available data are insufficient to warrant such a recommendation.

The results of five large studies

The recommendation that glucose levels be maintained no higher than 6.1 mmol/l has its origins in a key study conducted in Leuven, Belgium, by Van den Berghe and colleagues in 2001, showing a 34% reduction in all-cause hospital mortality rate in surgical patients who received intravenous insulin to maintain glucose ≤ 6.1 mmol/l compared with a control group managed with convention therapy [3]. The reduction in mortality rate in this study was due primarily to decreased multiple organ failure related to sepsis. The results of this study (henceforth referred to as the Leuven I study) are compared in Table 1 with the other four largest studies [4–7], including a second study by Van den Berghe and colleagues (Leuven II) in medical ICU patients [7], addressing the question of the impact of glycaemic control on outcomes in the critically ill and in which a glycaemic target was part of the study design. Two of these studies were observational, using historical controls [5, 6]. The difference in mortality rate between the two study groups of Leuven II was significant only when those with ICU stays of 3 days or less were considered separately, but the participants in this study were more critically ill and had by far the highest mortality rate of the five studies. Although there were significant differences in the designs of the studies, in the patient populations and in the blood glucose levels achieved, the results were for the most part concordant. Intensive therapy with intravenous insulin produced a consistent decrease in mortality rate in a variety of patient populations, as noted in Table 1. However, there were several important differences. In some cases, all the participants had diabetes, whereas in others most participants were non-diabetic. In addition, there were impressive differences in the blood glucose

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Table 1 Comparison of five large studies of intensive insulin therapy in critically ill patients (shown in chronological order)

Study [reference]	DIGAMI [4]	Leuven I [3]	Portland [5]	Stamford [6]	Leuven II [7]
Participants (<i>n</i>)	620	1,548	3,554	1,600	767 ^a
Patient population	Acute MI	Surgical	CABG	Medical ICU	Medical ICU
Diabetes (%)	100	13	100	17	15
Decrease in mortality rate (%)	30 ^b	34	53	29	18
Control group mortality rate (%)	26	11	5	21	53
Reason for decreased mortality rate	?	↓ Sepsis	↓ HF, VT, VF	?	Multiple
Hypoglycaemia frequency (%) (defined by glucose level, mmol/l)	17 (<3.0)	5.2 (<2.2)	0.8 (<3.3)	1.3 (<3.3)	25 (<2.2)
Mean glucose, intensive treatment (mmol/l)	9.2	5.7	9.8	7.3	5.8
Mean glucose, conventional treatment (mmol/l)	12.0	8.5	11.8	8.4	8.6
PN?	No ^c	Yes	<5% ^c	<5% ^c	Yes

^a Long-stayers (>3 days) in ICU only^b 1 year^c K. Malmberg [4], A. Furnary [5] and J. Krinsley [6], personal communications

CABG, coronary artery bypass graft; HF, heart failure; MI, myocardial infarction; ND, not determined; VF, ventricular fibrillation; VT, ventricular tachycardia

levels achieved: the glucose levels achieved in the control group of the Leuven studies were similar to, and in some cases lower than the levels in the intensive groups of the other studies. The differences in blood glucose levels between the conventional and intensive groups were similar in all five studies. If lowering glucose to 7.3–9.8 mmol/l produces comparable improvement in mortality rate in some populations of critically ill patients compared with the results of the study that is the basis for the 6.1 mmol/l goal (and in which the glucose levels in the control group averaged 8.5 mmol/l), then how firm is the recommendation for a 6.1 mmol/l goal?

Table 1 shows a second important difference among these studies. The two studies that achieved by far the lowest glucose levels in the intensively treated patients were also the only two studies in which parenteral nutrition (PN) was routinely given. The possibility that PN could confound the interpretation of the two Leuven studies was not considered by the expert panel that formulated the consensus statement [2], but it is our view that this feature of the study design makes it inappropriate to extrapolate the authors' findings to other populations of patients not receiving PN.

Does PN influence outcomes in the critically ill?

PN is widely used in the care of critically ill patients who are unable to eat and unable to be fed enterally. It is well known that PN can contribute to hyperglycaemia and hypertriglyceridaemia [8]. Moreover, there is considerable evidence that PN can be responsible for adverse outcomes. In the largest prospective, randomised study of the effects of PN vs no nutritional support, given perioperatively to malnourished surgical patients, the rate of infections was more than 100% higher in the PN group than the control group

($p=0.01$) [9]. In that study, the 90 day all-cause mortality rate was ~28% higher in those receiving PN than the control group. This difference was not statistically significant, possibly because of inadequate statistical power; using the χ^2 test, detecting a difference of this magnitude would require >2,000 patients in each group. It should be pointed out that the patients who received PN in that study received ~4,200 kJ (~1,000 kcal) in excess of their estimated basal energy requirements. An advisory committee sponsored by the USA National Institutes of Health, the American Society for Parenteral and Enteral Nutrition and the American Society for Clinical Nutrition concluded that routine postoperative PN in malnourished surgical patients increases postoperative complications [10]. In a meta-analysis of 27 studies comparing PN with enteral nutrition and involving >1,800 patients, Braunschweig et al. found a >50% higher incidence of infection in participants receiving PN, but no difference in mortality rate [11]. Prospective, randomised trials in other conditions such as acute pancreatitis have shown a higher incidence of infection, and longer hospital stays, when PN is given [12]. Although PN is not routinely administered in the care of patients after coronary artery bypass (see Table 1), nearly two thirds of the patients in the Leuven I trial had undergone cardiac surgery [3].

The implications of these findings in interpreting the Leuven I study [3] are obvious. Patients in the Leuven I study received PN, a treatment known to increase infection rates, and when glucose level was lowered with insulin infusion to an average of 5.7 mmol/l, an improvement in mortality rate, based largely on a reduction in infection rate, was observed. Is it not possible that intravenous insulin in this study merely reduced infectious complications to a level that would have been observed if PN had not been given in the first place?

It has long been known that hyperglycaemia during hospitalisation is associated with adverse outcomes [13]. In hospitalised patients, hyperglycaemia is associated with impaired immune function with increased risk of infection [14]. One of the mechanisms that may explain an increased rate of infection in diabetic individuals is a defect in the adherence properties of polymorphonuclear leucocytes [15]. An alternative explanation for the benefits of insulin infusion is that they were not a direct consequence of glucose lowering at all, but rather to other effects of insulin. An analysis of data from the 363 patients who remained in intensive care for >7 days in the Leuven I study revealed that lipid control rather than glucose control accounted for the beneficial effects of intensive insulin therapy [16]. There was a strong relationship between serum triacylglycerol (TAG) and ICU mortality rate by univariate analysis (an approximate 400% increase in mortality rate in patients with TAG >3.4 mmol/l compared with individuals with TAG <1.1 mmol/l), whereas LDL-cholesterol and HDL-cholesterol, the latter a strong correlate of TAG [17], were the chief determinants of mortality rate when multivariate analysis was employed [16]. TAG levels were significantly lower in intensively treated patients [1.2 mmol/l (102 mg/dl)] than in the control group [2.0 mmol/l (180 mg/dl)] ($p<0.05$).

Hypertriacylglycerolaemia is a common occurrence in critically ill patients, especially those receiving PN. It is noteworthy that by day 8 of the Leuven I study, patients were receiving fat at an average of 85 g/day and hypertriacylglycerolaemia was common [16]. We found that TAG concentrations were >1.7 mmol/l in approximately one-half and >2.3 mmol/l in one-third of a group of critically ill patients receiving PN, using lipid infusion rates that delivered an average amount of fat of only 48 g/day and a total energy supply equal to 109% of basal requirements (D. J. Jurgens, M. R. Litzow, M. R. Baker, L. R. Clifford, M. M. McMahon and J. M. Miles, unpublished results). Of the macronutrient components of PN, lipid emulsions are by far the most likely mediator of increased infectious risk [18–20]. The results of the Leuven I trial suggest that the link between infectious risk and exogenous lipid administration depends on the degree of hypertriacylglycerolaemia that results from feeding. The mechanism responsible for increased infectious risk in patients receiving lipid emulsions is not entirely clear, but may involve impairment of reticuloendothelial function [21].

Another potential salutary effect of insulin is lowering of elevated plasma NEFA levels as a result of inhibition of adipose tissue lipolysis, a process that is exquisitely sensitive to insulin, more sensitive than insulin's effects on glucose metabolism [22]. Considering that myocardial function is relatively inefficient when NEFAs are the heart's chief source of energy [23], and that elevated NEFA levels cause endothelial dysfunction [24] and raise blood pressure [25], decreased NEFA levels could contribute to improved

outcomes. Moreover, a reduction in NEFA has the potential to lower TAG levels by depriving the liver of substrate for VLDL-TAG synthesis.

The role of overfeeding

It is not known whether the increase in risk in PN-fed patients is due specifically to overfeeding or is intrinsically associated with PN. However, the fact that all of the patients in the Leuven I study received PN cannot be ignored. Among those who were in the ICU for >5 days (the group in which intensive insulin therapy reduced mortality rate), 40% were receiving PN exclusively and PN provided an average of one third of energy in the remainder [26]. There has been much debate over the years on the question of energy requirements in the critically ill. The most widely used method of estimating energy needs in hospitalised patients is the Harris–Benedict equation. In a recent review, energy expenditure in hospitalised patients was only 113% of basal energy requirements predicted by the Harris–Benedict

Fig. 1 Energy supply in the Leuven I study expressed as a percentage of estimated basal energy requirement (from the Harris–Benedict equation) for men and women. Estimates of isoenergetic feeding (Iso; based on [26]) and actual energy delivery are shown, as well as what would have been given using the guidelines of the American College of Chest Physicians (ACCP) and the European Society for Parenteral and Enteral Nutrition (ESPEN)

equation, and there was no convincing evidence for a relationship between illness acuity and energy expenditure [27]. We calculated the energy content of the feeds received by the patients (total energy supply $\sim 115 \text{ kJ kg}^{-1} \text{ day}^{-1}$) in the Leuven I study in relation to estimated basal energy requirements (Harris–Benedict equation), using the average age and BMI in that study (63 years and 26 kg/m^2) and assuming a height of 163 cm for women and 177 cm for men to determine weight (Fig. 1). Those results were compared with energy supply using the feeding recommendations of the American College of Chest Physicians (ACCP; $105 \text{ kJ kg}^{-1} \text{ day}^{-1}$) [28], and also using the upper limit of that recommended on the European Society for Parenteral and Enteral Nutrition (ESPEN) website ($125 \text{ non-protein kJ or } \sim 142 \text{ total kJ kg}^{-1} \text{ day}^{-1}$; <http://www.espen.org/npages/nespenguidelines>). Figure 1 shows estimates of energy supply in the Leuven I study expressed as a percentage of estimated basal energy requirements for both men and women. Also shown in Fig. 1 is the energy supply patients in the Leuven I study would have received using ACCP and ESPEN guidelines, all compared with average energy requirements in hospitalised patients (isoenergetic feeding). As can be seen, the average middle-aged, overweight individual in the Leuven I study received nutritional support that provided excess energy in relation to probable energy requirements. Although most of the participants in this study did not have diabetes, it is thus not surprising that 99% of them required insulin infusion at an average rate of 3 U/h to maintain near-euglycaemia [3]. We therefore believe that the patients in the Leuven I study were overfed, albeit consistent with North American and European guidelines for nutritional support.

Synthesis

The weight of available data indicates that intensified insulin treatment of the critically ill is associated with impressive reductions in mortality rate. Therefore, the value of intensive insulin treatment should not be in doubt. However, we do not believe that the data justify a glycaemic target of 6.1 mmol/l . This target is supported by a consensus statement [2], but is based almost exclusively on data from one study—Leuven I [3]. As pointed out above, the reduction in mortality reported in Leuven I was comparable to that in other studies, in spite of the fact that the blood glucose level in the control group of the Leuven I study was lower than the level in the intensive group of some of the other studies [4, 5]. Moreover, lipid control appeared to be more responsible than glucose control for the beneficial effects of intensive insulin therapy in the Leuven I study [16]. Since these are mere associations, additional research will be required—perhaps studies in which lipid levels are manipulated more directly—

before it can be known whether non-glucose effects of insulin are in fact responsible for apparent benefits of insulin. The use of PN in the Leuven I study imposes additional limitations of interpretation. Intensive insulin treatment in the Leuven I study may merely have prevented adverse effects of PN, a possibility that cannot be excluded by any post hoc analysis. Leuven I was simply conducted in too narrow a context to justify extrapolating its findings to other patient populations (i.e. those not receiving PN). Considering that in any case the Leuven I study was not designed to compare different glycaemic targets with intensive insulin treatment, judgments about whether a goal of 6.1 mmol/l will produce better outcomes than a goal of, say, 7.8 mmol/l must await the results of studies designed to answer that question.

Finally, aggressive lowering of glucose levels carries the risk of hypoglycaemia, which is potentially difficult to detect in mechanically ventilated (and in some cases presumably sedated) patients such as those in the Leuven I trial. Cryer has eloquently discussed the potential contribution of hypoglycaemia to morbidity in critically ill patients receiving insulin infusions [29]. Since hypoglycaemia is likely to be more frequent and more severe with lower targets, it seems prudent to reserve judgement until additional studies are available. Because it is clear that intensified insulin treatment (with intravenous insulin) has a favourable effect on outcomes, future studies should focus on potential differences in outcomes with different glucose targets.

Conclusions

Intensive insulin therapy in critically ill patients with hyperglycaemia reduces the mortality rate. The use of PN confounds the interpretation of some studies. Available data are insufficient to recommend specific glycaemic targets.

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Duality of interest The authors declare that there is no duality of interest associated with this paper.

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