

Clinical Potential of Insulin Therapy in Critically Ill Patients

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Abstract

Stress of critical illness is often accompanied by hyperglycaemia, whether or not the patient has a history of diabetes mellitus. This has been considered to be part of the adaptive metabolic response to stress. The level of hyperglycaemia in patients with acute myocardial infarction (MI) or stroke upon admission to the hospital has been related to the risk of adverse outcome. However, until recently, there was no evidence of a causal relationship and thus stress-induced hyperglycaemia was only treated with exogenous insulin when it exceeded 12 mmol/L (220 mg/dL). In patients with known diabetes, even higher levels were often tolerated. Recently, new data became available in support of another approach. In this review, we focus on the new evidence and the clinical aspects of managing hyperglycaemia with insulin in critically ill patients, drawing a parallel with diabetes management. Particularly, the 'Diabetes and Insulin-Glucose infusion in Acute Myocardial Infarction (DIGAMI) study' and the 'insulin in intensive care study' have provided novel insights.

The DIGAMI study showed that in patients with diabetes, controlling blood glucose levels below 12 mmol/L for 3 months after acute MI improves long-term outcome. In the recent study of predominantly surgical intensive care patients, the majority of whom did not previously have diabetes, it was shown that an even tighter control of blood glucose with exogenous insulin, aiming for normoglycaemia, dramatically improved outcome. Indeed, in this large prospective, randomised, controlled study, 1548 intensive care patients had been randomly allocated to either the conventional approach, with insulin infusion started only when blood glucose levels exceeded 12 mmol/L, or intensive insulin therapy, with insulin infused to maintain blood glucose at a level of 4.5–6.1 mmol/L (80–110 mg/dL).

Intensive insulin therapy reduced intensive care mortality by more than 40% and also decreased a number of morbidity factors including acute renal failure, polyneuropathy, ventilator-dependency and septicemia.

Future studies will be needed to further unravel the mechanisms that explain the beneficial effects of this simple and cost-saving intervention. Although available evidence supports implementation of intensive insulin therapy in surgical intensive care, the benefit for other patient populations, such as patients on medical intensive care units or hospitalised patients who do not require intensive

care but who do present with stress-induced hyperglycaemia, remains to be investigated.

With the discovery of insulin by Banting and Best in 1922, it became possible to treat patients with type 1 (insulin-dependent) diabetes mellitus, a previously lethal disorder as a result of the development of ketoacidosis. At the end of the 19th century, Claude Bernard described the link between acute trauma and the development of hyperglycaemia irrespective of underlying diabetes, which was considered to be an adaptive stress response. As in trauma, hyperglycaemia is commonly present during other types of critical illness. Until recently, treatment of hyperglycaemia during critical illness was only considered necessary when blood glucose levels became excessively elevated, a strategy primarily based on anecdotal evidence. It was only lately that evidence became available in favour of treating even moderate hyperglycaemia in critically ill patients.^[1] In this review on the potential of insulin therapy in critically ill patients, we focus on the published evidence and the clinical aspects of managing hyperglycaemia by the use of insulin. Throughout the review we draw a parallel with management of diabetes mellitus, which has been studied in much more detail.

1. Altered Glucose Regulation in Stress

The concept 'stress diabetes' or 'diabetes of injury' has been in the literature for almost 150 years. The cause of this stress-induced hyperglycaemia lays in the impact of integrated hormonal, cytokine and nervous 'counter-regulatory' signals on glucose metabolic pathways. In the acute phase of critical illness, it is assumed that increased levels of glucagon,^[2] cortisol^[3] and growth hormone jointly increase hepatic gluconeogenesis.

In addition, the catecholamines adrenaline and noradrenaline, released in response to acute injury, promote hepatic glycogenolysis.^[4] The cytokines interleukin (IL)-1,^[5,6] IL-6, and tumour necrosis factor (TNF)^[7] may directly or indirectly enhance both these hyperglycaemic responses. The regulatory

mechanisms for hyperglycaemia during protracted critical illness remain less clear. While in this more chronic phase the changes in glucagon levels are not well documented, growth hormone, cortisol, catecholamine and cytokine levels^[8] are usually decreased compared with the levels observed during the acute phase of critical illness.^[9] For detailed discussions on normal glucose regulation^[10] and mechanisms of hyperglycaemia^[11,12] we would like to refer to some excellent reviews in the literature.

2. Hyperglycaemia in the Critically Ill

In a normal individual, blood glucose levels are tightly regulated within the narrow range of 3.5–5.5 mmol/L (63–100 mg/dL). Diabetic hyperglycaemia is defined by the WHO as fasting blood glucose levels between 6.1–7 mmol/L, and fed blood glucose levels between 8.1–11 mmol/L.

Unlike the diagnostic criteria for diabetes, no clear guidelines have been set for defining hyperglycaemia in a critically ill patient. This explains the wide variations in the reported prevalence of hyperglycaemia in critically ill patients, ranging from 3–71%.^[13] Until recently, it was considered state of the art to tolerate blood glucose levels up to 12 mmol/L (220 mg/dL) in fed, critically ill patients.^[14] Motivation for treatment of blood glucose levels higher than 12 mmol/L was the occurrence of hyperglycaemia-induced osmotic diuresis and fluid shifts once glycaemia exceeds that threshold.

From the diabetes literature, it was also known that uncontrolled and pronounced hyperglycaemia predisposes to infectious complications.^[15,16] It was commonly accepted that moderate hyperglycaemia (blood glucose levels up to 12 mmol/L) in critically ill patients was beneficial for organs, such as the brain and the blood cells, that solely rely on glucose for their energy supply. This was an extrapolation from the survival response of the human body to acute injury, a concept suggested by Claude Bernard.

With the development of intensive care medicine over the last 3–4 decades, patients are able to survive conditions such as severe sepsis, multiple trauma and extensive burns. Hence, patients now frequently enter the chronic phase of critical illness.^[17] For this condition, nature possibly hasn't been able to develop survival mechanisms.

In the development of hyperglycaemia during critical illness the feeding should also be taken into account. In the pre-intensive care era, an acute insult such as a trauma or an illness was usually accompanied by temporary starvation. Hence, the body had to rely on endogenous production in order to provide the necessary nutrients for vital organs. With the advent of intensive care medicine critically ill patients are able to survive much longer. To prevent starvation when endogenous production becomes insufficient, continuous feeding has been implemented either entirely through enteral nutrition, total parenteral nutrition (TPN) or a combination of enteral and parenteral feeding. A possible drawback of this practice may be the induction or sustainment of hyperglycaemia. Similarly to diabetic patients, prolonged hyperglycaemia in the critically ill patient may lead to macro- and microvascular disease, neuropathy, increased susceptibility to infections, dyslipidaemia, and deranged inflammatory and coagulation responses.

3. Maintenance of Normoglycaemia in the Critically Ill

Recently, a large prospective, randomised, controlled trial^[1] was the first to challenge the classical dogma of beneficial stress hyperglycaemia and to examine the effect of strict glycaemic control below 6.1 mmol/L with exogenous insulin on mortality and morbidity of critically ill patients. Over a 1-year period, 1548 mechanically ventilated patients admitted to the intensive care unit (ICU) predominantly after extensive surgery or trauma, were randomly allocated to either intensive insulin therapy with blood glucose levels kept tightly between 4.5–6.1 mmol/L (80–110 mg/dL) or the conventional approach, which only recommended insulin therapy when blood glucose levels exceeded 12 mmol/L.

Strict blood glucose control below 6.1 mmol/L reduced intensive care mortality of critically ill patients by more than 40% (figure 1). The effect occurred particularly in the prolonged critically ill patient population, where mortality was reduced from 20.2% to 10.6% ($p = 0.005$). Even patients in the conventional insulin treatment schedule with only moderate hyperglycaemia (6.1–11.1 mmol/L) showed higher mortality compared with the patients in the strict glycaemic control schedule.^[18]

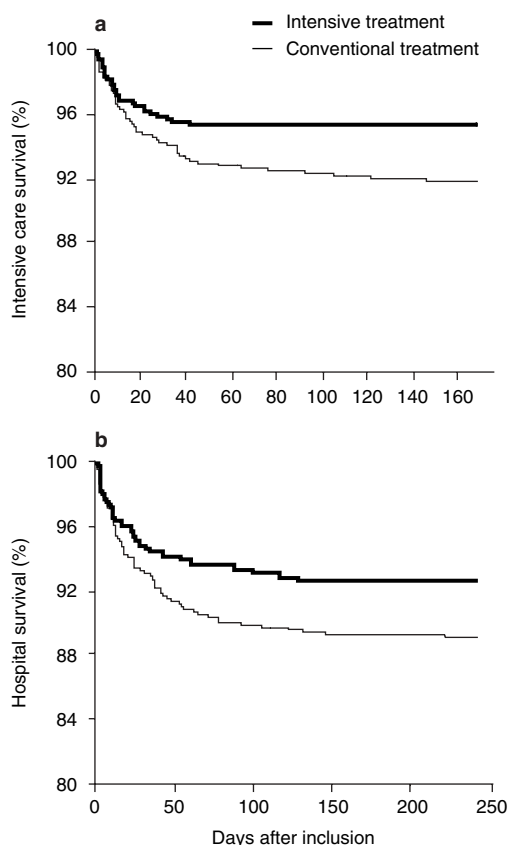


Fig. 1. Kaplan-Meier cumulative survival plots for intensive care and in-hospital survival, showing the effect of intensive insulin treatment in a study of 1548 critically ill patients. Patients discharged alive from intensive care (a) and hospital (b), respectively, were considered survivors. P-values were obtained by logrank (Mantel-Cox) significance testing. The difference between the intensive insulin group and the conventional group was significant for intensive care survival (unadjusted $p = 0.005$; adjusted $p < 0.04$) and for hospital survival (unadjusted $p = 0.01$) [reproduced from Van den Berghe et al.,^[1] with permission].

This is the first intervention since the introduction of mechanical ventilation to have such a pronounced beneficial effect on intensive care mortality. Intensive insulin therapy also had a major effect on morbidity. It decreased the duration of ventilatory support and intensive care stay, reduced the need for blood transfusions, and lowered the incidence of septicaemia and excessive inflammation. Even more striking, intensive insulin therapy caused a highly significant decrease in the development of critical illness polyneuropathy and of acute renal failure.

The exact underlying mechanisms of this dramatic improvement of outcome in the critically ill are as yet not known. In addition, it remains unclear to what extent the benefits are brought about by insulin, by the prevention of high blood glucose levels or both.

4. Complications of Deranged Glucose Regulation In Diabetes Mellitus and Critical Illness

The long-term complications of diabetes have been well described, and can roughly be classified as macrovascular, microvascular and other complications (table I).

The publication of the Diabetes Control and Complications Trial (DCCT) in 1993 settled the previously vigorous debate about whether tight glycaemic control was beneficial for individuals with type 1 diabetes. The study was powered to detect a significant difference in the rates of progression of diabetic retinopathy, which is the most prevalent complication in type 1 diabetes, but showed a highly

significant decrease in retinopathy, nephropathy, and peripheral and autonomic neuropathy.^[19] Similarly, evidence for the importance of tight glycaemic control in patients with type 2 (non-insulin dependent) diabetes mellitus became available with the publication of the United Kingdom Prospective Diabetes Study (UKPDS) in the late 1990s.^[20] This trial showed that a 0.7% decrease in glycosylated haemoglobin (HbA1c) lowered the incidence of retinopathy by 21%, microalbuminuria by 33%, cataracts by 24%, myocardial infarction (MI) by 16%, and resulted in a non-significant 5% decrease in the incidence of cerebrovascular accident. Although the UKPDS showed a trend to decreased mortality, neither study was appropriately powered to detect a significant decrease in diabetes-related mortality.

4.1 Metabolic Control and Macrovascular Disease

Patients with diabetes have a 1.5–2-fold increased risk of mortality following an acute MI compared with non-diabetic acute MI patients.^[21] Furthermore, in acute MI patients without previously diagnosed diabetes, hyperglycaemia on admission has been associated with increased volume of cardiac damage (i.e. larger infarcts), a higher incidence of cardiac failure and decreased 1-year survival.^[22] To what extent this association simply reflected the severity of illness and the accompanying stress response, or was explained by pre-existing but non-diagnosed diabetes remained unclear from these data.

A number of studies have examined the outcome benefits of tightening glycaemic control in diabetic patients with MI. The largest study, with the longest follow-up period was the DIGAMI Study (Diabetes and Insulin-Glucose infusion in Acute Myocardial Infarction). In that study, diabetic patients admitted to the hospital with an acute MI were randomly assigned to standard treatment (at the physician's discretion) or to 'intensive insulin therapy', which comprised an infusion of glucose and insulin, started as soon as possible and continued for 48 hours. Thereafter, the intensive insulin therapy patients were submitted to a 'stricter' blood glucose control

Table I. Long-term complications of diabetes mellitus

Macrovascular	Myocardial infarction
	Stroke
	Peripheral vascular disease
Microvascular	Nephropathy
	Neuropathy
	Retinopathy
Other	Infections
	Hepatic steatosis
	Cholelithiasis
	Cataract, etc.

regimen (below 12 mmol/L) with subcutaneous insulin continued for at least 3 months after discharge. Patients in the intensive treatment arm had improved 30-day and long-term survival (29% relative risk reduction at 1 year).^[23,24] Also, there was a significant decrease in re-infarction and new cardiac failure.^[25] A meta-analysis of all published randomised trials investigating the effect of glucose-insulin-potassium (GIK) infusion in previously non-diabetic individuals with acute MI supports the concept that this intervention indeed may be life-saving.^[26]

For other disease states such as cerebrovascular ischaemic insults, adverse outcome was shown to be significantly related to on-admission hyperglycaemia. Indeed, high blood glucose levels were associated with increased mortality and poorer neurological recovery. Also in patients with traumatic head injuries, postoperative hyperglycaemia was found to be an independent predictor of mortality.^[27] Again, these studies did not specifically investigate the effect of lowering glycaemia and thus did not provide conclusive evidence as to whether the degree of hyperglycaemia simply reflects the severity of illness or is actually contributing to adverse outcome of neurological insults. The only intervention study in patients with stroke, the Glucose-Insulin in Stroke Trial (GIST) examined the effect of glucose-insulin treatment. This trial, in which acute stroke patients were allocated to standard therapy or a 24-hour infusion of GIK, did not significantly lower glycaemia or mortality.^[28] It should be noted that studies on the benefits of GIK infusions in either cardiac or neurological ischaemic insults never targeted normoglycaemia.

4.2 Metabolic Control and Microvascular Disease

The pathophysiology of diabetic^[29] and critical illness^[30] nephropathy is substantially different. Diabetic nephropathy is mainly a glomerular disease with substantial thickening of the basolateral membrane, eventually leading to glomerulosclerosis. On the other hand, renal failure in critically ill patients is most commonly due to acute tubular necrosis.

Different factors play a part in the development of this form of acute renal failure:^[30] decreased glomerular permeability, back-leak of glomerular filtrate, tubular obstruction, and medulla hypoperfusion and ischaemia. The only therapeutic option at the present time is bridging time to spontaneous recovery by extracorporeal haemofiltration or dialysis, with the continuous veno-venous mode being the preferred method for unstable critically ill patients.^[31] Hence, preventive strategies are crucial and these include maintaining or optimising renal perfusion, diligence with monitoring of nephrotoxic therapies, such as aminoglycosides, and limiting the use of non-ionic radiocontrast materials. Evidence for specific preventative measures for acute renal failure in the critically ill patient was not available until the recently published study of intensive insulin therapy.^[1] This large, prospective, randomised trial revealed a 42% reduction in the occurrence of acute renal failure requiring extracorporeal replacement therapy.

The DCCT trial revealed that better metabolic control of type I diabetes was associated with a reduction in the development of retinopathy, without a cut-off value for blood glucose level below which no further risk reduction occurred.^[32] There are no data on the incidence of retinopathy in critically ill patients.

4.3 Metabolic Control and Neuropathy

In the diabetic patient, distal sensory neuropathy with the classic stocking distribution is the most frequent presentation of neuropathies.^[33] It starts gradually as a sensory neuropathy, which over time can evolve to some motor dysfunction with muscle wasting.

A wide array of factors are involved in the pathogenesis of diabetic neuropathy.^[34,35] It comprises, amongst others, elevated oxidative stress with increased reactive oxygen species and decreased scavengers, microangiopathy with platelet activation and endothelial cell dysfunction, changes in the polyol pathway, and the formation of advanced glycosylation end products.

The DCCT^[36] and UKPDS^[20] trials showed that tight glycaemic control lowers the incidence of diabetic polyneuropathy. This was independent of the method to achieve stable glycaemia.

Chronically critically ill patients often develop a diffuse axonal polyneuropathy.^[37] It presents as a tetraparesis with muscle atrophy but the diagnosis should be confirmed by electromyography. In most patients, the course is self-limited and good recovery should be expected if the underlying critical illness resolves. However, this critical illness polyneuropathy severely impairs weaning from the ventilator and early mobilisation.^[38] Factors that are known to contribute to the development of critical illness polyneuropathy include sepsis, the use of high-dose corticosteroids and the use of neuromuscular blocking agents. However, the exact pathogenesis is not understood and, until recently, specific prevention of or treatment for critical illness polyneuropathy was unavailable.^[39] Bolton described a strong link between the risk of critical illness polyneuropathy and increased blood glucose levels and decreased serum albumin levels, both metabolic manifestations of multiple organ failure and sepsis. Sepsis, and the accompanying release of cytokines, was considered to be the causal factor.^[40] Cytokines may indeed induce microangiopathy which may play a role, as in diabetic polyneuropathy.

The study by Van den Berghe et al.^[1] showed an important preventive effect of strict glycaemic control with insulin on the occurrence of critical illness polyneuropathy, which was associated with a decrease in duration of mechanical ventilation of protracted critically ill patients.

4.4 Metabolic Control and Infections

It has been known for a long time that hyperglycaemia of diabetes predisposes to infection.^[15] Possible mechanisms include the hyperglycaemia-induced inhibition of IL-1 release from macrophages and of the release of oxygen radicals from neutrophils.^[41] Hyperglycaemia also impairs phagocytosis by the macrophages.^[42,43] Importantly, the impairment of leucocyte oxidative burst and phagocytotic

activity could be improved by tight glycaemic control.^[44,45]

In critically ill patients with preexisting diabetes, such as those after open-heart surgery, an association between higher risk of infectious complications^[46] and blood glucose levels higher than 11 mmol/L (>200 mg/dL) has been documented. In a follow-up study, Furnary et al. showed that continuous intravenous insulin infusion reduced the incidence of post-cardiac surgery deep sternal wounds (0.8 vs 2% for subcutaneous insulin injections).^[47] Uncontrolled hyperglycaemia in burn patients also has been associated with failure of skin graft take and outcome.^[48] Again, the causal link between hyperglycaemia and higher risk of serious infections, regardless of a history of diabetes, was only provided recently by a large prospective, randomised, controlled trial.^[1] Indeed, strict maintenance of normoglycaemia using exogenous insulin during critical illness was found to reduce the incidence of bacteraemia to almost half and to largely prevent sepsis-associated mortality.

4.5 Metabolic Control and Dyslipidaemia

Insulin resistance and type 2 diabetes are associated with significant changes in the lipid metabolism, hallmarked by a proatherogenic lipoprotein profile of increased low-density lipoprotein particles, which are thought to be more atherogenic, increased very low-density lipoprotein and triglycerides, together with decreased high-density lipoproteins.^[49]

The increased free fatty acid flux towards the liver may lead to hepatic steatosis.^[50] The free fatty acids can be derived from triglyceride hydrolysis in the peripheral adipocytes, from dietary sources and through endogenous synthesis. The latter may be of significant importance in TPN-fed critically ill patients. Carbohydrate overfeeding results in a saturation of the hepatic glycogen stores, which shifts acetyl-CoA into the lipogenic pathway.^[51,52] In the past these practices frequently lead to the 'fatty liver syndrome'.

Contrary to the situation in the diabetic patient, the lipaemic profile in the critically ill patient con-

sists of high triglyceride levels combined with low cholesterol levels.^[53] This hypocholesterolaemia apparently relates to the severity of illness but the exact cause remains unclear.^[54] The increased risk of septic shock in patients with hypocholesterolaemia may be related to decreased endotoxin transport in the serum by lipoproteins^[55] and hence infusions with high-density lipoproteins could be a treatment.^[56] As the pathophysiology of the divergence of cholesterol and triglyceride levels during critical illness is largely unknown,^[57,58] the impact of feeding and strict glycaemic control with insulin on these lipids is worth investigating.

4.6 Metabolic Control and Inflammation/Coagulation

As mentioned in section 4.4, diabetes is a condition of immunosuppression with impaired leucocyte and macrophage function. It has also been clearly shown that intensive insulin treatment in critically ill patients prevented excessive inflammation.^[1] This was reflected in a reduced duration of leukocytoses/leucopenia and hypo-/hyperthermia. Intensive insulin treatment also suppressed the acute phase responses of C-reactive protein and mannose-binding lectin.^[59] The exact underlying mechanisms of insulin-induced anti-inflammatory effects have not yet been unravelled,^[60] but it has been suggested that insulin may suppress the secretion and antagonises the harmful effects of TNF α ,^[61,62] macrophage migration-inhibitory factor^[63] and superoxide anion.^[64]

Furthermore, diabetes is a hypercoagulable state,^[65] leading to an increase in thrombotic mortality (acute MI, peripheral vascular disease and stroke).^[66] Putative causes for this state include vascular endothelium dysfunction,^[67] increased blood levels of several clotting factors,^[68,69] elevated platelet activation^[70,71] and inhibition of the fibrinolytic system.^[69] Levels of the anticoagulant protein C are also decreased.^[72] In critically ill patients, a procoagulable state is present, most dramatically so in 'disseminated intravascular coagulation' (DIC).^[73] It involves a global activation of haemostasis and the formation of fibrin within the circulation, resulting in a widespread microvascular throm-

bosis with multiple organ failure. Amongst triggers such as major trauma, hypovolaemic shock, obstetric complications, malignancies and ABO-incompatible blood transfusions and sepsis, the latter appears to be the most prominent one. In a recent study by Bernard et al.^[74] it was shown that the administration of activated protein C (drotrecogin alfa) to septic patients improves the 28-day survival by 6%.

In view of the powerful preventive effect of intensive insulin therapy on septicemia, multiple organ failure and mortality,^[1] the effect of this simple and cheap metabolic intervention on the balance between coagulation and fibrinolysis in the critically ill should be investigated.^[75,76]

5. Hyper-, Normo- or Hypocaloric Nutrition?

It has been well documented that providing hypercaloric nutrition to critically ill patients, 'hyperalimentation' (35–40 kcal/kg),^[77] can lead to infections and severe metabolic complications. These range from hyperglycaemia, hypertriglyceridaemia and azotaemia to hepatic steatosis, fat-overload syndrome and hypertonic dehydration.^[78] Since the introduction of more accurate means to estimate energy expenditure and a cautious approach towards obese or highly oedematous patients, serious complications of feeding have been dramatically reduced.

On the other hand, in order to decrease hyperglycaemia and hence infectious complications, McCowen et al.^[79] evaluated the efficacy of hypocaloric TPN feeding (14 kcal/kg) compared with a standard weight-based regimen (18 kcal/kg). Contrary to expectation, the hypocaloric TPN did not lower the incidence of hyperglycaemia or infections. Caloric restriction only seems to be effective in conjunction with a hyperproteinic approach (about 1.8g protein per kg ideal bodyweight [IBW] compared with 1.2 g/kg IBW).^[80] This was also shown in a hypocaloric parental regimen with 2g protein/kg IBW in patients with morbid obesity.^[81] Overall, however, there doesn't appear to be a clear-cut benefit of hypocaloric over normocaloric nutrition. This might be

attributed to the ineffectiveness of hypocaloric nutrition to lower blood glucose levels.

Potential benefit of hypercaloric feeding combined with insulin infusions to enhance the anabolic effects of insulin still has to be assessed. This strategy would be quite similar to GIK infusions, in which high doses of insulin (0.1–1 IU/kg/h) and glucose (30–80 g/h) are combined. However, so far these GIK infusions should be seen as a distinct intervention, as infusion of GIK is not targeted to maintain normoglycaemia. The primary aim of GIK is to enhance myocardial metabolism of glucose instead of fatty acids when oxygen supply is compromised.

6. Does a History of Diabetes Imply a Specific Metabolic Management During Critical Illness?

The effect of intensive insulin therapy on morbidity and mortality of critically ill patients was equally present among those with and without previously diagnosed diabetes.^[1] Independent of a history of diabetes, blood glucose control during intensive care is best achieved with a continuous insulin infusion and oral agents should be discontinued during critical illness. As nutrition of critically ill patients is continuous in nature, either with TPN or with a combination of parenteral and enteral feeding, it is indeed quite logical to also administer insulin in a continuous fashion. In addition, intravenous administration is also more reliable and consistent than subcutaneous injections. Titrating a continuous insulin infusion is preferred to sliding scales as the former not only provides a baseline insulin level, but is also more easily and precisely titrated in response to the actual blood glucose levels. Insulin has a half-life of 3 minutes, which allows rapid cessation of effect if the patient develops hypoglycaemia.

This risk of hypoglycaemia is a major concern on intensive insulin therapy during critical illness. Clinical symptoms of the autonomic response (sweating, tachycardia, tremor) and central nervous symptoms like dizziness, blurred vision, altered mental acuity, confusion and eventually convulsions are often masked by concomitant diseases and by

inherent intensive care treatments such as sedation and mechanical ventilation. Brain damage could be an irreversible complication of severe hypoglycaemia (<1.67 mmol/L). Another insidious complication of hypoglycaemia is the induction of cardiac arrhythmias ranging from dispersed QT-segments^[82] and sinus bradycardias^[83] to ventricular tachycardias.^[84] To prevent hypoglycaemia in the critically ill, insulin should be administered together with carbohydrates, either dextrose or feeds, and blood glucose levels should be measured frequently and regularly. In the study by Van den Berghe et al.^[1] blood glucose levels were measured 1–2 hourly during the first 12–24 hours of the patient's admission to the ICU. Once the targeted blood glucose level was reached on a stable insulin dose, measurements were scaled down to every 4 hours. However, hypoglycaemia usually occurred after the first week of ICU stay when blood glucose levels were stable. Inadequate insulin dose reduction during interruption of enteral feeding was often the precipitating factor for the hypoglycaemias. Evidently, the hazard of hypoglycaemia warrants a strict and detailed insulin titration protocol,^[85] combined with sufficient training of the nursing and medical staff.

7. Focus on Insulin or Glycaemic Control?

Whether the effects of intensive insulin therapy during critical illness^[1] were due to maintenance of normoglycaemia or rather to a direct insulin effect remains speculative. It is conceivable that insulin may have had a direct role in the functional improvement of the insulin-sensitive organs. In a normal individual, the bulk of the insulin-stimulated glucose uptake is situated in the heart and skeletal muscles. Also, muscle catabolism is aggravated in hyperglycaemic conditions. This could partially explain the beneficial effects of intensive insulin therapy on duration of mechanical ventilation of the critically ill patients in the intensive insulin therapy trial.

The liver, the major site for gluconeogenesis, is another important insulin-sensitive organ that could be involved in the improved outcome of the patients

intensively treated with insulin. However, a recent study showed that serum and gene expression levels of insulin-like growth factor binding protein-1 (IGFBP-1) and gene expression levels of phosphoenolpyruvate carboxykinase (PEPCK), the rate-limiting enzyme in the gluconeogenesis, are not regulated by insulin. This may indicate that controlling gluconeogenesis was not the major factor in bringing about normoglycemia with exogenous insulin in the critically ill.^[86]

Another major insulin-responsive organ is the adipose tissue. The increased serum free fatty acid and triglyceride levels present during critical illness and the relative accruelement of adipose tissue as compared with lean body mass (muscle and bone tissue) with feeding in the chronically critically ill patient, jointly point to a deranged lipid metabolism. The effect of intensive insulin therapy on this imbalance remains to be investigated.

The positive effects of intensive insulin therapy on kidney function and the decreased incidence of critical illness polyneuropathy may in part be explained by maintenance of normoglycaemia, as both organs are supposedly, at least in part, insulin-insensitive. Here, although on a totally different time scale, a parallel with type 2 diabetes emerges. Long-term studies have indeed shown that meticulous blood glucose control decreases the incidence and the severity of diabetic nephropathy and the onset of diabetic neuropathy, and 'glucose-toxicity' may be the underlying mechanism. However, the rapid onset of critical illness polyneuropathy and of acute renal failure suggest that other factors, which predispose the critically ill to the toxic effects of hyperglycaemia on neurons and kidneys, must play a role.

Similarly, avoiding hyperglycaemia may be important for prevention of bloodstream infections. The suppression of the immune system conceivably results in increased risk of postoperative infections, as discussed in section 4.4.

However, the exact underlying mechanisms of the clinical benefits of intensive insulin therapy in critically ill patients remain at this stage unknown. Future clinical and experimental studies will un-

doubtedly provide the answer to this fascinating pathophysiological question.

8. Conclusion

In the last few years a renewed interest in the potential of insulin in the treatment of 'stress hyperglycaemia', both in diabetic and non-diabetic patients, has emerged. Evidence in favour of better glycaemic control (below 12 mmol/L) during serious illnesses such as MI and stroke was generated by the DIGAMI and the GIST studies. In a recent study, of which the goal was even more stringently aiming for normoglycaemia (4.5–6.1 mmol/L) with exogenous insulin, a dramatic decrease in mortality and morbidity was demonstrated.

A rough calculation of the financial implications of the demonstrated reduction in ICU stay with intensive insulin therapy, brings the yearly cost saving to at least \$US40 000 (2001 values) per ICU bed, which is likely to be an underestimation as it does not take into account the reduced need for expensive treatments such as dialysis, transfusion and antibacterials.

Future studies will be needed to assess the real impact on health economy and to further unravel the underlying mechanisms of this simple, cheap but highly effective intervention. Furthermore, the benefit for other patient populations, such as patients on medical ICUs or hospitalised patients who do not require intensive care but who do present with stress-induced hyperglycaemia, remains to be investigated.

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