Clinical benefits of tight glycaemic control: effect on the kidney

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Introduction

Acute kidney injury is a frequent and life-threatening complication of critical illness. Prevention of this condition is crucial. Two randomized single center trials in critically ill patients have shown a decrease in acute kidney injury by tight glycaemic control, an effect that appears most pronounced in surgical patients. Subsequent randomized trials did not confirm this renoprotective effect. This apparent contradiction is likely explained by methodological differences between studies, including different patient populations, insufficient patient numbers, comparison with a different control group, use of inaccurate blood glucose analyzers, and differences in the degree of reaching the target blood glucose level. The optimal glycaemic target for renoprotection in critical illness remains to be defined. Possible mechanisms underlying the renoprotective effect of tight glycaemic control are prevention of glucose overload and toxicity and the associated mitochondrial damage, an anti-inflammatory or anti-apoptotic effect, prevention of endothelial dysfunction, and an improvement of the lipid profile.

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criteria for classification of AKI. At present, this multilevel scoring system, based on changes in serum creatinine and/or in urine output, has been validated in multiple clinical studies. Compared to patients without AKI, there is a stepwise increase in the risk of death, going from RIFLE-Risk to RIFLE-Injury to RIFLE-Failure. As treatment of AKI is largely supportive, prevention is crucial. At present, no pharmacological intervention has demonstrated a protective effect on kidney function in critically ill patients and maintaining adequate hydration and haemodynamics and avoiding nephrotoxic substances remain the mainstay in prevention of AKI.

About one third of patients with diabetes mellitus develop kidney disease and diabetes is the leading cause of end-stage renal disease in developed countries. The mechanism of diabetic nephropathy is incompletely elucidated. As well hemodynamic, metabolic and genetic factors are thought to be involved. The role of strict glycaemic control in the management of diabetes has recently been questioned after three large randomized trials found no effect on macrovascular disease in patients with risk factors. One of these trials was even prematurely stopped because of an increased mortality. However, previous randomized trials have clearly shown a protective effect of strict glycaemic control on the development and progression of diabetic microangiopathy including nephropathy and also one of the recent studies focusing on macrovascular complications, established a reduction in the incidence of nephropathy with more strict glucose control.

Patients in the ICU commonly develop hyperglycaemia, the so-called stress-induced hyperglycaemia, which is directly associated with adverse outcomes, including kidney dysfunction. Indeed, several observational studies found an association between pre- or intraoperative hyperglycaemia and postoperative AKI after cardiac surgery, between hyperglycaemia at cardiac catheterization and contrast nephropathy, between hyperglycaemia during total parenteral nutrition and the development of AKI and between hyperglycaemia and glomerular filtration rate (GFR) in brain dead organ donors. The induction of diabetes or acute hyperglycaemia in animals also increases the susceptibility to renal ischemia-reperfusion injury.

In the past, stress-induced hyperglycaemia was interpreted as a beneficial metabolic adaptation and was not treated unless excessive (>200 mg/dl [11.1 mmol/l]). This dogma was challenged by two single center randomized trials (the Leuven studies) showing a beneficial effect of tight glycaemic control (TGC) with intensive insulin therapy (IIT) on morbidity and/or mortality of critically ill patients. After these positive studies, many centers worldwide adopted IIT as part of their usual care, and this treatment was implemented in several guidelines. Subsequent trials, assessing the external validity of the results obtained in Leuven, showed conflicting results, resulting in a lively debate.

This chapter aims to give an overview of the studies evaluating the effect of glycaemic control on kidney function in critical illness, as well as a discussion of potential underlying mechanisms.

Clinical studies

The first study that investigated the effects of IIT in critical illness was performed in Leuven in a predominantly surgical intensive care unit (ICU) and randomized 1548 patients to TGC (target 80–110 mg/dl [4.4–6.1 mmol/l]) or conventional glucose management. In the conventional group, insulin was only initiated when blood sugar levels exceeded 215 mg/dl (11.9 mmol/l), and insulin infusion was stopped when glycaemia dropped under 180 mg/dl (10 mmol/l). Mean morning blood glucose was 153 mg/dl (8.5 mmol/l) in the group with TGC. Mortality was decreased by 42% (from 8 to 4.6%; \(P < 0.04\)) by TGC and also morbidity was significantly reduced, including a decreased incidence of renal impairment. More specifically, both the number of patients with peak plasma creatinine of >2.5 mg/dl [220 \(\mu\)mol/l] or doubling of the admission serum creatinine, and the need for renal replacement therapy (RRT) were significantly lowered (respectively from 12.3% to 9.0%, \(P = 0.04\) and from 8.2% to 4.8%, \(P = 0.007\)).

Subsequently, the same investigators conducted a similar randomized trial in their medical ICU. Glycaemic target in both groups was the same as in the previous trial. Mean morning blood glucose decreased from 153 mg/dl (8.5 mmol/l) in the group with TGC to 111 mg/dl (6.2 mmol/l) in the group with IIT. In the intention-to-treat group of 1200 patients, mortality was unaffected, but
there was significantly less morbidity, with a reduced incidence of new onset kidney injury (defined as either a doubling of the admission serum creatinine or a peak serum creatinine of >2.5 mg/dl [220 μmol/l]) (decrease from 8.9% to 5.9%, $P = 0.04$). The need for RRT was not significantly affected.\textsuperscript{33}

A more detailed analysis of the renoprotective effect of TGC was performed by secondary analysis of the two Leuven studies using a RIFLE classification system with admission creatinine as baseline. In this analysis patients with pre-admission end-stage renal disease were excluded. The outcome parameters were RIFLE-Risk (peak/admission creatinine between 1.5 and 1.99), RIFLE-Injury (peak/admission creatinine ratio between 2 and 2.99), RIFLE-Failure (peak/admission creatinine ratio $\geq 3$), oliguria (daily urine output of $<400$ ml at any ICU day), need for RRT or AKI (any of the adverse renal outcomes). The incidence of all these adverse renal outcomes was significantly higher in the medical than in the surgical patients. In the pooled database IIT significantly reduced the incidence of both RIFLE-Injury (6.1 → 3.0%; $P = 0.03$) and RIFLE-Failure (3.1 → 1.5%; $P = 0.005$). The renoprotection was more pronounced in the surgical subgroup, where there was also a significant decrease in oliguria (5.6 → 2.6%; $P = 0.004$), of the need for RRT (7.4 → 4.0%; $P = 0.008$) and of the combined endpoint of AKI (13.7% → 10.0%; $p = 0.03$). In the medical patients only the combined incidence of RIFLE-Injury and RIFLE-Failure was significantly reduced (9.2% → 6.0%; $p = 0.04$). Compared with the surgical patients, the medical patients were more severely ill on admission with, in particular, a significantly higher admission serum creatinine. The use of this (already increased) admission creatinine to define the RIFLE criteria explains why the need for RRT (17%) was much higher than the incidence of RIFLE-Failure (3%). Amongst the medical patients that required RRT, 42% did so within the first 2 days after ICU admission. After exclusion of 16 surgical and 85 medical patients requiring early RRT, the effect of TGC on the need for RRT became statistically significant (8.8% → 6.7%; $p = 0.05$).\textsuperscript{46} This underscores the fact that TGC with IIT is a protective strategy that cannot prevent kidney damage that is already present on admission. Independent of randomization, the incidence of RIFLE-Injury or Failure was lowest (4%) in patients with a mean blood glucose $<110$ mg/dl (6.1 mmol/l), compared to 6.3% in patients with mean blood glucose levels of 110–150 mg/dl (6.1–8.3 mmol/l) and 8% in those with mean blood glucose above 150 mg/dl (>8.3 mmol/l) ($p = 0.0009$). This underlies the importance of strict glycaemic control in achieving renoprotection.\textsuperscript{49,50}

Two observational studies investigated the effect of implementing TGC on the incidence of AKI. Krinsley et al. studied 1600 consecutive patients in a mixed medical/surgical ICU. In this cohort, the incidence of kidney injury (defined as serum creatinine >2.5 mg/dl [220 μmol/l] or a doubling of the admission creatinine) decreased by 75% after implementation of TGC.\textsuperscript{51} Lecomte et al. studied 1050 patients undergoing on-pump cardiac surgery. The number of patients reaching the RIFLE criteria was significantly reduced from 60.4% to 46% ($p = 0.001$) after institution of the TGC protocol, a difference that was mainly attributed to a reduction of RIFLE-Injury and RIFLE-Failure.\textsuperscript{52} Obviously, these implementation studies have limitations by the non-randomized design and the use of historical controls.

Subsequent randomized controlled trials, trying to confirm the benefit of TGC in other centers, have shown conflicting results.\textsuperscript{39–42} Their general outcome will be discussed in other chapters of this issue. The effect on kidney function has only been reported in three studies. The VISEP (Volume substitution and Insulin therapy in Severe Sepsis) was a multicenter four-arm study designed to investigate both two choices of resuscitation fluid and the efficacy and safety of IIT in 537 patients with severe sepsis. The insulin arm was stopped prematurely, because the risk of hypoglycaemia was considered too high. Renal morbidity was defined as acute renal failure (at least doubling of baseline creatinine) or need for RRT. In these severely ill patients, neither of these outcome parameters was significantly affected by the intervention.\textsuperscript{39} Two single center randomized trials, conducted in a mixed ICU and including respectively 532 and 504 patients, also could not establish an effect of TGC on the incidence of AKI or the need for RRT.\textsuperscript{40,41}

The NICE-SUGAR (Normoglycaemia in Intensive Care Evaluation and Survival Using Glucose Algorithm Regulation) trial was a trial designed to assess the effectiveness of tight glycaemic control “in the real world”. This multicenter trial was conducted in a mixed (medical-surgical) ICU population, and compared TGC with a target of 81–108 mg/dl (4.5–6 mmol/l) with a more liberal glucose control (target glycaemia $\leq 180$ mg/dl [10 mmol/l]). 6104 patients were included. Mean morning
blood glucose levels decreased from 145 mg/dl (8.1 mmol/l) in the liberal glucose control group to 118 mg/dl (6.6 mmol/l) in TGC group. Unlike the Leuven studies, NICE-SUGAR investigators found an increased mortality risk in the intensively treated group (90 day mortality 27.5% vs. 24.9% in the control group; $P = 0.02$). Excess mortality was attributed to cardiovascular causes, but it remains unclear what triggered this. Renal outcome was not different, with both incidence and duration of RRT being similar in both groups. No information was given concerning milder forms of renal injury.43

A meta-analysis, conducted before the NICE-SUGAR results were available, studied the effect of TGC on need for renal replacement therapy. Nine trials were included (including 2 small surgical studies, 3 abstracts and 1 unpublished manuscript). No difference was found between the two groups.53

How to explain these apparent conflicting results between the Leuven and the other trials? First, it should be emphasized that the effect of TGC on kidney function was a secondary endpoint in all randomized trials, and none of the studies was adequately powered to show or exclude such an effect. The Leuven studies have proven the concept that TGC can affect mortality and morbidity, including kidney injury, of critically ill patients compared with a conventional approach where hyperglycaemia was only corrected above 200 mg/dL. The conflicting results in the other randomized trials can be explained by differences in the design and particularly in the execution of the TGC. Design differences are mainly related to the type of patients included (surgical versus medical, severe sepsis versus general critical illness) and to the level of glycaemic control in the control group, that e.g. in NICE SUGAR was much lower than in the Leuven studies. Differences in the execution of TGC relate to difference in (the reliability of) the devices used to measure blood glucose level,54 differences in blood sampling (arterial versus capillary), differences in achieving the target blood glucose level, the degree of overlap between the intervention and the control group and differences in the experience of the nursing staff.48 Recent evidence suggests that glucose variability might even be more important than the mean blood glucose level.55–57

Animal data

Because of the difficulty to dissociate the effect of insulin from that of glucose control in the clinical setting, blood glucose and insulin levels were manipulated independently in a burn-injured parenterally fed rabbit model of critical illness. After suppression of endogenous insulin production by alloxan, rabbits were randomly allocated to four study groups: normal insulin-normoglycaemia, high insulin-normoglycaemia, normal insulin-hyperglycaemia or high insulin-hyperglycaemia. This model confirmed the survival benefit and the renoprotective effect of TGC and demonstrated the deleterious effect of high blood glucose levels on the kidney, irrespective of the insulin level.58

Renoprotection by glycaemic control with insulin during critical illness: how does it work?

A first question is whether the renal protection results from prevention of hyperglycaemia or from a direct effect of insulin. A pooled analysis of the Leuven studies showed that both glucose and insulin levels were higher in patients developing AKI, pointing to a predominant role of glucose normalization in determining outcome.49,50 The association between insulin levels and outcome likely reflects a more pronounced insulin resistance in sicker patients, rather than a deleterious effect of hyperinsulinaemia per se. The importance of the normalization of glycaemia was confirmed in the previously mentioned animal model of critical illness, where normoglycaemia decreased kidney injury whereas hyperinsulinaemia did not protect the kidney.58

IIT could have an indirect renoprotective effect by diminishing the incidence of sepsis and, consequently, septic AKI. Although in the surgical Leuven study bacteraemia was decreased by TGC,32 this was not confirmed in the medical study, with many patients being septic already on admission.33 A direct effect on the kidney seems therefore more plausible.

The pathophysiology of AKI is complex and not fully understood. Research points to a complex interplay between ischaemia-reperfusion and inflammation affecting both endothelial and tubular epithelial cells and leading to oxidant injury, mitochondrial dysfunction, and cell death by
apoptosis/necrosis. Most of these pathways are also involved in the development of diabetic complications and are affected by hyperglycaemia and insulin.

**Prevention of oxidative and nitrosative stress**

Oxidative stress is considered a key factor in the pathogenesis of both diabetes complications (including diabetic nephropathy) and AKI. Cells that do not rely on insulin for glucose uptake and are exposed to elevated blood glucose levels, normally decrease the transport of glucose across the plasma membrane into the cytosol by downregulating facilitative glucose transporters. In critical illness however, glucose transporters have shown to be upregulated. Hence, critically ill patients may be more vulnerable to acute hyperglycaemia. In these patients hyperglycaemia will induce cellular glucose overload with concomitant increased formation of reactive oxygen species (ROS) that may be produced both in the mitochondria and the cytosol. These ROS cause oxidation of macromolecules including proteins, lipids, carbohydrates and DNA and result in cellular damage. Superoxide reacts with NO to form peroxynitrite, another reactive species. In critically ill patients, ischaemia-reperfusion- or sepsis-induced oxidative stress and upregulation of inducible NO synthase (iNOS) may further amplify the generation of reactive species. A recent animal study indeed found more severe kidney damage and more evidence of oxidative stress if renal ischaemia-reperfusion was preceded by the induction of hyperglycaemia. In a subpopulation of the surgical Leuven study including patients with prolonged ICU stay, elevated NO levels appeared to be an independent predictor of AKI and were decreased by TGC.

**Mitochondrial dysfunction**

The mitochondria seem particularly vulnerable to glucose toxicity. Indeed, in the surgical Leuven study ultrastructural abnormalities of mitochondria in human liver biopsies taken immediately postmortem could be prevented by strict glycaemic control, which also improved the activity of respiratory chain complex I and IV. Similar results were seen in the renal cortex, in hepatocytes and cardiomyocytes of critically ill rabbits. In this rabbit experiment, as already stated before, hyperglycaemia induced an increase of serum creatinine. This increased serum creatinine correlated with cortical glucose levels, whereas mitochondrial respiratory chain activities showed an inverse correlation with serum creatinine and with cortical glucose, pointing to a role of cellular glucose overload in the induction of mitochondrial dysfunction and kidney injury.

**Anti-inflammatory effects**

Inflammation is an important contributor to the development of AKI. Hyperglycaemia has been shown to have pro-inflammatory effects whereas insulin has anti-inflammatory effects. In the surgical Leuven study, TGC with IIT lowered C-reactive protein (CRP) levels, independently of the prevention of infections. However, no effect was observed on a series of cytokines. The effect on CRP was confirmed in a rabbit model of critical illness. In the medical Leuven study, the effect on CRP was only present in the long-stay patients.

**Prevention of endothelial dysfunction**

The role of the endothelium in the pathogenesis of both diabetes complications and AKI is increasingly recognized. In a subgroup of the surgical Leuven study with prolonged ICU stay, TGC with IIT has shown to improve endothelial function, reflected by reduced circulating ICAM-1 and E-selectin levels. In this subgroup patients with AKI had higher levels of ICAM-1 and E-selectin which may point to an important contribution of endothelial activation/damage to AKI. However, higher levels of adhesion molecules in AKI may also have resulted from decreased clearance. In a rabbit model of critical illness, endothelial function, measured by endothelium-dependent relaxation of isolated aortic rings, was better preserved in the presence of normoglycaemia vs. hyperglycaemia, irrespective of insulin levels.
Antiapoptotic effects

Evidence suggests that apoptosis is a major mechanism of cell death in ischaemic AKI.59,62 The role of apoptosis in septic AKI is less clear.64 In vitro experiments in human proximal tubular epithelial cells show an induction of apoptosis by exposure to high glucose concentrations.80–82 In contrast, insulin can exert antiapoptotic effects through the PI3-kinase-Akt pathway.83 A renal ischaemia-reperfusion model in diabetic rats demonstrates renoprotection and inhibition of apoptosis with insulin pretreatment.84

Improvement of lipid profile

Critical illness is associated with disturbances in lipid metabolism. Besides achieving normoglycaemia, IIT has shown to improve the lipid profile of critically ill patients.85 A post hoc analysis of the Leuven studies suggests that an improved lipid profile might contribute to the renoprotective effect.49 This is supported by an animal model of renal ischaemia-reperfusion, administering HDL before ischaemia. Reduced endothelial activation and protection against oxidative stress might play a role.86

Summary

In summary, the Leuven studies have shown that glycaemic control can protect the kidney of critically ill patients on condition that the intervention is started early in the course of the disease process (as is mostly the case in surgical patients), that the intervention reaches the preset targets and that a reliable method is used to measure blood glucose and to administer insulin. Subsequent randomized trials could not confirm the renal benefit, which is probably related to differences in the design and the execution of the studies. Future trials, taking into account the above mentioned requirements, should establish the optimal glycaemic target and the patient population benefiting most from TGC. These trials should also establish the optimal indicator to evaluate the quality of blood glucose control.

Practice points

- Hyperglycaemia in critically ill patients is associated with AKI.
- Prevention of excessive hyperglycaemia in critical illness appears renoprotective, although study results are conflicting.
- The evidence for a renoprotective effect of tight glycaemic control is strongest for patients admitted after elective major surgery.
- Differences between trials may be explained by methodological differences, including the inclusion of different types of patients, a different glucose target in the control group, the use of inaccurate glucose analyzers and inadequate sampling sites and the degree of success in reaching the glycaemic target.

Research agenda

- Further research is needed to identify the optimal glycaemic target in specific patient populations, and to improve practical tools for implementation in clinical practice.
- Mechanisms involved in renoprotection by glycaemic control/insulin administration should be further clarified.
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Conflict of interest

We declare to have no conflict of interest.

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