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Is hypoglycaemia dangerous?

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Tight glycaemic control (TGC) for patients treated in an intensive care unit ICU is associated with an increased risk for hypoglycaemia. Since hypoglycaemia mainly occurs in the sickest patients, no matter whether TGC is applied or not, it might be a marker for severity of illness or a harmful event in itself. Furthermore, it remains a matter of debate whether harmful effects of hypoglycaemia outbalance the clinical benefits of TGC. This review focusses on the clinical manifestations of hypoglycaemia in the critically ill and highlights its potential short- and long-term consequences specifically concerning neurocognitive function.
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Is hypoglycaemia dangerous? This question appears to be answered effortlessly on first sight, but indeed, only on first sight. In view of current evidence the answer is anything but simple. At least for critically ill patients treated in an intensive care unit (ICU) many questions remain a matter of debate. Fearing hypoglycaemia intuitively appears founded, since the brain cannot synthesise or store substantial amounts of glucose and thus requires a nearly continuous supply of glucose from the circulation as the main metabolic fuel.[1,2] Facilitated diffusion of glucose from the blood into the brain is a direct function of the arterial plasma glucose concentration and of the number of transporters integrated in the cell membrane.[3] The rate of blood-to-brain glucose transport exceeds the rate of brain glucose metabolism at normal (or elevated) plasma glucose levels. When blood glucose concentration falls from a normal level of about 100 mg dl^{-1} (6–7 mmol l^{-1}) to about 50 mg dl^{-1} (2.5–3 mmol l^{-1}), cerebral glucose content decreases in a directly proportional manner[4], while brain's energy demand remains unchanged. Hence glucose supply becomes limiting to brain glucose metabolism when arterial glucose concentrations fall to low levels. Consecutively, the brain has a unique vulnerability to

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hypoglycaemia, whereas all other tissues, including the heart, can largely function normally even during severe hypoglycaemia.[3]

Without this potentially hazardous impact of hypoglycaemia on the brain, management of patients' blood glucose levels would be rather straightforward. The symptoms and devastating effects of hyperglycaemia can be eliminated by application of exogenous insulin to lower the plasma glucose concentration to the physiological range. However, since this therapy is linked to an increasing risk of hypoglycaemia and its potential effects on the central nervous system, the management of hyperglycaemia is complex and only partially successful.

This article gives a critical review of current evidence on the pathophysiology of low blood glucose levels, its impact on brain function and on potential long-term consequences of hypoglycaemia, with a focus on the critically ill.

Definition and clinical manifestations of hypoglycaemia

Hypoglycaemia is a syndrome characterised by reduction in plasma glucose concentration to a level that induces symptoms, which are in general non-specific. The clinical diagnosis is based on the 'Whipple triad' characteristically including the documentation of low blood glucose, presence of symptoms and reversal of these symptoms when the blood glucose level is restored to normal. These criteria expose the intensivist to some startling challenges.

Defining a laboratory measure, range or cut off for normal blood glucose and hypoglycaemia is not as trivial as it seems on first sight.[5] The range of fasting blood glucose considered normal in the healthy varies among individuals and depends at least on age; for example, for an adult normoglycaemia is 70–110 mg dl^{-1} (3.9–6.1 mmol l^{-1}) and for a neonate 30–40 mg dl^{--1} (1.7–2.2 mmol l^{-1}). In neonates, even very low glycaemia below 25 mg dl^{-1} (1.4 mmol l^{-1}) is common and only rarely associated with (permanent) neurological impairment.[5,6] Moreover, individuals can adapt to low glucose levels and, in this case, do not show any symptoms even at very low blood glucose levels. This might be due to several adaptive mechanisms to increase brain glucose uptake even with very low blood glucose values.[7]

The second claim of the Whipple triad also connotes a challenge for the intensivist since symptoms of hypoglycaemia might be camouflaged in the ICU setting (see below). Blood glucose concentrations can rapidly decrease within minutes after exogenous insulin, even after subcutaneous application. In the worst scenario, pronounced hypoglycaemia could even occur within frequent, short monitoring intervals of blood glucose levels. Thus, awareness of the first counter-regulatory symptoms of hypoglycaemia would be crucial to take appropriate corrective action. Classically, those symptoms of (moderate) hypoglycaemia can be classified as autonomic and neuroglycopenic, with the latter largely being related to altered cognitive functioning.[8]

Autonomic counter-regulation

Initially, neurogenic (or autonomic) symptoms occur as a counter-regulatory activation of the autonomic nervous system, designed to increase blood glucose levels by breaking down the body's own storages.[1,9,10] Principally, all three efferent components of the autonomic nervous system – sympathetic and parasympathetic, neural, and adrenomedullary – are activated by hypoglycaemia, but the sympathicoadrenergic activation is thought to cause the most prominent autonomous symptoms.[1] They include pallor and diaphoresis, followed by an increased heart rate and systolic blood pressure. Hunger, paraesthesia and anxiety also commonly occur. The sympathetic activation triggers insulin resistance, glycogenolysis, lipolysis and gluconeogenesis; meanwhile, it reduces glycolysis and thus shifts glucose away from the organs that do not rely solely on glucose as fuel to the cells that largely need glucose as exclusive fuel. Recent studies have reported separate glucose thresholds for the onset of autonomic and neuroglycopenic symptoms.[7] First, the counter-regulatory activation of the autonomic nervous system occurs, and only later does cognitive dysfunction appear. This hierarchy of responses and symptoms of hypoglycaemia is important to initiate early corrective action.

Neuroglycopenia

Significantly low blood glucose levels lead to neurological symptoms, which are, in general, non-specific and – if hypoglycaemia is severe and prolonged – embrace a syndrome including neurocognitive impairment, epileptic seizures, loss of consciousness, permanent brain damage and even death.[1,9,11]

The reported cognitive impairment, acute or persistent, varies widely. Numerous studies conducted in healthy individuals have consistently indicated that acute moderate hypoglycaemia (35–50 mg dl^{-1} (2.0–3.0 mmol l^{-1}) impairs general cognitive functions, for example, attention, reaction time, verbal fluency, verbal and visual memory, and arithmetical ability.[7,12] The reported blood glucose thresholds, at which cognitive dysfunction started, mainly ranged between 40 and 55 mg dl^{-1} (2.6 and 3.1 mmol l^{-1})[13], but the impact of hypoglycaemia on cognitive function might be a function of habituation.[14–16] Reports of hypoglycaemia's impact on specific cognitive functions in humans vary widely, mainly due to variations in experimental methodology, for example, the relative imprecision of measurements of cognitive function, which limits comparisons between studies.[7,17] In particular, the frequently used brief, repeatable test of cognitive speed revealed inconsistent results. Secondly, commonly used tasks such as the Trail Making Test, the Digital Symbol Substitution Test and the Stroop tasks, as well as very simple tests including choice reaction time or finger tapping, appear to involve multiple brain processes with considerable overlaps.[17,18] Apparently, the major effect of hypoglycaemia might be on working speed rather than absolute ability.[19–22] Since most commonly used tests are timed, the hypoglycaemic effect might have been overstated in these studies. In addition, most studies include small sample sizes, thus some negative results could be type 2 errors. However, some evidence for the different sensitivity of specific brain processes to hypoglycaemia does exist. In particular, working memory, as well as short- and long-term memory, attention and basic sensory information processing, both visual and auditory, were significantly deteriorated, whereas finger tapping and simple reaction time were relatively insensitive to hypoglycaemia.[22–25] In general, complex, attention-demanding and speed-dependent responses seemed to be more susceptible to hypoglycaemia, whereas simple tasks could be completed despite moderate hypoglycaemia, even though completion time is prolonged.[8]

However, with regard to critically ill patients, some pathophysiological distinctions from the above-mentioned symptoms have to be considered. Sedation, medication or the underlying disease might mask symptoms of neuroglycopenia and of the vegetative counter-regulation in critically ill treated in ICU. In addition, several other individual- and disease-related factors such as the concentration of ketone bodies determine the risk of hypoglycaemia.[5] Ketone-body levels can be drastically increased during critical illness and might serve as an alternative fuel for neurons to, at least partly, alleviate the consequences of neuroglycopenia. Current data suggest that a great part of ICU survivors develop ongoing and persistent cognitive impairment.[26,27] Hence, critically ill patients seem to be at risk for neural damage *per se*, and it is tempting to speculate that these patients might be particularly sensitive to low blood glucose levels. Moreover, the duration of the hypoglycaemic episode, glucose reperfusion injury and the rate of the decrease of glycaemia might play their roles in its risks (see below).

Defining a universal threshold for hypoglycaemia, meaning that glycaemia below this laboratory value causes harm, therefore appears impossible. For practical reasons, in most clinical trials conducted on ICU, glycaemia below 40 mg dl^{-1} (2.2 mmol l^{-1}) is considered hypoglycaemia. However, this value is an interpolation from a healthy population, since below this threshold severe neurological symptoms can be expected in healthy individuals, and hence must be interpreted with caution.[28]

Acute hypoglycaemia and neural affection

Certainly, systematic and prospective research on the consequences of acute and severe hypoglycaemia and its effect on the human brain does not exist. However, in several case series, cerebral lesions attributable to incidental acute hypoglycaemia have been visualised by neuroimaging techniques.[29–34] Most of these hypoglycaemic incidences were caused by an overdose of insulin or oral hypoglycaemic agents in people suffering from diabetes mellitus, and, more rarely, by an undiagnosed insulinoma, sepsis, renal or hepatic failure or Addison's disease.[32]

There appears to be selective vulnerability of different brain regions to neural damage due to hypoglycaemia. On cranial computerised tomography (CT) and magnetic resonance imaging (MRI), lesions in the cerebral cortex, particularly the temporal lobe and/or hippocampus[29] and the basal ganglia[35] have been described (Fig. 1). MRI seems to be more sensitive than cranial CT scan for the detection of these lesions.[36] Brain lesions are well visualised on late fluid-attenuated inversion recovery (FLAIR) imaging and T2-weighted MR sequences, and, in particular, on diffusion weighted MRI during the acute phase.[32,37] Lo et al. report different patterns of transient white matter abnormalities and conclude that widespread cortical lesions on diffusion weighted MR are associated with poor outcome and death, while an early involvement of the basal ganglia and the corpus callosum might be associated with complete recovery.[32] Thus, although the MRI abnormalities could be transient and were reversible by glucose infusion in some cases, the MRI findings could also reflect permanent damage to neurons and persistent disruption of cerebral functions. Recent studies using more sophisticated MRI techniques have revealed that episodes of hypoglycaemia are associated with less gray matter density[38] and smaller white matter volume in parietal regions[39] in voxel-based analysis of brain volumes. However, data on hypoglycaemia-induced affections are not univocal. Diffusion tensor imaging (DTI), a type of MRI that quantitatively measures subtle white matter disintegration, shows no correlation of severe hypoglycaemia and cerebral abnormalities in patients with type 1 diabetes mellitus.[40] Functional MRI also does not show large effects on brain activation after acute hypoglycaemia.[41]

Animal models have clearly demonstrated that acute episodes of severe hypoglycaemia reproducibly induce irreversible neural damage. Neural necrosis was observed when blood glucose levels were titrated below 18 mg dl^{-1} (1 mmol l^{-1}) for an extended period of time.[3,42–44] Similarly to the neuroimaging studies, patho-anatomic findings have also demonstrated that not all neurons are equally sensitive to acute hypoglycaemic injury. Neurons in the cerebral cortex and the hippocampus are preferentially affected, followed by neurons in the thalamus and the basal ganglia[3,45], whereas neurons in the brainstem, the cerebellum and the spinal cord are commonly spared. Human autopsy studies in patients dying after severe hypoglycaemia show similar patterns of neural damage as observed in the animal models.[7,42,46,47] Hence, although the underlying pathogenic mechanism is still unknown, neuroimaging techniques likely visualise hypoglycaemia-induced neural injury or even cell death in the central nervous system.

Interestingly, the hierarchic order of vulnerability is at least partially comparable to that seen with global ischaemia–reperfusion. In addition, studies focussing on the bioenergetic processes in

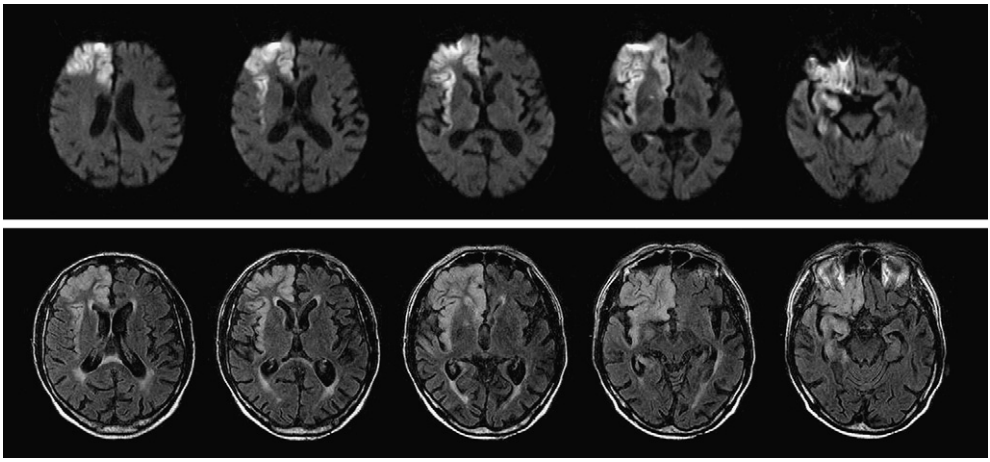

Fig. 1. Diffusion-weighted (upper row) and fluid attenuated inversion recovery (FLAIR) MR images (lower row) of a 52-year-old man in a diabetic coma showing unilateral hyperintensities of the fronto-temporal cortex (contributed by Dr. A. Kemmling, Department of Clinical Radiology at the Hospital of the University of Muenster, Germany).

hypoglycaemia have revealed failure of astrocyte–neuron interactions and its involved metabolism (primarily reduction of glutamate uptake), as is the case in ischaemia.[3,48] Although a common final metabolic pathway of ischaemic and hypoglycaemic neural dysfunction remains hypothetic, it at least underlines the unique bioenergetic properties of the central nervous system.

Long-term and persistent effects of hypoglycaemic episodes

When acute hypoglycaemia is survived, hypoglycaemia-induced neurocognitive impairment shifts into the focus of caregivers. Indeed, cognitive impairment is primarily observed during acute hypoglycaemia. However, it should be noted that the apparent resistance of many neural populations to hypoglycaemia is relative.[3] Virtually all neural populations can be affected by hypoglycaemia of sufficient severity and duration. Although most biochemical studies have focussed on cell death, more recent studies indicate that mild, recurrent hypoglycaemia can cause synaptic dysfunction even in the absence of neuron death, particularly in hippocampal neurons.[49,50] More profound hypoglycaemia causes more severe dysfunction, but even moderate hypoglycaemia produces a significant increase in low-frequency electroencephalographic (EEG) activity[51] and increased latency of the P300 wave[52,53], indicating a significant neural dysfunction. Thus, although the episodes with less profound hypoglycaemia do not cause instant coma, permanent brain damage or death, they remain potentially dangerous in the long run.

Clearly, there is no fixed blood glucose threshold at which structural cerebral damages and subsequent permanent functional brain abnormalities occur or not. Several studies have demonstrated that acute hypoglycaemia can provoke long-term effects, even after normoglycaemia has promptly been restored.[7,12] The neuroendocrine response to hypoglycaemia has been reported to take between 6 days and 4 weeks to return to a normal level.[12,54] Even after a single episode of hypoglycaemia, recovery of acute cognitive impairment takes 1.5 days.[12]

Persistent cognitive impairment and other long-term effects such as mood changes and affected general well-being after exposure to repeated episodes of even moderate hypoglycaemia have been demonstrated in several studies[7,12,18,24,55,56], although this has been disputed.[49,57–59] Some of the divergent results may be due to the above-mentioned methodological difficulties to determine cognitive function. Since most of the studies included diabetic patients, who frequently experienced hypoglycaemia in the context of psychosocial problems, erratic lifestyle and vascular disease, the findings cannot automatically be translated to other groups of patients.[7] Furthermore, the major prospective studies on diabetic patients that dealt with an association of repeated hypoglycaemia and mental ability have revealed negative results.[57–60] However, it has been argued that the population of these studies had atypical low rates of hypoglycaemia.[7] Other negative studies may not have been sufficiently long to detect a significant effect. In addition, the associations between intellectual disadvantage and previous episodes of hypoglycaemia may exist simply because less able patients manage their insulin treatment less accurately, and so suffer more hypoglycaemia.[61] On the other hand, Langan et al. estimated the pre-morbid and present IQ in diabetic patients with and without a history of repeated hypoglycaemia.[55] A decline in IQ associated with hypoglycaemia was found and confirmed in a subsequent study with a similar design.[56] In general, most authors concluded that a persistent impaired cognitive performance and mood disturbance demonstrated by numerous studies may be long-term consequences of repeated exposure to episodes of hypoglycaemia.

What are the functional and structural correlatives of these long-term effects on cognition? Enduring functional brain abnormalities that have been associated with recurrent hypoglycaemia include EEG abnormalities[62], and cerebral blood flow changes with increased frontal lobe perfusion. These were shown to become permanent in diabetic patients with recurrent hypoglycaemia.[63] Permanent structural brain afflictions associated with hypoglycaemia have been reported as well, but seem to be less apparent. White matter lesions are consistently demonstrated in neuroimaging studies of type 1 diabetes mellitus, and the authors formulate the concept of 'diabetic encephalopathy'.[64,65] Apart from hypertension, hyperglycaemia and vasculopathy, some trials have demonstrated an independent effect of hypoglycaemia on these structural cerebral changes. Since cerebral blood flow has been reported to be decreased during hypoglycaemia, it is hypothesised

that some of the microvascular white matter lesions may develop even in uncomplicated hypoglycaemia.[66] In addition, as mentioned above, more advanced MRI techniques have demonstrated both gray and white matter volume loss due to recurrent hypoglycaemic episodes, suggesting a long-term effect of even moderate hypoglycaemia. Although brain MRI of patients after accidental acute hypoglycaemia show a particular vulnerability of the hippocampus that correlates with neuropychological deficits[67], neuroimaging studies have failed to demonstrate permanent damage of hippocampal areas after repeated hypoglycaemic episodes. The hippocampus is of special interest in this context as it is a key area for learning and memory. Since most of the reported long-term effects of hypoglycaemia include these cognitive domains, an involvement of the hippocampal regions would be expected. Indeed, neuropathological studies in both animals and humans have consistently demonstrated permanent neural damage in regions of the hippocampus, especially in the dentate gyrus.[45,66,68,69] Although the underlying pathomechanisms of the long-term cognitive deficits remain unclear, some findings indicate that dopaminergic functional disturbance in the hippocampus[70], changes in brain glucose transporters[71] or astrocyte–neuron interactions may play a major role.[3] Using conventional neuroimaging techniques might be too rough a measure of such subtle cerebral changes, which would explain some of the negative imaging findings in patients with persistent cognitive impairment.

Hypoglycaemia in the critically ill

Incidence and risk factors for hypoglycaemia in the ICU population

When TGC protocols are implemented during anaesthesia, the intra-operative period, for example, for cardiac surgery, hypoglycaemia must be considered a very rare incident.[72] This is not surprising since blood gas analyses are performed quite frequently during high-risk surgery to control a bundle of important laboratory parameters. Since the interval of laboratory analyses in the ICU is mostly longer, those patients are prone to a higher risk of hypoglycaemia.

The incidence of hypoglycaemia in ICU patients in the area before the widespread implication of TGC is difficult to determine. A recent meta-analysis of randomised controlled trials indicates that, under conventional glycaemic control, 1.5% of the ICU patients experience at least one episode of hypoglycaemia, defined as blood glucose levels below 40 mg dl^{-1} (2.2 mmol l^{-1}). In the published studies, the risk increases by about sixfold (to about 10%) when TGC is applied.[73] Since the body's carbohydrate stores might be depleted and the counter-regulatory capacity deranged, the incidence is related to the severity of the illness.[74,75] For example, in sepsis, depending on the severity of the medical disorder[76,77] or liver dysfunction[78–80], the incidence appears maximal. One might speculate that the incidence might be higher in a non-study setting or lower when glycaemic targets are set more liberally; however, data undermining these notions are lacking. In the surgical ICU of our institution, the incidence of hypoglycaemia was about 3%, whereas we achieved a mean blood glucose level of about 135 mg dl^{-1} (7.5 mmol l^{-1}) after implementation of a TGC protocol.

Sophisticated (computer-based) protocols have been implemented and it was possible to decrease the incidence of hypoglycaemia below 1%. For instance, a pop-up message in the patient data management system can serve a good job when dosing errors occur or, judging from the prior course of glycaemia, the control interval gets too long. However, sophisticated control algorithms should rather be considered clinical pathways since they have showed to effectively improve protocol adherence, decrease the incidence of hypo- and hyperglycaemia and decrease the time to reach glycaemia target with less than six glucose measurements on average per day.[81]

In ICU patients the detection of hypoglycaemia is mainly based on blood glucose measurements since detection of the clinical signs of hypoglycaemia are frequently misinterpreted or camouflaged. Hence, the detection of hypoglycaemia might be delayed. Moreover, the counter-regulatory mechanisms are hampered by the disease, exposing patients to an increased risk for hypoglycaemia. Glucocorticoid and catecholamine levels are already high in the critically ill. An additional rise in response to hypoglycaemia in this highly activated system might thus be impossible or insufficient. Beta-blockers and other medications such as aspirin, oral glucose-lowering drugs or octreotide are

linked to hypoglycaemia. Especially when a bicarbonate-based substitution fluid is used, veno-venous hemofiltration and mechanical ventilation[77] are associated with an increased risk of hypoglycaemia.[82] In addition, human errors play a critical role and hypoglycaemia often occurs when several adverse conditions cumulate[83] such as changes in glucose intake without adequately adapting insulin infusion. Frequent hazards are thus the reduction of parenteral nutrition, for example, due to stopping glucose infusion during a transport or diagnostic procedure, or reduced enteral nutrition intake because of vomiting or delayed gastric emptying.

Mostly, hypoglycaemia does not occur in the acute phase but after several days in ICU. This can be interpreted thus that after stabilisation of the patient, laboratory analyses are taken less frequently and other patients move into the focus of the caregivers. Furthermore, workload must be blamed for poor glycaemic control and hypoglycaemia. Henry and colleagues also point out the lack of necessary resources and equipment, lack of knowledge about the long-term outcomes resulting from glycaemic control and the expected discomfort to patients caused by the frequent blood draws as reasons for poor glycaemic control and adherence to the TGC algorithms.[84]

In our institution, we have conducted a follow-up study of patients who experienced hypoglycaemias for quality control reasons, but without any scientific claim in the first month after implementing a TGC protocol. In all cases, a protocol violation due to several understandable reasons was detected as the basis for the hypoglycaemia. There is little reason to believe that this is fundamentally different in other institutions and our experience could be quite representative for daily ICU life elsewhere.

Hypoglycaemia and prognosis in the critically ill

To prove or refute a causal connection between hypoglycaemia, impaired survival and increased morbidity would require prospective trials. Since these will never be possible due to ethical reasons, we have to rely on animal models, *post hoc* analysis, mathematic modelling and case-control studies.

Caregivers fear that hypoglycaemia accounts for death and neural damage with consecutive neurological and neurocognitive impairment. The body's fuel metabolism is severely affected on different levels during sickness, yet little detail is known about glucose supply and fuel metabolism of the nervous system in critically ill patients treated in ICU.[85] Potentially alternative fuel sources such as ketone bodies that are excessively produced during illness can serve as fuel supply for the brain, especially when nutritional carbohydrates are limited.[86] There is thus no evidence to exactly determine the detrimental effects of hypoglycaemia conclusively for critically ill patients.

The occurrence of hypoglycaemia correlates with impaired prognosis of critically ill patients; however, it is a matter of discussion whether hypoglycaemia occurs mainly in the sickest patients and might thus be considered a marker of the severity of illness, rather than is causally linked to harm.[74] What is the cause and the consequence? Hypoglycaemia that spontaneously occurred in non-diabetic patients on a regular ward has been shown to be a marker of the severity of illness, but not an independent risk factor for mortality.[87] Van den Berghe et al. report an increased risk of hypoglycaemia with TGC in their patient population from medical and surgical ICUs ($n = 2748$). Patients, especially on the medical ward, who experienced hypoglycaemia had a worse outcome.[79] However, hypoglycaemia did not emerge as an independent risk factor for a poor prognosis.[88] These results are largely confirmed by Vriesendorp and colleagues using a nested case-control design and Cox regression analysis.[89] In their population, they found two cases of hypoglycaemia-associated coma occurring after implementing a TGC protocol. In both cases, coma was conclusively explained by the medical condition. However, an effect of hypoglycaemia cannot unerringly be ruled out. Seizures were also detected in two patients, one treated in a TGC and one had a spontaneous hypoglycaemia without being treated according to a TGC protocol. These data suggest that adverse neurological events after hypoglycaemia are not always associated with TGC or impaired neurological long-term outcome. In fact, they construe hypoglycaemia rather a marker of severity of illness than as a harmful event.

This notion has been disputed by Brunkhorst and colleagues who point out hypoglycaemia as an independent risk factor for increased mortality in their multicentre trial (VISEP) using Cox regression

analysis.[76] Similarly, the as-yet-unpublished multicentre GluControl trial reports a high incidence of hypoglycaemia and was stopped preliminary by the safety board since hypoglycaemia tended to be linked to impaired prognosis. Similarly, the third prospective, randomised multicentre trial on glycaemic control (NICE-SUGAR) including more than 6000 patients detects an almost 14-fold increase of hypoglycaemia under TGC as compared to conventional care.[90] In general, all three multicentre trials could not detect any clinical benefit of TGC, the incidence of hypoglycaemia was high and the accuracy of TGC rather poor (only <30% of blood glucose measures of GluControl were within target range). The work of Krinsley and colleagues might partly explain these findings.[74] In their sizable retrospective database review of a mixed medical and surgical ICU, including a case-control analysis ($n = 5365$), they identify hypoglycaemia as an independent predictor for mortality. A sensitivity analysis suggests that quadrupling the rate of hypoglycaemia and doubling the mortality attributable to severe hypoglycaemia would negate the survival benefit of tight glycaemic control in this cohort. In the same population, also the variability of blood glucose levels has been identified as a strong independent predictor of mortality.[91]

Cognitive impairment in ICU patients

Current data suggest that a great proportion of ICU survivors develop ongoing and persistent cognitive impairment, independently from hypoglycaemia.[92,93] Thus, critically ill patients *per se* seem to be at risk for neural damage, and it is tempting to speculate that these patients might be particularly sensitive to low blood glucose levels and/or blood glucose fluctuations. On the other hand, recent studies have demonstrated that hyperglycaemia, but not hypoglycaemia, is associated with adverse effects on the brain. For example, the polyol pathway activity, neural structural changes and impaired long-term spatial memory have been found to be affected by hyperglycaemia.[94] This finding suggests that the hyperglycaemic component may even have a greater adverse effect on brain functioning than intermittent, short hypoglycaemia. Moreover, the degree of neural death increased with rising glucose concentrations during the glucose reperfusion after hypoglycaemia.[95] These results suggest that high blood glucose concentrations following hypoglycaemic episodes, a sort of overshooting treatment, might be the reason for neural death. In another study, insulin accelerated the neural cell death in the hippocampus during low glucose levels, and the authors conclude that insulin has a double-edged effect on the neural cell death dependent on glucose concentration.[96] Thus, not only hypoglycaemia but also prolonged hyperglycaemic episodes and even its treatment might have a negative impact on cognitive function.[97,98] Considering those findings, minimisation of blood glucose level fluctuations should be the intention in the management of critically ill patients, with a prudent treatment of hypo- and hyperglycaemic episodes.

In contrast to the common presumption, data on any connection between hypoglycaemia and cognitive dysfunction in ICU survivors are scarce. From diabetes mellitus, we understand that cognitive function differs among patients who experienced episodes of hypoglycaemia as they occur in ICU and those who did not have hypoglycaemia[57–60] (see above). However, diabetes of injury and diabetes mellitus represent different pathophysiologic mechanisms, and extrapolating data from diabetics to ICU patients appears improper.

In neurotrauma patients, Van den Berghe and colleagues pointed out that, despite an increased incidence of hypoglycaemia, patients under TGC revealed an improved long-term neurological outcome.[99] In our surgical ICU, we performed an analysis of neurocognitive function in all patients suffering from hypoglycaemia between 2004 and 2008 in a nested case-control design. A total of 188 patients suffered from hypoglycaemia, 44 of whom did not fulfill exclusion criteria (e.g., prior neurocognitive dysfunction, psychiatric disorder, brain injury or stroke). A battery of well-validated neurocognitive tests investigating different domains of neurocognitive function were performed in those 44 individuals and in matched partners who did not suffer hypoglycaemia (see http://clinicaltrials.gov Nr.: NCT00662922 for details). We were unable to detect major differences between the two groups in any of the tested domains, but did find a moderate but significant impairment in the spatiovisual capacity and the visual memory in the hypoglycaemia patients compared with their matched controls. Thus, complex cognitive performance, for example, visuospatial skills, seems primarily affected (published as abstract, Abstract CD, DAC 2009). These findings collate the results

from experiments conducted in diabetes mellitus models and thus appear coherent. However, whether impairment in a single neuropsychological domain will have an effect on overall daily function of these patients has to be verified.

Conclusion

In conclusion, there is some evidence that even moderate and short hypoglycaemic episodes might lead to permanent brain damage. The cerebral involvement might cause long-term cognitive deficits, primarily affecting complex cognitive demands, learning and memory performance, and mood disturbance having a significant impact on patients' quality of life and overall daily function. Since there is no fixed glucose threshold or number of moderate hypoglycaemias at which permanent neurological deficits occur, it appears reasonable to avoid any hypoglycaemic episodes.

However, data mainly based on studies conducted in patients with diabetes mellitus, and some of the findings may also be attributable to co-morbidities such as hypertension and vasculopathy. Due to the absence of studies on long-term effects of hypoglycaemia in critically ill patients at present, any conclusions remain rather hypothetic. In addition to studies concerning any association of hyper- and hypoglycaemia with mortality in ICU patients, also their impact on subtle brain damage and permanent cognitive decline demands further investigations. Recent data from clinical trials have largely undermined the survival benefits attributable to TGC. It appears that the published monocentric studies revealed a very good glycaemic control, avoiding hyperglycaemia and extreme blood glucose fluctuations, and consecutively demonstrated a positive effect of TGC. By contrast, in a multicentre design and possibly in daily practice, where glucose control has been poor and worse than in the monocentric trials, the effect could not be confirmed.[73,91]

Control algorithms serving as effective tools to perform the state-of-the-art TGC with reasonable effort have been validated and are capable of reducing the incidence of hypoglycaemia to below the incidence occurring in the pre-TGC area.[81,100] Hence, it seems reasonable to use the state-of-the-art protocols in future trials that largely avoid hypoglycaemia to define the true impact of TGC on the prognosis of ICU patients. Furthermore, further studies on this issue will require precise measurements of cognitive function, with a limited range of tests that are mainly focussed on memory performance, more complex tasks and on absolute ability rather than on speed. The neuropsychological tasks should be combined with advanced imaging techniques such as DTI or high-resolution MRI volumetry to elucidate if long-term subtle neural damage is present after hypoglycaemic episodes, and whether specific cerebral areas are involved. However, due to the heterogeneous group of patients treated in ICU, with often complex and different metabolic co-morbidities, the relationship between glycaemic control and cognition will unfortunately remain somewhat difficult to decipher.

Is hypoglycaemia dangerous? Well, there are much more data available to make the caregiver fear hyperglycaemia as a reason for increased mortality and impaired long-term (neurocognitive) outcome than to support the fear from hypoglycaemia that precludes proper TGC. However, since hypoglycaemia as an independent risk factor for mortality and permanent impaired neurocognitive function after surviving critical illness cannot be ruled out and appears reasonable, it should be avoided by the state-of-the-art glucose control algorithms.

In summary, TGC increases the risk of hypoglycaemia in the critically ill. However, appropriate protocols can reduce this risk substantially. Since the clinical signs of hypoglycaemia are camouflaged in the ICU setting, the diagnosis of critical hypoglycaemia is not trivial and often delayed. Hypoglycaemia persisting over a longer time appears to be a possible independent risk factor for mortality. Hippocampal regions are particularly vulnerable to glucose deprivation, and therefore complex cognitive demands, for example, learning and memory performance, could as well be induced by hypoglycaemic episodes, which might have a significant impact on patients' quality of life and overall daily function. However, besides hypoglycaemia, hyperglycaemia and fluctuations of blood glucose levels are associated with long-term neurocognitive dysfunctions and with an increased mortality.

Practice points

- Hypoglycaemia occurs independently from TGC protocols, especially in the critically ill patients.
- Clinical signs of hypoglycaemia can be camouflaged in the ICU setting and the diagnosis can be delayed.
- A high incidence of hypoglycaemia or fluctuation of blood glucose levels might outweigh the clinical benefits of TGC and can result in increased mortality and permanent neurological disability.
- Hypoglycaemic episodes and also prolonged hyperglycaemia and even its treatment could have an impact on cognitive impairment that might have a significant impact on overall daily function and patients' quality of life.
- Appropriate control algorithms and strict protocol adherence can reduce the risk of hypoglycaemia to a minimum.

Research agenda

- Does hypoglycaemia cause relevant neurocognitive dysfunction apart from other relevant factors such as acute respiratory distress syndrome (ARDS) in critically ill patients?
- What is the pathomechanism behind hypoglycaemia-induced structural and functional cerebral changes?
- Since hyperglycaemia after an overshooting treatment of hypoglycaemia also causes neural death, what is the best treatment regimen of hypoglycaemic episodes?
- Is the cognitive performance of patients after ICU treatment associated with abnormalities in distinct brain regions on advanced imaging techniques, and are hypoglycaemic episodes linked to these changes?
- Further studies on this issue will require precise measurements of cognitive function, with a limited range of tests that are mainly focussed on memory performance, more complex tasks and on absolute ability rather than on speed, preferably combined with advanced imaging techniques such as DTI or high-resolution MRI volumetry.

Conflict of interest

The authors hereby disclose that there are no financial and personal relationships with other people or organisations that could inappropriately influence the content of this article.

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