Acute consequences of hypoglycaemia in diabetic patients

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Abstract
Strict glycaemic control is a major concern in many people with diabetes, hypoglycaemia being the most limiting factor in the daily management of patients with diabetes. Acute consequences of hypoglycaemic attacks are not precisely evaluated. Acute cardiovascular (CV) complications as myocardial ischaemia or stroke seem to be rare, but possibly ignored mainly in older frail patients. Recent large trials in type 2 diabetic patients have not shown the anticipated mortality benefits of strict glycaemic control, and reported a higher frequency of severe hypoglycaemia in the intensive treatment arms with an excess of CV deaths. The authors of these trials persist to deny a direct link between CV deaths and hypoglycaemia. In young type 1 diabetics “dead in bed” syndrome represents a rare but devastating consequence probably due to arrhythmia and prolonged QTc interval. Driving mishaps represent another complication but with a controversial frequency. Neurologic syndromes are frequent during severe hypoglycaemia but usually reversible. Major brain damages are scarce, but cognitive defects or dementia should be underestimated in older and frail type 2 diabetics. Thus, iatrogenic hypoglycaemia due to insulin or sulphonylureas may cause recurrent morbidity in type 1 and type 2 diabetic subjects, and should be prevented by a reevaluation of glycaemic targets in some patients, patient education and the use of new antidiabetic drugs without hypoglycaemic risk.

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Keywords: Diabetes; Hypoglycaemia; Cardiovascular complication; Brain damage; Driving; dead in bed syndrome; Review

Résumé
Conséquences à court terme des hypoglycémies chez les diabétiques

Un contrôle glycémique strict est une préoccupation majeure chez beaucoup de diabétiques dont l’hypoglycémie est le principal facteur limitant au quotidien. Les conséquences aigus et graves des hypoglycémies ne sont pas précisément évaluées. Les conséquences cardiovasculaires (CV), ischémie myocardique ou accidents vasculaires cérébraux semblent rares, mais peut-être ignorées surtout chez des patients âgés fragiles. De récents essais menés chez des diabétiques de type 2 n’ont pas montré les bénéfices anticipés du contrôle glycémique strict sur mortalité et rapporté une fréquence plus élevée d’hypoglycémies sévères dans le groupe de traitement intensif avec un excès de décès CV. Leurs auteurs ne retiennent aucun lien direct entre décès CV et hypoglycémies. Chez les jeunes diabétiques de type 1, le syndrome "du décès dans son sommeil" est une conséquence rare mais dramatique, sans doute due à des arythmies par allongement de l’intervalle QTc. Des accidents automobiles sont une autre complication, mais de fréquence controversée. Des syndromes neurologiques déficitaire sont fréquents au cours de l’hypoglycémie sévère, généralement réversibles. Les lésions cérébrales majeures sont rares mais les défauts cognitifs ou les démences restent sous-estimés chez les plus âgés. Ainsi, l’hypoglycémie iatrogène due à l’insuline ou aux sulfamides hypoglycémiants peut causer une morbidité significative chez des diabétiques de type 1 et 2. Elle devrait être évitée par une réévaluation des objectifs glycémiques chez certains patients, l’éducation thérapeutique et l’utilisation de nouveaux antidiabétiques sans risque d’hypoglycémie.

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Mots clés : Diabètes ; Hypoglycémie ; Complications cardiovasculaires ; Lésions cérébrales ; Conduite automobile ; Syndrome de décès nocturne ; Revue générale
1. Introduction

Subjects with diabetes are at increased risk of micro and macrovascular complications. The benefit of glycaemic control in decreasing the risk for microvascular disease is well documented in both type 1 and type 2 diabetic patients [1-2]. By contrast, the importance of strict glycaemic control to limit the risk of macrovascular complications remains controversial. Whether numerous observational studies have clearly shown a relationship between hyperglycaemia and cardiovascular (CV) disease, some recent studies as the ACCORD, VADT trials [3-4] failed to show that intensive glucose control significantly reduces CV events. Moreover in these studies, intensive glucose control increases the risk and the severity of hypoglycaemia and, in the ACCORD study, the incidence of CV events and of all cause of mortality [3]. A benefit of strict glucose control on CV complications has been only suggested in the UKPDS Follow-up study in type 2 DM [5] and the EDIC in type 1 DM [6], in favor of a legacy effects that takes many years before being eventually translated into protection from CV events. Thus, strict glycaemic control being a major concern in many people with diabetes, hypoglycaemia is the most prevalent acute clinical complication and limiting factor in the daily management of patients with diabetes. Thus, iatrogenic hypoglycaemia may cause recurrent morbidity in type 1 and type 2 diabetic subjects [7-8]. In this article we review the acute consequences of hypoglycaemia in both type 1 and type 2 DM, defined as the immediate or short term morbidity or mortality attributable to severe hypoglycaemia conversely to delayed complications.

2. Incidence and risk factors of hypoglycaemia in type 1 diabetic patients

The incidence of hypoglycaemia varies in the literature because of a lack of universal definition and in the absence of reliable data. In most cases data are merely declarative. Severe hypoglycaemia (SH) is defined as all episodes for which, help from others was required. SH are divided into uncomplicated SH (i.e. SH episodes not complicated by coma, seizure, or treatment with glucagon or intravenous dextrose) and complicated SH (i.e. SH episodes complicated by coma, seizure, or treatment with glucagon or intravenous dextrose). Regarding this definition SH affects 40 to 56 % of type 1 people with diabetes [1,9]. In a recent study [9], an overall incidence of SH of 150 episodes/100 patient-years affected 40.5% of an unselected population. This includes 40 episodes/100 patient-years of hypoglycaemic coma. The presence of long-term complications, mainly neuropathy, a threshold for symptoms of < 3 mmol/l, alcohol use, and (nonselective) ß-blockers were associated with SH during the previous year. For the authors, the recurrence of SH during the period under investigation (1 year) may indicate that SH itself contributed to an increased risk of subsequent SH, as reported previously [9]. In comparison, in the DCCT, the subjects receiving intensified insulin treatment had a 3-fold increase in the incidence of SH compared with subjects treated conventionally with an occurrence of 62 SH episodes/100 patient years, including 16 episodes of hypoglycaemic coma [1]. These data have been recently confirmed by the results of the UK Hypoglycaemia Study Group, type 1 diabetic patients treated for more than 15 years having significantly higher incidence of SH when compared to those treated for 5 years or less [10]. It is however possible that the incidence of hypoglycaemia has decreased since the use of new long acting analog insulin as glargine. The ORIGIN study might answer this question in type 2 diabetics with short duration of diabetes [11]. Some study have compared patients “and relatives” assessments of rates of severe hypoglycaemia and state of awareness and explored the influence on involvement and concern of relatives [12]. Cohabitants recalled more episodes of severe hypoglycaemia than patients (2.7 vs. 1.6 episodes/patient year; P < 0.001). The discrepancy may be due to different perceptions of hypoglycaemic episodes among patients and spouses. The transient mental impairment of the patients during these episodes of hypoglycaemia may lead to underestimation by the patients. In terms of awareness, there was a poor concordance between patients and cohabitants. This confirms the unreliability of reports and the underestimation of hypoglycaemia by type 1 diabetic patients previously described. Moreover some patients with diabetes, may deliberately ignore episodes due to embarrassment or fear of impact in their professional activity or the risk of losing their driving license. In addition, discrepancies in definitions and assessments of SH and differences in duration of diabetes, age, diabetes management and patient education may explain differences in the occurrence of SH among various studies. Among these factors, duration of diabetes plays a major role. Ample evidence suggests that the glucagon response is lost within five years, as is insulin secretion measured by residual C-peptide. In some people, catecholamine responses are also diminished over a longer diabetes duration [13]. Obviously, a threshold for symptoms at lower blood glucose levels is a frequent consequence of recurrent previous hypoglycaemia, generating a vicious circle. In short, hypoglycaemias are common, particularly at night and often not felt or ignored for different reasons. Despite the huge number of studies on the frequency and severity of hypoglycaemia in type 1 diabetic patients, few details are reported regarding the acute and/or long-term consequences of these episodes. However a subgroup of young type 1 diabetic patient seems to be at high risk of severe hypoglycaemia mainly nocturnal, with potentially devastating consequences. This acute complication seems to be a major cause of an increased incidence of premature death in this population when compared to non-diabetic young people.

3. Incidence and risk factors of hypoglycaemia in type 2 diabetic patients

In type 2 diabetes, frequency of hypoglycaemia is more difficult to evaluate regarding the extreme heterogeneity of these patients, age, frailty, duration of diabetes, renal function,
treatment modalities as oral treatment containing sulfonylurea (SU), insulin use. In the recent UK Hypoglycaemia Study Group trial [10], about 7% of people with type 2 diabetes who were followed for an average of 9 months, had experienced at least one episode of severe hypoglycaemia in the first 2-3 years of insulin therapy, a proportion similar to those treated with sulfonylurea, 10 times less frequent than in patients with long standing type 1 diabetes [1]. This incidence is much higher than that reported in the UKPDS and other trials [4]. A retrospective study has reported 15% severe hypoglycaemic episodes in type 2 insulin treated patients directly related to the duration of insulin use > 5 years [14]. As in type 1 diabetes, a negative relationship was found between hypoglycaemia frequency and low residual insulin secretion. People with type 2 diabetes constitute a disparate group, the ability of each patient to secrete glucagon in response to hypoglycaemia being related to the degree of insulin deficiency [8]. Glucagon secretion was almost absent in type 2 diabetic patients who exhibit total insulin-deficiency. By contrast, glucagon secretion is intact in tablet-treated patient and in type 2 diabetic patients who have recently started insulin. These patients do not experience hypoglycaemia more frequently than patients taking SU at similar \( A_1 \) levels. In the UKPDS the rate of major hypoglycaemia was 1.4% in the glibenclamide group, and 1.8% in the insulin treated group [2]. In the 4-T study, median rates of hypoglycaemia per patient per year were lowest in the basal insulin treated group, 1.7, higher in the biphasic aspart insulin group, 3.0, and highest in the prandial aspart insulin group, 5.7 [15]. In a retrospective cohort of Medicaid patients, recent hospital discharge was the strongest predictor of subsequent hypoglycaemia in SU or insulin treated patients aged ≥ 65 years [16]. In the Fremantle Diabetes Study severe hypoglycaemia frequency was studied in older patients with cognitive impairment [17]. Hypoglycaemia requiring health services assistance was three times higher in patients with cognitive impairment or dementia. These patients were older, 76 ± 4.6 years, 27.5% treated with insulin + OAD and 45% by SU, 46.4% having an \( HbA_1c \) ≤ 7%. Dementia was present in 9.3% and cognitive impairment without dementia in 19.9%. Many studies support that the risk factors of hypoglycaemia in type 2 diabetic patients are: older age, decreased food intake, depression, cognitive dysfunction, as shown in the ADVANCE Trial [18], dementia, even exercise and alcohol. Ageing, per se, has potential effects on counter-regulatory hormones and symptomatic response to hypoglycaemia. At last, in type 2 as in type 1 diabetic patients, antecedent hypoglycaemia (i.e. repetition of hypoglycaemic episodes) can modify the glycaemic thresholds for response of counter-regulatory hormones to hypoglycaemia and may promote HAAF (hypoglycaemia-associated autonomic failure). Thus, estimation of the incidence of hypoglycaemia is likely underestimated by many patients and impossible to truly determine without blood glucose testing in regard of any “malaise” or, in prospective studies by continuous glucose monitoring.

4. Mortality in childhood-onset type 1 diabetes: hypoglycaemia as a cause of death in bed syndrome and traffic accident?

Although the main part of excess mortality in type 1 diabetes is due to long-term complications, an excess death rate has also been reported from several studies, in different countries, in subjects with short duration of diabetes and in absence of marked signs of long-term complications [19]. If one exclude initial or subsequent ketoacidosis, this excess mortality remains unexplained and mainly due to deaths in bed and traffic accidents. Few data are available for death or serious injuries due to traffic accident secondary to driving errors in diabetic people. This incidence of traffic accident linked with hypoglycaemia remains controversial [20]. A systematic trial has been conducted in Sweden for analyzing survival of children who were diagnosed with diabetes at age 0-14 years during the period of 1977-2000 (23.5 years). A cohort of 10,200 diabetic children was recorded and matched with 371 referents death in non-diabetic people [19]. A total of 78 case subjects, 49 males and 29 females, had died over the 81,600 person-years of observation and with a mean duration of diabetes of 8.2 ± 7.1 years (0-20.7). The mean, age and sex Standard Mortality Rates (SMRs) was 2.15 (95% CI 1.70-2.68). The SMRs was higher in females than males (2.65 vs. 1.93), whereas young males have a higher death rate than female in the general population. Mean age at death was 15.2 ± 8.6 years (1.2-27.3). Children with an onset before 2 years had an excess death rate of more than 4, whereas for older age at onset the death rate has doubled, and was about three times before 10 years. The peak in mortality is determined at 10-12 years of diabetes duration. Twenty-three deaths were clearly related to diabetes, 14 Keto-Acetosis (KA) among them 6 were onset deaths. Ten KA were found living alone. One death with alcohol intoxication was probably related to hypoglycaemia. Seventeen cases of diabetic subjects (22%) were found deceased in bed at home without a precise cause at forensic serious autopsy (17/78 vs. 2/364 in general matched controls). All the cases, mean age 18 years, diabetes duration 8 years, were found deceased in bed by relatives and the deaths were absolutely unexpected. This confirms the original observation of Tattersall et al in 1990 [21] that diabetic subjects, even very young, seem to run a significant risk of sudden death during sleep, related to their diabetic state. In their series, they describe patients who had gone to bed in apparently good health and been found dead in the morning, the majority of them sleeping alone at the time of death and 20/22 lying in an undisturbed bed. Most of them have uncomplicated diabetes, no lesion at autopsy, no proof or no certainty about the role of hypoglycaemia. But the timing of death and other circumstances strongly suggest that hypoglycaemia or hypoglycaemia-associated event was responsible [19,21]. The link between nocturnal hypoglycaemia and death in bed syndrome will be discussed further when addressing the topic “QTc prolonged syndrome”.

5. Hypoglycaemia as a cause of cardiovascular events?

5.1. Myocardial ischemia and CV mortality

Chest pain consistent with myocardial ischemia has been early reported in type 1 diabetic patients [22]. However many data did not confirm this assertion. If hypoglycaemia is often considered as a predictor of all-cause of mortality, no direct evidence supports that hypoglycaemia increased coronary heart disease or favor myocardial ischemia during hypoglycaemic episodes. There are, of course, more cardiovascular events in the glycaemic intensified groups than in control groups of large studies as VADT, 32 vs. 20% [4]. In the Bari 2D study, more frequent hypoglycaemia were reported in the insulin-provider treatment than in the insulin-sensitizer one (9.2 vs. 5.2%) but without difference for major cardiovascular events [23]. In 2008, an excess mortality in the intensive arm of the ACCORD study led to discontinuation of study [3]. This has prompted many conjectures about the likely reasons and potential principal mechanisms possibly responsible for this increased mortality in diabetic subject submitted to a strict glycaemic control. Thus in ACCORD the rate of hypoglycaemic episode was three times higher in the intensive arm with an annual prevalence of 3.3% vs. 1.1% for the standard treatment. Mortality was three times higher in both group, control and intensified, in patients who have had severe hypoglycaemia. Nevertheless, the authors of the ACCORD trial persist to deny a direct link between cardiovascular deaths and hypoglycaemia. Moreover, the delay between hypoglycaemic episodes and cardiovascular events was judged too long to retain a direct consequence of low glycaemic levels on CV events. In all these studies, conducted in relatively old type 2 diabetic patients, CV events cannot be considered as an acute effect of hypoglycaemia. In the DCCT who enrolled type 1 diabetic patients a high rate of severe hypoglycaemia in the intensified group was not associated with increased CV mortality [1]. In 1960, Egeli et al [24] have conducted a study on the effects of insulin and hypoglycaemia on ECG changes (Fig. 1). Sixty-eight patients with diabetes were made hypoglycaemic with insulin (around 2.5 mmol/L) and ECG changes on the ST segments and T waves were reported. These changes could be partly ameliorated with beta-blockers or administration of serum potassium. Ischemic changes were noted in the ECGs of 5/6 patients with type 2 diabetes when they were submitted to low blood glucose, brady-arrhythmia occurred in one patient paralleling with loss of consciousness. Few studies have simultaneously monitored glycaemia and electrocardiogram. In one study, De Souza et al have registered 54 episodes of hypoglycaemia and 10 were associated with clinical symptoms or ECG evidences of ischemia, whereas one episode of chest pain occurred during 59 period of hyperglycaemia [25].

In diabetic patients, seriously ill, admitted for an acute coronary syndrome, those who experienced severe hypoglycaemia at some point of their stay, exhibited double mortality rate compared with those who had no hypoglycaemia [26]. The CV cause of death in patients who had recent hypoglycaemia suggested that the susceptibility of those patients to cardiac arrhythmia may have been increased by preceding exposure to low glycaemic levels.

5.2. Hypoglycaemia, prolonged QT interval and arrhythmia

As above detailed sudden nocturnal death are sometimes reported in type 1 diabetes [27]. Mc Gill has recently demonstrated that in type 1 diabetic patients severe nocturnal hypoglycaemia was associated with a prolonged, lengthened, corrected QT interval (QTc) and in some episodes, cardiac rate and rhythm abnormalities [27]. Interestingly, this occurred during the recovery phase (CGM 3.4 mmol/l) of a more severe hypoglycaemic event. None of these abnormalities were seen during normoglycaemia with the exception of the patient with P wave abnormalities. This is also found in non-diabetic subjects [28] and in type 2 diabetic patients [29]. It was observed a strong relationship between the increase of epinephrine and the increase in QTc and a weaker relationship between the decrease of potassium and QT. QT dispersion was also recorded during hypoglycaemia, another measure of cardiac repolarization [28]. This degree of abnormal repolarization has been associated with sudden death caused by “torsade de pointes” ventricular tachycardia (VT). It is possible that special susceptibility affected some individuals having a congenital QT syndrome, an inherited condition due to mutation in genes that code the voltage-gated ion channels responsible for the cardiac action potential [30]. This could explain or contribute to the sudden death of young people with diabetes in hypoglycaemic situations. The pathophysiology of this accident should be a direct effect of hypoglycaemia on the myocardium through sympathoadrenal activation and/or hypokaliemia caused by hyperinsulinemia and catecholamines on myocyte sodium-
5.3. Hypoglycaemia in the hospital setting

Outside intensive care unit (ICU) the effect of hypoglycaemia in the hospital setting has been few investigated for diabetic patients. Hypoglycaemia during the stay was associated with increased length of stay, one year mortality and inpatient mortality: 2.96% for patients who had at least one hypoglycaemic episode during the hospital stay vs. 0.82% for patients who had none [33].

5.4. Coagulation and endothelial dysfunction during hypoglycaemia

Insulin is a coronary vasodilator and has proinflammatory actions [34]. The administration of intravenous insulin induces an immediate activation of sympathoadrenal and neural systems, increasing left ventricular ejection fraction, before any fall in blood glucose occurs. These changes become more pronounced with a decline in blood glucose, with maximal responses at the glucose nadir. Significant increments in cardiac output also occur during hypoglycaemia. The hemodynamic changes during hypoglycaemia are attenuated in some people with type 1 diabetes who have strict glycaemic control, this has been attributed to attenuated sympathetic stimulation. Many humoral markers changes have been reported during hypoglycaemia. Thus, C-reactive protein, TNF-α, endothelin-1, interleukin IL-6 and IL-8, factor VIII, vWF, certain growth factors (VEGF), have been reported to increase during hypoglycaemia [34]. This leads to abnormal coagulation, increased plasma viscosity, endothelial damage, neutrophils and platelets activation, reduced blood flow, capillary closure. Increased vessel wall stiffness has been described in longer duration type 1 diabetic patients during hypoglycaemia. This could explain the possible deleterious effect of hypoglycaemia in a subset of diabetics with longer diabetes duration and/or a preexisting cardiovascular disease as discussed in the ACCORD and mainly in the VADT study [3-4].

5.5. Stroke, hypertension and hypoglycaemia

Obviously, hypoglycaemia induces transient focal neurocognitive deficits including shortly reversible ischemic attacks by correcting blood glucose. By contrast, the question whether severe hypoglycaemic episodes could increase the risk of stroke, remains highly controversial. However a potential link between hypoglycaemia and CV risk should have been “hypoglycaemia-induced hypertension”, which seems to be augmented in patients having frequent and severe hypoglycaemia, as observed in intensive insulin therapy programs, DCCT in type 1 and ACCORD in type 2 diabetes [1,3]. This should increase the risk of hypertension-related complications and could have played a role in the unpredicted cardiovascular results of these intensive glucose control studies in type 2 diabetes. However, no study was designed to assess the direct relationship between hypoglycaemia and hemodynamic changes, since the occurrence of hypoglycaemic events was not documented at all.

Feldman-Billard et al have recently investigated the relationship between glycaemia and blood pressure (BP) swings in patients with diabetes under everyday conditions [35]. They have performed 24-hour home monitoring of subcutaneous glucose levels using a continuous glucose monitoring and simultaneous ambulatory BP measurement in patients with type 1 or type 2 diabetes (mean duration, 18 years). Their results demonstrate a close temporal relationship between hypoglycaemia and BP increase. Among patients with marked hypoglycaemia, no patient reported any symptom. The authors draw attention on the fact that cardiovascular disease and all-cause mortality being closely linked to BP elevation in diabetic subjects of both types, increased BP variability, paralleling with recurrent post-hypoglycaemic BP rises, may have played a role in the results of some recent studies, ACCORD VADT [3-4].

6. Hypoglycaemia and brain damages

The discovery of insulin in 1921 generated the initial interest in the possibility of brain damages resulting from hypoglycaemia. The first reason was due to the occurrence of intentional or most often, unintentional overdosage. The second was the deliberate administration of high enough dose of insulin to produce coma for treating schizophrenia and other psychosis by Sakel in 1933 [36]. It was early suspected that this treatment modality had major side effects and acts by brain damage. During the 1930s, many few controlled experiments were conducted to address the question of short or long term brain damage resulting from excess insulin administration. The effects of various degrees of hypoglycaemia have been carefully summed by B Frier [37]. A progressive decline in blood glucose triggers a series of events that occur at different glycaemic thresholds. Early changes are slight, and progressively greater cognitive impairment occurs around 2.8-2.6 mmol l⁻¹, with deteriorating performance, inappropriate attitudes and interferes with the patient’s ability to self-treat hypoglycaemia. This state is well investigated by several cognitive tests. Hypoglycaemia also induces non-cognitive changes in mood and behavior, including feelings of tiredness,
sadness, fear, despondency, and, sometimes, anger, violence, aggressive behaviors leading, rarely, to forensic situations. Autonomic symptoms appear around 3.0 mmol l⁻¹, and the effects on neurophysiological function (sensory-evoked potentials and electroencephalographic abnormalities) become more prominent as blood glucose falls further. If the condition is untreated, ≤1.5 mmol l⁻¹, neuroglucopenia is considered as severe and accompanied by reduced conscious level, drowsiness, confusion, and progresses to loss of consciousness and coma. The coma may be complicated by convulsions. Significant brain damage is rare and occurs only if the neuroglucopenia is prolonged, leading to brain death, irreversible lesions and death of the patient. In very young type 1 diabetic patients, it is important to keep in mind that hypoglycaemia-associated symptoms tend to be distinctive from one child to another. Thus it may be difficult for younger child to recognize and verbalize, leaving the parents to distinguish hypoglycaemia from other transient physical states and behaviors. So far, hypoglycaemia (glucose deficiency) was considered to be a form of ischemia (i.e. oxygen deficiency) and the two insults were described as having the same neuropathology. The assumption was that in condition of either oxygen or glucose deprivation, energy deficiencies developed, resulting in necrosis of neurons before glia [38]. But accumulating data prompted a reexamination of this hypothesis. For example, in profound hypoglycaemia, enough to cause cessation of electrical activity, ATP levels are still over one third of the normal values, due to oxidation of alternative fuels (proteins and fats), whereas in ischemia ATP drops to less than 5% of normal. These data indicate that cerebral energy deprivation per se, as measured in whole brain, does not account for the phenomenon of selective necrosis. Furthermore, blood flow is not a critical determinant of hypoglycaemia-induces neuronal necrosis. The current concept is that hypoglycaemic coma is associated with the release of endotoxins (excitotoxins) in the CSF spaces, mainly glutamate and aspartate, 3 to 4-fold rise in tissue, which activate subtypes of excitatory amino acid receptors. This increase in aspartate occurs even in spite of normal serum glucose levels, indicating the metabolic abnormality to be due to inhibition of glycolysis, rather than to low glucose levels per se. The duration of electro-cerebral silence roughly determines the degree of resultant brain damage. In rodents, cells die within two hours regarding the location of the damage, however neuronal necrosis is absent in hypoglycaemia unless the EEG becomes isoelectric. Recent data suggest that a pro-oxidant state is promoted in certain brain regions during hypoglycaemia and after the glucose reperfusion phase, which might result from the activation of several oxidative stress pathways and may be related to subsequent cell death [39]. Oxidative stress is known to be present in different pathological conditions in the CNS such as ischemia and various neurodegenerative diseases. The presence of oxidative stress during hypoglycaemia has been recently suggested although its temporality and regional distribution in brain have been few explored in detail. Recent studies suggest that oxidative stress is increased by hypoglycaemia and glucose perfusion. Thus, membrane depolarization occurs and can lead to major brain damage as neuronal necrosis. Cerebral cortex and hippocampus are most sensitive to neuroglucopenia, brain stem and spinal cord are much more resistant. In fatal cases of hypoglycaemic coma, the neuropathology of the brain is variable. To date, it is not known whether regional differences in the antioxidant machinery might help to explain the differential regional susceptibility of brain to hypoglycaemic damage [39]. In the patients who survive of severe prolonged hypoglycaemic coma they develop cortical and hippocampal atrophy, with ventricular enlargement, often associated with a chronic vegetative state. The mechanisms underlying this selective vulnerability to hypoglycaemic damage are unknown. Some case report of hemiplegia has been reported as a possible result of hypoglycaemia and was first described in 1928. In a case report, a 58-year-old male with diabetes, who developed left hemiplegia during a severe hypoglycaemic event, diffusion-weighted magnetic resonance imaging has shown an increased signal intensity in the pons, indicating that the patient’s hemiplegia resulted from acute brain injury [40]. Some reports provide evidence that acute brain injury may be a cause of the neurological deficit. Cortical laminar necrosis have been described after severe hypoglycaemia [41]. Many transient neurological defects have been described in young type 1 diabetics, in adult or older type 1 or type 2 diabetics. Hemiplegia and hemiparetic attacks are the most frequent and rapidly or slowly reversible even after many hours of neurological deficit until glucose infusion. Various clinical presentations have been reported as paroxysmal dyskinesia. When symptoms are clearly associated with hypoglycaemia, imaging evaluation is probably not warranted. In older patients, having previous CV complications, irreversible defects have been sometimes reported. Cases of central pontine myelinolysis have been reported after hypoglycaemic attacks, in mild forms symptoms may resolve within few months with only minimal residual neurological deficits, for some others severe irreversible sequels may persist till a vegetative state. Experimental studies show that in response to insulin-induced severe hypoglycaemia, diabetes may increase the vulnerability of specific brain areas to neuronal damage. The cumulative effects of recurrent severe hypoglycaemia may cause intellectual impairment in the developing brain of infants and young children, but in adults (principally those with insulin-treated diabetes) the effect on cognitive impairment appears to be modest, with occasional anecdotal exceptions. Nevertheless, higher-level skills seem to be more sensitive to hypoglycaemia than simple, repetitive cognitive or motor tasks explaining why some patients remain highly suited to situations such as driving or manual work. Thus usual tests (RPM) may be unable to identify low performances during acute hypoglycaemia, regarding several facets of attention as non verbal intelligence [45]. Recurrent moderate hypoglycaemia induces a maladaptive response that limits symptoms of hypoglycaemia (hypoglycaemia unaw-
and thus jeopardizes patient safety. On the other hand, antecedent recurrent moderate hypoglycaemia preconditioned the brain and markedly limited both the extent of severe hypoglycaemia-induced neuronal damage and associated cognitive impairment. Recurrent moderate hypoglycaemia can be viewed, paradoxically, as providing a beneficial adaptive response in that there is mitigation against severe hypoglycaemia-induced brain damage and cognitive dysfunction. Putative mechanisms for these beneficial adaptations could include glycogen supercompensation (increased brain glycogen content above pre-hypoglycaemic levels). This may explain the seemingly incongruous clinical findings that intensively treated patients who experience recurrent moderate and severe hypoglycaemia may be paradoxically protected from severe hypoglycaemia-induced brain damage and may not suffer from associated long-term cognitive damage [46-47]. In older type 2 diabetic people, hypoglycaemia is three times more frequent in patients with cognitive impairment or dementia than in those with normal cognition. However hypoglycaemia in older people many studies didn’t find evidences that hypoglycaemia adversely significantly affects cognition or favors dementia [17]. For other authors [48] among older patients with type 2 diabetes, a history of severe hypoglycaemic episodes is associated with a greater risk of dementia. This suggests that hypoglycaemic episodes severe enough to require hospitalization, or an emergency department visit, are associated with increased risk of dementia, particularly for patients who have a history of multiple episodes. Older individuals are thought to have less brain reserve or brain plasticity, and therefore may be unable to recover from neurological insult as well as younger individuals. Epidemiologic findings from the DCCT [1] suggest that in young adults with type 1 diabetes, hypoglycaemic episodes are not associated with higher risk of subsequent cognitive impairment during 18 years of follow-up (mean age 45 years at follow-up). Thus, hypoglycaemia may not cause large adverse effects on cognitive performance in adults younger than 60 years of both types of diabetes, but could have a greater effect on neurocognition in older individuals.

Whether severe hypoglycaemia induce limited acute irremediable brain damage in diabetic subjects below 60 years, severe hypoglycaemia or even intermediate low blood glucose levels may have serious consequences by impairing driving performance or by inducing other situations leading to conflicts with law [49].

7. Hypoglycaemia and driving

Hypoglycaemia caused by insulin or sulphonylureas, can bring diabetic patients into conflict with the law. Aggressive behavior and the consequences of impaired driving skills are its commonest manifestations [49]. Most of the older studies have either found no association between diabetes and traffic accident or a small, usually not statistically significant increase, of the relative risk [50]. More recent U.S. research, however, indicated a clear trend. Cox et al in a recent study, found hypoglycaemia as a common (when monitored prospectively) and unique risk factor for driving mishaps among some drivers with type 1 diabetes with a higher incidence than the general population [51]. These accidents were not related to sex, duration of disease, A1c, self reported hypoglycaemic awareness, availability of glucose in the car, or blood glucose thresholds for, when to treat or when not to drive. They were related to the use of insulin pumps, history of collisions, severe hypoglycaemia, and hypoglycaemia-related driving mishaps [51]. Hypoglycaemia preceding fatal car collisions has been clearly demonstrated in some case reports [52]. Analyze of memory meter data for 3 months before these fatalities reported frequent episode of low blood glucose values and one or more severe hypoglycaemias before these accidents [52]. The authors conclude that exposure to frequent hypoglycaemia, not low HbA1c, increases the risk of severe hypoglycaemic episodes and that these deaths may have been avoided. Collisions are more common among drivers with type 1 diabetes than among their non-diabetic spouses [53]. Drivers with type 1 diabetes, with history and without a recent history of recurrent hypoglycaemia-related driving mishaps, drove a virtual reality driving simulator. During euglycaemia, participants with history, reported more autonomic and neuroglycopenic symptoms and tended to require more dextrose infusion to maintain euglycaemia with the same insulin infusion. During progressive hypoglycaemia, these subjects demonstrated less epinephrine release and greater driving impairments. This increased risk appears to be attributable to a subgroup of drivers with type 1 diabetes who must be identified and trained for avoiding accidents.

Many younger type 2 diabetic patients are obese and sleep apnea (SA) is highly frequent in this people [54]. Sleep apnea causes impairment in performance and is associated with an increased risk of motor vehicle crashes compared with the general population of drivers [55]. Despite this increased risk, the actual number of accidents due to SA is considered as low. However it is conceivable that sleep apnea or alcohol abuse in diabetic patients as in the general population, are most often involved in driving mishaps as hypoglycaemic episodes. Nevertheless patient’s education centered on this risk with adapted practical preventive trainings must be widely proposed in the future to diabetic patients treated with insulin or sulfonylureas.

8. Conclusion

Strict glycaemic control is a major concern in many people with diabetes to prevent microangiopathy and long term CV complications, hypoglycaemia is a major limiting factor in the daily management of patients with diabetes. In the current literature acute consequences of hypoglycaemic attacks are not precisely evaluated. Acute cardiovascular (CV) complications as myocardial ischemia or stroke seem to be rare but possibly ignored mainly in older frail patients. Continuous ECG and
blood capillary glucose might highlight this question in the future. Whether recent large trials in type 2 diabetic patients have not shown the anticipated mortality benefits of strict glycaemic control and reported a higher frequency of severe hypoglycaemia in the intensive treatment arms with an excess of CV deaths, the authors of these trials persist to deny a direct link between CV deaths and hypoglycaemia. However after the large communication of these trials, strict blood glucose targets have been discussed in older type 2 diabetic patients with long diabetes duration and a frail situation. In young type 1 diabetics “dead in bed” syndrome represents a rare but devastating consequence probably due to arrhythmia and prolonged QTc interval, this risk is probably due to a special susceptibility, which affects some individuals having a congenital QT syndrome, an inherited condition. Driving mishaps represent another complication but with a controversial frequency. Experimental studies using driving simulator could contribute to clarify this issue in the future. Neurologic syndromes are frequent during severe hypoglycaemia but usually reversible. Major brain damages are scarce but cognitive defects or dementia should be underestimated in older and frail type 2 diabetics. Thus, iatrogenic hypoglycaemia due to insulin or sulphonylureas, may cause recurrent morbidity in type 1 and type 2 diabetic subjects and should be prevented by a reevaluation of glycaemic targets in some patients, patient education and the use of new antidiabetic treatments without hypoglycaemic risk.

9. Conflicts of interests

S Halimi has received speaker and consulting fees from Abbott, Amgen, Astra-Zeneca, Bayer, Boehringer Ingelheim, Eli Lilly, GlaxoSmithKline, Lifescan, Merck Sharp & Dohme-Chibret, Novartis, Novo Nordisk, Pfizer, Roche Diagnostics, Roche Pharma, Sankyo, Sanofi Aventis, Servier, Takeda and Therval.

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