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# Sudden death and hypoglycaemia

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## Introduction

In 1989, a forensic biochemist giving evidence at an inquest in the UK claimed that he was aware of a number of deaths of young people with diabetes that were related to human insulin. The case generated considerable press interest and led the British Diabetic Association to commission a survey of all such deaths in the UK. The resulting publication identified a number of patients with a similar mode of sudden death and highlighted circumstantial evidence implicating nocturnal hypoglycaemia. The term 'dead in bed syndrome' was coined by Dr Ian Campbell in an accompanying editorial in *Diabetic Medicine*<sup>1</sup>.

Subsequent research has confirmed an increased risk of sudden death in young people with diabetes that is unrelated to ischaemic heart disease. The potential of hypoglycaemia as a cause of sudden death has recently been highlighted by the early termination of the ACCORD study due to an increased rate of sudden cardiac death among intensively treated patients with type 2 diabetes. The precise causes of this finding remain to be determined, but hypoglycaemia is a strong candidate.

The pathophysiological changes that occur during hypoglycaemia may increase the risk of sudden death in patients with advanced cardiovascular disease. This article reviews the studies examining sudden death in young people with diabetes, and considers the potential mechanisms and therapeutic interventions. Nocturnal hypoglycaemia is a common side effect of insulin treatment and is feared by many patients. The often unstated anxiety that such attacks might prove fatal appears to have some basis in fact. If healthcare professionals are to address these concerns they need to provide patients and their families with a better understanding of this intriguing and thankfully rare condition.

## The risk of death from hypoglycaemia in diabetes

Hypoglycaemia has been recognised as a potential cause of death ever since the introduction of insulin therapy, particularly due to cerebral damage. Tattersall and Gale reviewed the published literature and concluded that although some studies report hypoglycaemia rates of up to

20%, most suggest rates of between 2 and 6%.<sup>2</sup> The studies considered in this review were undertaken before the publication of both the Diabetes Control and Complications Trial (DCCT) and the United Kingdom Prospective Diabetes Study (UKPDS), which established the potential benefit of glycaemic control on the risk of microvascular disease. In an era when tight control is recommended for all patients with diabetes, and HbA1c targets are set at less than 7%, an increase in the proportion of deaths due to hypoglycaemia seems likely. This expectation is supported by the early termination of the ACCORD study due to increased mortality in the group of participants that were intensively treated to lower HbA1c.<sup>3</sup>

## The problem of identifying deaths due to hypoglycaemia

One of the problems in establishing the risk of death from hypoglycaemia is the inaccuracy of death certification. Diabetes itself may be omitted from the death certificate of those dying suddenly, and in patients with diabetes death is frequently attributed to ischaemic heart disease or stroke in the absence of an autopsy. Furthermore, many episodes of hypoglycaemia remain unrecognised, particularly at night. A number of studies in which glucose concentrations have been monitored overnight have demonstrated rates of nocturnal hypoglycaemia of 30-60%, with blood glucose falling to concentrations approaching 1mmol/l (18mg/dl); patients have remained asleep during most of these episodes.<sup>4,5</sup> The fact that nocturnal hypoglycaemia is so common yet sudden death among those with diabetes is rare is reassuring, since it indicates that a single episode of even severe hypoglycaemia is extremely unlikely to result in sudden death. It also means, however, that the risk of hypoglycaemia-induced mortality is almost impossible to calculate accurately.

## Identifying hypoglycaemia at post-mortem

Even where post mortem examination is possible, other factors can prevent an accurate diagnosis of hypoglycaemia. Blood glucose levels change after death, rising on the right side of the heart due to hepatic glucose release from post mortem glycogenolysis. In the periphery blood glucose levels fall as a result of continued glycolysis within the erythrocytes. Post-mortem glucose concentrations may therefore vary depending upon the site of the sample. As glucose values

continue to fall after death, a normal or raised glucose concentration excludes hypoglycaemia as a cause of death, but low concentrations are unhelpful.

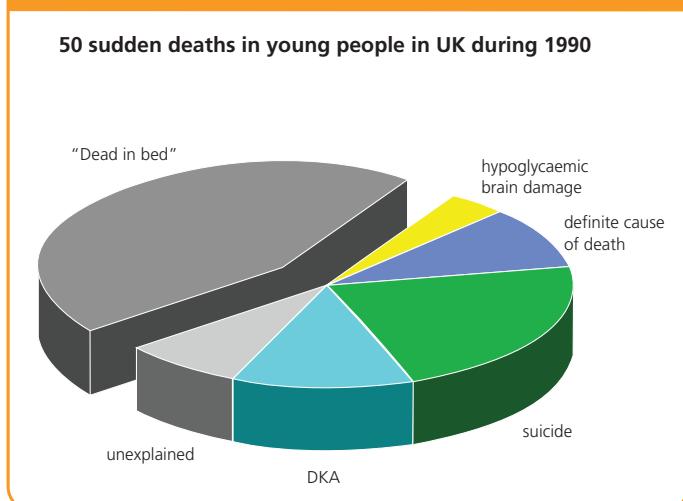
A post-mortem examination will be able to establish hypoglycaemia as a cause of death where it leads to characteristic pathological changes, for example, in hypoglycaemia-induced cerebral damage.<sup>6</sup> A fatal cardiac dysrhythmia caused by hypoglycaemia leaves no histopathological clues, however, and since cardiovascular disease is so common among people with diabetes, the cause of death may often be attributed to ischaemic heart disease even in the presence of minimal atherosclerosis.

### Sudden death and the dead in bed syndrome

The hypothesis that hypoglycaemia may cause sudden death is not new. In 1968 Malins reported a series of 14 patients under his care who had apparently died of hypoglycaemia.<sup>7</sup> Eight were over 60 years old, had a history of nocturnal hypoglycaemia and were alone at the time of death.

In 1991 Tattersall and Gill performed detailed analysis of fifty deaths of people with type 1 diabetes, under 50 years of age, which were considered sudden and unexpected (*Figure 1*).<sup>8</sup> A definite cause of death was identified in 16, another 11 died due to suicide or self-poisoning and five due to natural causes established at post-mortem. Two patients died from hypoglycaemic brain damage, six from diabetic ketoacidosis and four deaths remained unexplained. That left 22 individuals with a similar mode of death, described in the paper and the accompanying editorial as 'dead in bed'.<sup>1</sup>

Figure 1. Causes of death of the original 'Dead in bed' paper<sup>1</sup>



These 22 patients were aged between 12 and 43 years, with a diabetes duration ranging from 3 to 27 years. Most were on twice daily insulin although one was on multiple injections and another injected once a day. The use of human insulin was not implicated in these deaths. Where

information on diabetic complications was available, four patients had severe microvascular complications, while 12 had none, or minimal microvascular disease. Of the 22 patients, 20 were found dead in an undisturbed bed, 19 were sleeping alone, and 15 died overnight.

Fourteen patients had a history of recurrent severe nocturnal hypoglycaemia; most were apparently well on going to bed and were discovered dead on the following morning. Where post-mortem examinations had been performed there was no evidence of hypoglycaemic brain damage. The clinical picture was consistent with a prolonged period of nocturnal hypoglycaemia resulting in death, possibly from cardiac or respiratory arrest. The authors proposed that "circumstantial evidence implicates nocturnal hypoglycaemia in many cases". They also noted that there had been little research in the area of hypoglycaemia and cardiac rhythm disturbances.

This study has been followed by a number of other surveys of mortality in young people with diabetes, particularly from Scandinavia where epidemiological data are robust.

Sartor and Dahlquist reported a study of 4919 childhood-onset type 1 diabetes cases, which were assessed for 13.5 years.<sup>9</sup> Their mortality rate was three times higher than in a matched, non-diabetic population. A total of 33 deaths were seen, of which nine had been found 'dead in bed' after previously appearing to be healthy. Hypoglycaemia appeared to be the most likely cause of death in this group although the authors were unable to test any relationship between mortality and glycaemic control. A more recent study assessed these patients for a further 10 years; an additional eight cases had been found 'dead in bed', with no cause of death that could be established.<sup>10</sup>

Thordarson and Sovik examined 240 deaths in diabetic patients from Norway, who were aged under 40 years.<sup>11</sup> They identified 16 'dead in bed' cases, accounting for 7% of the overall deaths. Nine of these were on multiple insulin injections, with ten having recorded recurrent nocturnal hypoglycaemia. The precise cause of death had not been established in these patients, although 13 had undergone post-mortems; hypoglycaemia was thought to have been the most likely cause of death.

A further Norwegian study found only four of 103 deaths meeting the 'dead in bed' criteria (for this study – patients found dead in an undisturbed bed; observed to be in good health the day before; autopsy not informative) among all Norwegian type 1 diabetic patients diagnosed between 1973 and 1982, and aged less than 15 years at diagnosis.<sup>12</sup> A more recent study from Australia, however, found that sudden unexpected death in individuals with type 1 diabetes under the age of 40 years who had undergone autopsy was four times more common compared to an age matched non-diabetic control group.<sup>13</sup> Ten of these 15 sudden unexpected

deaths met the criteria of the 'dead in bed' syndrome, indicating that this syndrome remains a rare but important cause of death in patients under the age of 40 years.

### Risks of sudden death compared to the non-diabetic population

An important issue is whether the risk of sudden death among young people with diabetes differs from non-diabetic individuals. Studies on sudden death in young people have reported rates of between 1.3 and 8.5 per 100,000 patient-years. This suggests that patients with diabetes have an overall risk of around three to four times higher, a figure supported by the above post-mortem study from Australia.<sup>13</sup>

### Possible causes of sudden death in young people with diabetes

Sudden death in non-diabetic individuals is most commonly caused by a cardiac arrhythmia induced by ischaemic heart disease. Since coronary artery disease is generally more advanced in people with diabetes this may explain their increased risk, at least in part. This is particularly true for the older patient and for those with type 2 diabetes. Additional factors are likely to be operating, however, and these will contribute to a proportionately greater extent in the younger patient with type 1 diabetes.

Hypoglycaemia induced seizures could conceivably increase the risk of sudden death which is also more common in epileptic patients. There are similarities between the syndromes of the 'dead in bed syndrome' and sudden death in epilepsy.<sup>14</sup> However, the observation that the diabetic patients who died have been found in an undisturbed bed argues against a contribution by seizures.

Other possible risk factors for sudden death include autonomic neuropathy, and hypoglycaemia induced cardiac dysrhythmias.

### Autonomic neuropathy

Autonomic neuropathy has been associated with an increased risk of sudden death in individuals with diabetes.<sup>16</sup> Some studies have proposed that this may be due to respiratory arrest,<sup>17</sup> while others have implicated cardiac dysrhythmias.<sup>18</sup> It is unlikely however, that autonomic neuropathy causes the 'dead in bed syndrome' in the absence of other factors. The patients studied were generally young without severe diabetic complications, and few had been reported as having severe autonomic neuropathy. It is possible that those affected had lesser degrees of autonomic neuropathy, which may have contributed to an increased vulnerability to sudden death in the presence of additional risk factors.<sup>22</sup>

### Hypoglycaemia as a cause of sudden death

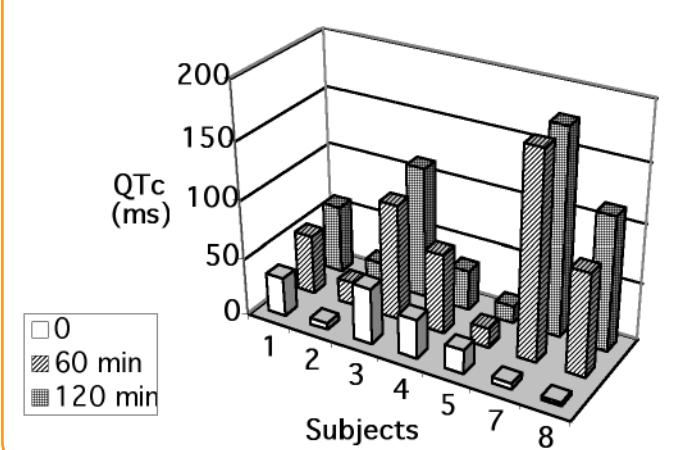
Studies examining sudden death in young people with

diabetes conclude that there is strong circumstantial evidence implicating hypoglycaemia. Deaths generally occur at night when hypoglycaemia is common, and many of those who died had experienced problems with hypoglycaemia, particularly at night.

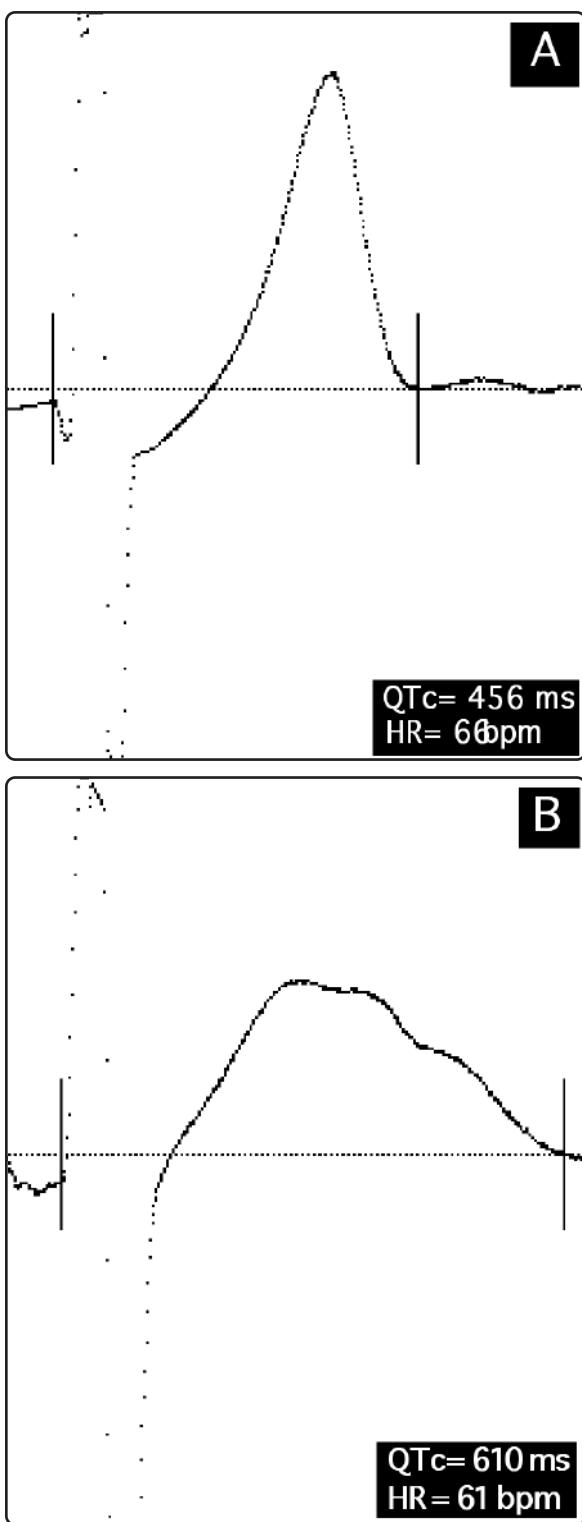
The absence of cerebral damage at autopsy makes it unlikely that hypoglycaemia had caused death through this mechanism, and attention has focussed on whether hypoglycaemia may cause cardiac arrhythmias. An increasing body of work has explored the effects of hypoglycaemia on the heart, particularly its electrophysiology. This research ranges from clinical descriptions of cardiac arrhythmias observed during clinical episodes of hypoglycaemia, through to detailed physiological studies and investigations at the cellular level.

Hypoglycaemia leads to activation of the autonomic nervous system with a resulting increase in circulating plasma adrenaline and subsequent falls in potassium. Consistent changes in the ECG include flattening or inversion of the T wave and ST depression.<sup>23,24</sup> There is also evidence that the QT interval lengthens as a direct result of hypoglycaemia in both type 1 (Figure 2) and type 2 diabetes.<sup>25,26</sup> Profound increases in QT interval have been observed in some individuals (Figure 3), and a relationship between the increase in QT interval and the rise in plasma adrenaline have been observed in some studies. Both β-blockade and potassium infusion can prevent QT lengthening during hypoglycaemia, suggesting that both responses may contribute to these changes.<sup>27-29</sup> Similar changes also occur during clinical episodes of nocturnal hypoglycaemia in both adults and children with type 1 diabetes,<sup>27,30</sup> although their magnitude is less than those observed during experimental hypoglycaemia. This is probably due to the generally lower intensity of the sympathoadrenal response during clinical nocturnal episodes.

Figure 2. Changes in QT interval in 8 individuals with Type 1 diabetes during experimental hypoglycaemia (2.5mmol/l, 40mg/dl) lasting 120 min



**Figure 3.** Changes in T wave morphology in a subject during euglycaemia (5.0 mmol/l) and hypoglycaemia (2.5 mmol/l) showing prolonged repolarisation and prominent U wave.



potential.<sup>19,31</sup> Certain therapeutic agents (some anti-arrhythmic agents, antibiotics and antihistamines) can also cause an acquired long QT syndrome and sudden death.<sup>32</sup> Interactions between genetic factors and environmental effects (including age, sex, state of sympathoadrenal activation, K<sup>+</sup> concentration) can determine whether a cardiac arrhythmia is triggered.

QT lengthening only leads to a cardiac arrhythmia after months or years, and fatal events may be infrequent because the combination of factors which lead to a fatal cardiac arrhythmia occur only rarely. Indeed, severe hypoglycaemia which causes a profound sympathoadrenal discharge without alerting the patient or partner is relatively unusual. The 'substrate' for a lethal cardiac arrhythmia, however, might be the combination of a severe hypoglycaemic attack at night (which fails to wake patients until symptoms are intense), and a cardiac conduction system affected by sub-clinical autonomic neuropathy in an individual who has inherited polymorphisms in the LQT genes causing exaggerated QT lengthening during sympathoadrenal activation. (Table 1)

**Table 1.** Potential mechanisms which may combine to cause fatal cardiac dysrhythmias

A direct effect of hypoglycaemia on ventricular myocardium

Rises in circulating adrenaline concentrations and falls in circulating potassium levels caused by insulin induced hypoglycaemia

Increased activity in sympathoadrenal fibres innervating the heart

Subclinical or overt autonomic neuropathy within the heart

Mutations or polymorphisms affecting the relevant proteins concerned with the cardiac action potential

It is very difficult to test this hypothesis directly, as sudden death occurs so rarely. Case reports of hypoglycaemia induced arrhythmia would be supportive, although such events may be modified by the presence of ischaemic heart disease. Most have been observed during spontaneous clinical episodes, although some have been identified during experimentally induced hypoglycaemia. Atrial fibrillation and supraventricular tachycardia have been reported during clinical episodes of hypoglycaemia,<sup>33,34</sup> but these are not associated with sudden death. There are also reports of profound sinus bradycardia<sup>35</sup> which could conceivably lead to sudden death. Very few cases of ventricular arrhythmias have been reported,<sup>36</sup> and there is a single report of transient ventricular tachycardia during experimental hypoglycaemia in a non-diabetic patient with coronary heart disease,<sup>37</sup> plus ECG evidence of sustained ventricular tachycardia, ventricular fibrillation and asystole during hypoglycaemia in diabetic patients.<sup>38</sup> This small number of reports does not, however, disprove the hypothesis that prolonged QT intervals may cause sudden death.

QT lengthening is widely recognised as a cause of cardiac arrhythmias and sudden death in other circumstances. The congenital long QT (LQT) syndrome is an inherited condition due to mutations within genes that code the voltage gated ion channel proteins responsible for the cardiac action

The majority of sudden deaths in young patients with diabetes remain unexplained, and we have hypothesised that these were due to ventricular arrhythmia. They may have resulted from an increase in plasma adrenaline and fall in potassium accompanying hypoglycaemia, producing prolongation of the QT interval. It is possible that this occurs on a background of autonomic instability caused by early autonomic neuropathy.

### Hypoglycaemia and sudden death in patients with type 2 diabetes and cardiovascular disease

As acute hypoglycaemia induces a sympathoadrenal response, if activation is profound and adrenaline levels rise to high levels, the effects on the cardiovascular system (CVS) may be intense. This has been demonstrated in some experimental studies, although patients with ischaemic heart disease have obviously been excluded for ethical reasons. The heart rate increases seen are generally modest, rarely rising above 100 beats per minute. There is generally a widening of the pulse pressure, with a rise in systolic and a fall in diastolic blood pressure.<sup>24,39,40</sup> Cardiac output rises and systemic vascular resistance falls. The effect of hypoglycaemia on cardiac function is less pronounced in patients with type 1 diabetes, as such patients generally have reduced sympathoadrenal responses to hypoglycaemia compared to non-diabetic individuals.<sup>40</sup> Few studies have explored the effect of hypoglycaemia on cardiac function in type 2 diabetes, but the increased cardiac workload and myocardial oxygen demand clearly have the potential to aggravate established ischaemic heart disease.

Ambulatory ECG monitoring has confirmed that hypoglycaemia can aggravate ischaemic heart disease. A case report of hypoglycaemia provoking ischaemia during 24-hour monitoring<sup>41</sup> has been followed by a more systematic study in which continuous glucose monitoring was combined with ECG recording in 21 patients with insulin treated diabetes and known cardiovascular disease (CVD).<sup>42</sup> Both symptomatic and asymptomatic hypoglycaemia were associated with angina and ECG abnormalities, confirming the potential of hypoglycaemia to precipitate ischaemia.

Establishing hypoglycaemia as a cause of myocardial infarction (MI) is even more difficult since blood glucose is frequently raised in hypoglycaemia due to the release of stress hormones. This tends to mask the link between a low glucose concentration and a subsequent MI. The evidence is therefore confined to a few case reports where the connection between severe hypoglycaemia and MI was particularly strong.<sup>43,44</sup> The recent early termination of the ACCORD trial provides additional support for the potential of hypoglycaemia to aggravate existing ischaemic heart disease.<sup>3</sup> More work is needed to establish the precise pathogenic mechanisms, but hypoglycaemia may have

contributed to the increased cardiac mortality observed in the intensively treated arm during the conduct of this trial.

### Conclusion

There is considerable evidence implicating hypoglycaemia as a rare cause of sudden death in individuals with type 1 diabetes, with a risk around 3-4 times that of non-diabetic individuals. The available information indicates an arrhythmic death which most often occurs at night. Its sporadic nature, in contrast to the high frequency of nocturnal hypoglycaemia, suggests that additional factors increase susceptibility. These could include sub-clinical autonomic neuropathy, or polymorphisms or mutations in the genes coding for the proteins involved in generating the cardiac action potential.

Hypoglycaemia may also increase the risk of ischaemia and sudden death in individuals with type 2 diabetes, although it is unclear whether the same mechanisms operating in type 1 diabetes are responsible – a hypothesis which requires considerable further research.

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