

# The dead in bed syndrome revisited: a review of the evidence

Philip J Weston\*



### Practice Points

- The dead in bed syndrome describes the death of young patients (40 years old or younger) with Type 1 diabetes who have normal autopsies but who suffered sudden unexpected death. They characteristically are seen in good health the night before their death and are found dead in undisturbed beds.
- Nocturnal hypoglycemia appears to be the common precipitating factor for death.
- Nocturnal hypoglycemia is common amongst patients with Type 1 diabetes. Why some patients should die suddenly has been a topic of speculation for 20 years.
- Possible theories for the dead in bed syndrome are hypoglycemia-induced ventricular arrhythmias in patients with subtle autonomic dysfunction and QTc lengthening.
- Recent work has suggested that there may be a genetic predisposition to ventricular arrhythmias in some cases of the dead in bed syndrome.
- Avoiding nocturnal hypoglycemia in patients with Type 1 diabetes is crucial.  $\beta$ -blockers and angiotensin-converting enzyme inhibitors have been proposed as preventative treatments in high-risk patients.
- A national/international registry of such deaths and detailed genetic examination are key steps for the future.

**SUMMARY** The dead in bed syndrome describes the sudden death of patients with Type 1 diabetes in characteristic circumstances. The victims are found dead in undisturbed beds having previously been in good health. Post-mortem examinations in these patients consistently reveal no anatomical cause for death. The initial reason for investigating these deaths was to look for an association with human insulin. No link was found but there was circumstantial evidence to suggest that the deaths were due to hypoglycemia. Only a small minority of these patients had ante-mortem complications of diabetes. These devastating deaths and the pathophysiology associated with the deaths have been studied in some detail over the intervening years and the outcomes of those studies will be described in this review.

\*Royal Liverpool University Hospital, Liverpool, Merseyside, L7 8XP, UK  
Tel.: +44 151 7063472; Fax: +44 151 706 5871; philip.weston@rlbuht.nhs.uk

## Methods

The literature was searched using PubMed and Medline databases. The search was limited to papers published in the English language from 1970 until September 2011. Keywords used were: Type 1 diabetes, sudden death or dead in bed syndrome; hypoglycemia; autonomic neuropathy; cardiovascular autoregulation; QTc; hypokalemia. The references cited were also searched for key papers not identified elsewhere. A total of 438 articles were identified. Those that specifically looked at the epidemiology, pathophysiology and proposed mechanisms for the dead in bed syndrome were selected.

## Sudden death in patients with Type 1 diabetes

The first suggestion of an increased risk of sudden death in patients with Type 1 diabetes was reported by Tunbridge [1]. He examined the factors contributing to the deaths of 448 patients with diabetes aged less than 50 years. Understandably, the major cause of death was confirmed myocardial infarction and other macrovascular diseases. Hypoglycemia was the cause of death in 16 of the study group and of these, seven had features suggestive of the dead in bed syndrome.

In 1989, a coroner's inquest suggested that there had been an increase in the risk of sudden death in young patients with Type 1 diabetes [2]. Suspicions were cast on the role of human insulin, the use of which had rapidly increased after its launch in 1982. It was proposed that human insulin was in some way leading to an increased risk of sudden death possibly by causing more frequent, unexpected, hypoglycemic episodes. The British Diabetic Association (now Diabetes UK) asked the public and healthcare professionals to report any episodes of sudden unexplained death and Tattersall and Gill were tasked with investigating these deaths for the British Diabetic Association [2,3].

A total of 53 deaths were reported and all patients had undergone an autopsy. The investigators undertook detailed investigations into these deaths to clarify a cause. This involved reviewing death certificates, speaking to relatives and reviewing GP and hospital records, as well as speaking to the healthcare professionals responsible for the care of the patients. Causes of death were found in 16 patients (mostly due to suicide). Twenty two of the patients had no autopsy cause of death found but the

circumstances around the deaths were remarkably similar. Twenty of the 22 were found lying in undisturbed beds with no signs of a terminal struggle. In the other two cases, the rooms were disturbed and dextrose tablets spilled around the room. Ten of these patients had had diabetes for less than 15 years duration. A minority (four) had severe complications of their diabetes, while 13 had no evidence of microvascular complications. However, 14 of the 22 had a history of severe hypoglycemic episodes prior to death. The authors concluded that nocturnal hypoglycemia was a contributory factor to the deaths of these patients.

Following on from this original report similar surveys were conducted in other countries, initially in Scandinavia and then around the world [4–8]. All have found sudden unexplained deaths in young Type 1 diabetes patients. Typically these patients are below 40 years of age, they are healthy apart from their diabetes, they have no significant complications of diabetes and they are found dead in undisturbed beds having been observed to be in good health the night before death. The autopsy examination is normal. These features define the dead in bed syndrome [3].

From these data it has been estimated that 5–6% of deaths in patients with Type 1 diabetes that are 40 years of age or younger are attributable to the dead in bed syndrome. The most recent survey of causes of death in Type 1 diabetes patients analyzed two related patient registries [8]. They found up to 7.6% of deaths in patients 50 years or younger that could be ascribed to the dead in bed syndrome. When compared with sudden unexplained deaths in a general population of people less than 50 years of age, sudden unexplained deaths occurred ten-times more often in Type 1 diabetes [8]. Other studies looking at comparisons to patients without diabetes but of the same age group report that the dead in bed syndrome 'contributed' approximately 30% of the excess deaths associated with Type 1 diabetes. The diabetes group had a three- to four-times excess mortality.

Reviewing the case series of the dead in bed syndrome it appears to be more common in males, associated with higher HbA1c and be more common in patients who have a past history of frequent hypoglycemic episodes [2,4–8].

The estimates of deaths due to the dead in bed syndrome probably underestimate the actual numbers. What of patients with Type 1 diabetes

who are over 40 years old but who otherwise meet the dead in bed criteria or those whose sudden death does not occur in bed. Such patients would not be included in the dead in bed syndrome statistics, but may well otherwise meet the diagnostic criteria.

We can conclude from these studies that the dead in bed syndrome is particularly associated with Type 1 diabetes and the association with hypoglycemia as a 'cause' of dead in bed syndrome is consistent throughout the literature. There is one case report documented in the literature of a patient who was coincidentally attached to a continuous blood glucose meter when he experienced a fatal hypoglycemic episode [9]. The patient fitted the criteria for the dead in bed syndrome.

### Dead in bed syndrome & hypoglycemia

From the earliest days of insulin therapy it has been associated with an increased risk of hypoglycemia [10,11]. Nocturnal hypoglycemia is extremely common amongst patients with Type 1 diabetes with reported frequencies of 29–56% [12]. Even with advances in insulin technology it remains a common problem and is not always recognized by the patient. The earliest descriptions of the dead in bed syndrome have implicated nocturnal hypoglycemia as a precipitating cause [1,2,4–6].

The diagnosis of hypoglycemia post-mortem is extremely difficult. Owing to glycogenolysis blood taken from the right side of the heart at post-mortem has a spuriously high glucose value. By contrast, blood glucose concentrations from left-sided blood samples are often low owing to continued glycolysis by red blood cells. Some pathologists rely on vitreous humor glucose levels, but these are also unreliable, particularly if the sample is taken some hours after death. The dead in bed case series found no features to suggest hypoglycemia brain injury, such as neuronal cell damage in the cerebral cortex and hippocampus, but it seems that hypoglycemia, or at least a past history of repeated hypoglycemic episodes, was a feature in the majority of the dead in bed cases.

Whilst nocturnal hypoglycemia is a common occurrence amongst Type 1 diabetes patients [10–12], this rarely leads to death. Similarly, massive insulin overdose and associated hypoglycemia rarely results in sudden death [13]. It is clear, therefore, that other factor(s) alongside hypoglycemia must predispose patients to sudden death.

The remainder of this review will discuss the proposed pathophysiological mechanisms that lead to the dead in bed syndrome.

### The autonomic dysfunction hypothesis

It has been known for some time that diabetes patients with symptomatic autonomic neuropathy have an increased mortality [14,15]. Often these patients will succumb to sudden, unexplained deaths with normal autopsies. It has been proposed that patients with symptomatic autonomic neuropathy die from cardiorespiratory arrest due to impaired cardiorespiratory reflexes [16]. The dead in bed series of patients did not have any features to suggest symptomatic autonomic neuropathy so this mechanism of death can be discounted.

More subtle types of autonomic dysfunction have been described in patients without symptoms of autonomic neuropathy and with normal bedside tests of autonomic function [17–19]. These bedside tests are too crude to pick up subtle changes in autonomic function, which usually requires detailed examination of cardiac autoregulation [17]. One way of looking at this is to perform a beat-by-beat analysis of heart rate and blood pressure and then using statistical tools, such as Fourier transformation, analyze the changes between measurements. Heart rate (and blood pressure) is not constant but changes in a rhythmic regular way in resting conditions. Using spectral analysis techniques on heart-rate data reveals three rhythmic oscillations, all with a period of less than 1 min [20,21]. Oscillations with a frequency of approximately 0.2–0.4 Hz, a frequency similar to that of normal respiratory activity, are defined as high frequency [17,22]. They are predominantly under the control of the parasympathetic arm of the autonomic nervous system. Oscillations with a frequency of approximately 0.1 Hz are defined as low frequency and are under the influence of the sympathetic arm of the autonomic nervous system [17,22–25]. Calculating the ratio of low-frequency to high-frequency power gives a measure of sympathovagal balance [17,22,25,26].

Type 1 diabetes patients without evidence of symptomatic autonomic neuropathy and normal bedside autonomic function tests have been shown to have impaired cardiovascular autoregulation [17–19]. More specifically, there is a relatively greater reduction in parasympathetic function compared with sympathetic function [17–19].

Therefore, the sympathovagal balance is shifted towards a sympathetic predominance.

In other clinical settings, such as in patients' postmyocardial infarction, similar changes in sympathovagal balance have been associated with an increased risk of sudden death due to an increased predisposition to fatal ventricular arrhythmias [27,28]. Similarly, in Type 1 diabetes patients it is proposed that hypoglycemia further increases the sympathetic predominance in asymptomatic patients who have already shifted their sympathovagal balance, and this leads to fatal ventricular arrhythmias [29]. Only circumstantial evidence exists to support this hypothesis [30].

Using beat-by-beat heart rate and blood pressure data it is possible to calculate a baroreceptor function [18,31,32]. The baroreceptors are stretch receptors found in the wall of the great vessels. Stimulation of the baroreceptors leads to a vagally mediated slowing of heart rate and peripheral vasodilatation. Baroreflex sensitivity has been shown to be impaired in patients with Type 1 diabetes with direct correlations to duration of diabetes and HbA1c [18]. This reduction in baroreceptor function has been directly linked to the subtle changes in autonomic function described above [17,18].

Baroreflex sensitivity is not constant but is affected by preceding episodes of hypoglycemia [33]. In a study looking at these effects, autonomic function was assessed using a variety of techniques, including assessing baroreflex sensitivity, in normal subjects. The autonomic tests were performed prior to and 1 day after laboratory-induced hypoglycemia. The hypoglycemia was induced using hyperinsulinemic clamp techniques and lasted for 90 min. The day after the hypoglycemic episode autonomic function tests were attenuated, including baroreflex sensitivity.

Similar data are not available for patients with Type 1 diabetes although one study has shown a progressive reduction in cardiac vagal activity during laboratory-induced hypoglycemia [34]. This reduction in vagal activity associated with prolonged hypoglycemia may increase the risk of fatal ventricular arrhythmias.

It is therefore possible to hypothesize that the dead in bed patients had subtle changes in cardiac autoregulation that resulted in a sympathetic predominance. These subtle changes may be associated with recent antecedent episodes of hypoglycemia that led to arrhythmia-prone

changes in cardiovascular autoregulation. With the further sympathetic drive associated with nocturnal hypoglycemia this could lead to ventricular cardiac arrhythmias and to sudden death.

### QT interval prolongation & dispersion

The QT interval on the surface ECG is, to some extent, determined by the activity of the autonomic nervous system [35]. Prolongation of the QT interval in congenital conditions, such as the long QT syndromes, is associated with an increase in sudden arrhythmic death. Similarly, a prolonged QT interval has been associated with sudden cardiac deaths amongst Type 1 diabetes patients with abnormal bedside tests of autonomic function [36,37] as well as being identified as an independent marker of increased mortality in patients with Type 1 diabetes [38].

Studies have suggested an association between the cardiovascular autoregulatory abnormalities described above and lengthening of the QT interval [39]. The reduction in parasympathetic function and the relative increase in sympathetic predominance are positively correlated to the length of the QTc.

What seems to be more relevant to the dead in bed syndrome is that the QTc is not a static measurement. Dynamic changes in QT interval have been reported with changes in blood glucose concentration [40,41]. During experimentally induced hypoglycemia, using a hypoglycemic hyperinsulinemic clamp, there is prolongation of the QTc, which returns to normal length when the low blood sugar is corrected [40,41]. Possible mechanisms for this prolongation are a reduction in plasma potassium level resulting from activation of Na/K ATPase or, more likely, from the hypokalemia resulting from an increase in catecholamines induced by the hypoglycemia [42]. Interestingly, in laboratory-induced hypoglycemia the QT changes can be obliterated by concomitant administration of  $\beta$ -blockers. This is in keeping with the hypothesis that sympathoadrenal stimulation by the hypoglycemic episode is the drive to the QTc lengthening [42,43].

The laboratory induction of hypoglycemia raises some issues when trying to relate these studies to the dead in bed syndrome. In patients with diabetes who are experiencing iatrogenic hypoglycemic episodes, the adrenaline response to hypoglycemia is impaired – so-called hypoglycemia-associated autonomic failure [44–46].

We have also already seen that antecedent hypoglycemia is associated with impaired cardiac autonomic regulation in normal control subjects. These so-called metabolic and cardiovascular hypoglycemia-associated autonomic failures may reduce the sympathoadrenally mediated effect of hypoglycemia on QTc even with the sympathoadrenal response associated with severe hypoglycemic episodes.

In addition, studies using the hypoglycemic clamp technique use higher doses of insulin than would be found in patients using conventional subcutaneous insulin.

More recently, similar effects on QTc have been found in diabetes patients with spontaneous nocturnal hypoglycemia [47–49]. In the most recent of these studies, patients with Type 1 diabetes, with no significant diabetes complications, between 20 and 50 years old (i.e., similar to the dead in bed population) were studied at home using continuous glucose monitoring and 24-h ECG monitoring [49]. Significant episodes of spontaneous hypoglycemia were seen in these patients with blood sugars falling below 2.2 mmol/l at night on a number of occasions. During the hypoglycemic period QTc was significantly prolonged. Interestingly, a number of abnormalities in heart rate and rhythm were recorded during the episodes of nocturnal hypoglycemia.

The other studies looked at children [48] and adults [47] with Type 1 diabetes whilst sleeping in a clinical laboratory. Similar changes were seen in QTc with spontaneous nocturnal hypoglycemia. The investigators found a concomitant increase in adrenaline level during the hypoglycemic episodes. This rise was blunted compared with the studies in healthy individuals and experimentally induced hypoglycemia. Interestingly, no statistically significant change in plasma potassium level was seen during the hypoglycemic episodes, but potassium did fall.

One study has looked at the relationship between the QTc changes and hypoglycemia and autonomic function [50]. This study measured baroreflex sensitivity as well as bedside tests on autonomic function and the subjects underwent hyperinsulinemic hypoglycemic clamp. Those with abnormal bedside tests of autonomic function showed a blunted response in hypoglycemia-induced QTc lengthening. These patients also have attenuated sympathoadrenal responses to hypoglycemia as indicated by lower adrenal levels during the

hypoglycemia. Furthermore, those patients with subtle changes in cardiac autoregulation, as assessed by cardiac baroreflex sensitivity, retained similar QTc changes in response to hypoglycemia as those with normal autonomic function [50].

It is possible to propose, therefore, that spontaneous nocturnal hypoglycemia results in an increase in catecholamines, which in turn may lead to a reduction of serum potassium. The combined effect of these changes are to prolong QTc during the hypoglycemic episode so increasing the patient's risk of ventricular arrhythmia which could possibly lead to sudden death.

This is clearly not the complete picture. As has been shown, nocturnal hypoglycemia is common and the QTc changes only persist for the duration of the hypoglycemia. Why then should this lead to sudden death when patients with congenital prolongation of QTc survive for many years? There must be other mechanisms at play that result in sudden death in at-risk groups.

### Genetic factors

In other types of sudden death, genetic studies have identified some of the genes responsible for the metabolic abnormalities leading to presumed fatal cardiac arrhythmia [51].

Interest has focused on genes coding for proteins making up the sodium, potassium and calcium channels in the myocardium. Ion channel flux is essential for normal cardiac action potential initiation, propagation and repolarization, so would seem to be an ideal area of research when studying the dead in bed syndrome.

Mutations in the *SCN5A* gene, encoding the  $\alpha$  subunit of the Na1.5 sodium channel have been seen in some causes of adult sudden death syndrome [51]. The abnormality leads to sudden death due to an increase in ventricular tachyarrhythmias.

In dead in bed syndrome, one paper has looked for and found *SCN5A* polymorphisms in a small number of dead in bed syndrome patients with one patient having a protein changing gene variant [52]. This starts to raise the possibility of an individual susceptibility based on genetic factors that could predispose a patient with Type 1 diabetes suffering a fatal cardiac arrhythmia. The trigger to the arrhythmia could be hypoglycemia and associated QTc prolongation.



## Other proposed factors contributing to the dead in bed syndrome

### ■ Orexin A

Orexin A (also called hypocretin) is a polypeptide hormone released from the hypothalamus and is thought to regulate sleep. In laboratory animals, recurrent hypoglycemic episodes lead to a reduction in orexin-A production and administration of orexin-A to sleep-deprived animals, including primates, increases arousal and attention span [53]. It has been proposed that a similar reduction in orexin-A production in adult patients with Type 1 diabetes may be, in part, responsible for the dead in bed syndrome [54]. In theory, patients with Type 1 diabetes and recurrent hypoglycemic episodes have reduced levels of orexin-A. This in turn could lead to a reduction in arousal response to stimuli, such as hypoglycemia, as well as a reduction in upper airway tone. The patient would fail to wake in response to the low blood sugar and the reduced upper airway tone leads to obstructive sleep apnea and suffocation. There is no evidence, as yet, to support this mechanism for the dead in bed syndrome, but it does warrant further research.

### ■ Mitral valve prolapse

Mitral valve prolapse is associated with sudden cardiac death due to arrhythmias and has an increased prevalence in patients with Type 1 diabetes [55]. One author has proposed that concomitant mitral valve prolapse is the 'other' mechanism that predisposes patients with Type 1 diabetes to the dead in bed syndrome [56]. The author proposes that during hypoglycemic episodes the QTc lengthen and it is those patients with mitral valve prolapse that suffer the fatal cardiac arrhythmias.

The difficulty with this theory is that all of the initial dead in bed cases had post-mortems and the paper specifically says that no cardiac abnormalities were found. Structurally the hearts were normal. Subsequent dead in bed epidemiological studies have all excluded structural cardiac abnormalities as an explanation for the arrhythmia.

### ■ Basal renin activity

Another possible mechanism has been proposed for the dead in bed syndrome [57]. In patients with low basal activity of the renin-angiotensin system that were exposed to experimentally induced hypoglycemia the QTc prolongation

associated with the low blood sugar was more marked than in those with high basal activity [57]. The patients with the lowest activity in the renin-angiotensin system had the greatest rise in adrenaline in response to hypoglycemia, although this did not meet statistical significance. Plasma potassium fell by similar amounts in the groups of high and low basal activity. ACE inhibitors are associated with a shortening of the QTc in resting conditions so these results are difficult to comprehend. At present the role of the renin-angiotensin system is unclear in the pathogenesis of the dead in bed syndrome; however, further studies are warranted.

## Reducing the risk

It is important that we understand the pathogenesis of the dead in bed syndrome as this will allow us to identify at-risk patients and to initiate appropriate treatment for those of highest risk.

As with any diabetes complication the priority rests on improving overall diabetes control. Simple measures should be employed initially with all Type 1 diabetes patients with every effort being taken to avoid nocturnal hypoglycemia. This is particularly important in those patients with hypoglycemic unawareness.

For patients with prolonged QTc at rest then any medication associated with further prolongation should be stopped.  $\beta$ -blockers seem the most effective treatment at preventing the sympathoadrenally mediated QTc prolongation associated with hypoglycemic episodes [43].

ACE inhibitors may also have a role to play in at-risk patients. Studies suggest that ACE inhibitors and angiotensin 2 receptor blockers reduce the sympathetic predominance found in essential hypertension. This has the added effect of increasing heart rate variability and improving baroreceptor sensitivity [58]. With angiotensin receptor blockers evidence also suggests that this change in sympathovagal balance is associated with shortening of QTc and reduced QT dispersion [59]. In summary, drugs that act on the renin-angiotensin system appear to have beneficial effects on aspects of cardiovascular autoregulation that have been implicated in the dead in bed syndrome.

## Conclusion & future perspective

The dead in bed syndrome is a devastating complication of Type 1 diabetes and the current definition probably underestimates the actual number of deaths attributed to this condition.

Nocturnal hypoglycemia seems to be the precipitating factor but why some patients should succumb to such a common occurrence remains unclear.

Two related theories predominate. First, patients at risk of the dead in bed syndrome have subtle, undetected abnormalities of cardiovascular autoregulation. These subtle changes may be due to antecedent episodes of hypoglycemia, which leads to a transient metabolically induced autonomic dysfunction [46]. These changes lead to a relatively increased sympathetic nervous system activity that, during hypoglycemic episodes, predisposes the patient to fatal ventricular arrhythmias. Second, is the theory that QTc lengthening associated with hypoglycemia (driven by the sympathoadrenal response) predisposes the patient to fatal ventricular arrhythmias. These two hypotheses are not mutually exclusive. The recent genetic studies would appear to offer the best option for identifying those patients at

risk of the dead in bed syndrome but more work is needed to identify further suspect genes.

There is a great need to create a national/international database of such patients and appropriate tissue for genetic samples should be taken at autopsy of any patient with Type 1 diabetes who has a sudden unexplained death. This will enable us to start to identify at-risk individuals. Only by such work can we hope to fully understand the dead in bed syndrome.

#### Financial & competing interests disclosure

*The author has no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.*

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