Review

The management of diabetes in terminal illness related to cancer

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Summary

The management of diabetes during terminal illness is complex, with lack of agreement and consensus among physicians and multidisciplinary teams. Despite the plethora of guidelines available for the management of diabetes, there exists no agreed, evidence-based strategy for managing diabetes during terminal illness and at the end of life. A number of physiological factors may influence glycaemic control during terminal illness. These factors include anorexia, cachexia, malabsorption, renal and hepatic failure. Furthermore, controversy exists on the frequency of blood glucose monitoring, the optimum blood glucose range and how to achieve this. We review the factors influencing blood glucose during terminal illness and provide a suggested approach to managing patients with type 1 and type 2 diabetes during the early and late stages of terminal illness.

Introduction

Diabetes mellitus is a common and increasingly prevalent condition, with a prevalence of 4–5% in the UK.¹ Furthermore, estimates suggest that there is one person with undiagnosed type 2 diabetes (T2DM) for every two patients with a diagnosis.² The Health Survey for England 2003 suggests that 3.1% of men and 1.5% of women over the age of 35 years have undiagnosed diabetes.³ T2DM, like other chronic conditions, such as degenerative diseases and cancer, becomes more prevalent with age.⁴–⁶ In the population over 65 years of age, the prevalence of T2DM is 10%¹ and in patients with newly diagnosed cancer the prevalence of T2DM is between 8% and 18%.⁷ Furthermore diabetes is associated with certain cancer types.⁸–¹⁰ Therefore, it is likely that there will be an increase in the prevalence of diabetes and cancer as the older proportion of the population increases. Traditionally, these two conditions have been managed by different specialities and when both co-exist particularly in the terminal stages of life there is little guidance on the best course of management. Surveys among diabetes and palliative care physicians and diabetes specialist nurses (DSN) show disagreement on best practice.¹¹ In routine clinical practice, the objectives of treating diabetes are firstly to reduce macrovascular and microvascular complications and secondly to reduce osmotic symptoms related to diabetes. Both objectives need to be achieved without treatment-associated side effects, in particular hypoglycaemia. At the end of life, the main reason for managing hyperglycaemia is not...
to avoid long-term complications, but to avoid unpleasant osmotic symptoms and at the same time to avoid treatment-associated hypoglycaemia. Within this review, we have examined the available published literature focussing on the management of hyperglycaemia in terminal illness relating to malignant disease and suggest a possible treatment algorithm. Similar principles might also apply to other protracted non-cancer-related terminal illnesses in patients with diabetes. We conducted a full MEDLINE literature search for all relevant articles. Keywords searched for, either individually or in combination were: diabetes, palliative care, end of life, terminal illness, cancer, hospice, insulin, glucose and management. Limits were made to those articles in English, published from 1969 to 2009. Results yielded 21 papers applicable to the search criteria, of which only four were relevant to the management of diabetes at the end of life.

Issues relating to managing diabetes with terminal illness

Diabetes during terminal illness may be complex from a physiological, clinical and ethical perspective. Routine diabetes care outside terminal illness aims for meticulous blood glucose control. Specific challenges associated with terminal illness include the frequency and method of monitoring blood glucose and the choice of medication to avoid hypoglycaemia and control osmotic symptoms. Other challenges include the management of pre-existing diabetes, steroid induced diabetes and diabetes developing after cancer diagnosis. Quality of life may be affected by osmotic symptoms when blood glucoses are running high. Clearly each patient has a different threshold for the development of symptoms, but these are inevitably present with a blood glucose >20 mmol/l. Hypoglycaemia may not only be related to therapies such as insulin and oral hypoglycaemia agents (OHA), but hepatic glycogen reserves may be diminished particularly if the patient is malnourished or in the setting of hepatic metastases. There may also be difficulties for the patient and family relating to the more liberal approach to glycaemia in terminal illness. Below we discuss other factors which challenge the management of hyperglycaemia in the terminally unwell patient.

Gastrointestinal disturbance

Advanced cancer is associated with the anorexia-cachexia syndrome. Both the anorexia and weight loss complicate diabetes therapy. The doses of insulin and OHA may need to be reduced. Of particular importance metformin is associated with nausea, vomiting and gastrointestinal (GI) disturbance. With respect to long acting sulphonylurea therapy, the risk of hypoglycaemia would also be increased. The mechanism responsible for the anorexia associated with advanced cancer is the result of a chronic inflammatory process associated with elevated levels of cytokines such as tumour necrosis factor alpha and interleukin-6. These have profound effects on the hypothalamic control of hunger and food intake. Paradoxically these cytokines may also be associated with insulin resistance within certain tissue such as the liver, skeletal muscle and adipose. The net effect in patients with diabetes is a complex picture of a reduction in food intake, an increase in basal metabolism and reduced insulin sensitivity. This may be further complicated by inadequate hepatic glycogen reserves and therapy with insulin, sulphonylureas or metformin resulting in hypoglycaemia. Nausea and vomiting in association with anorexia may also be exacerbated by chemotherapy and opiate analgesics.

During terminal illness, disturbance in GI motility may occur due to a neoplastic process per se, for example, bowel obstruction associated with large tumours, or associated with medication use such as opiate analgesics. Malabsorption due to primary GI tumours, previous surgery, bacterial overgrowth or as a result of chemotherapy and radiotherapy will influence the absorption of oral nutrients and medications.

Altered hepatic metabolism

As already described, anorexia and GI disturbance will clearly cause a mismatch between nutrient intake and the action of insulin or OHA in patients with diabetes. Table 1 summarizes the potential problems associated with oral diabetes therapies in the setting of terminal illness. Metformin is not typically associated with hypoglycaemia except in the presence of hepatic dysfunction, for example in association with liver metastases or biliary obstruction. This is likely to be the result of reduced hepatic glycogen reserves associated with anorexia and poor food intake. Similarly, hypoglycaemia is also associated with sulphonylurea therapy and dipeptidylpeptidase-4 (DPP-IV) inhibitors in the setting of hepatic failure. In this setting, consideration may be made to a short acting sulphonylurea such as repaglinide. Thiazolidinediones (TZD) are contraindicated in the presence of hepatic derangement because of the risk of acute hepatic failure.
Table 1  Oral agents for the treatment of type 2 diabetes mellitus

<table>
<thead>
<tr>
<th>Medication</th>
<th>Example(s)</th>
<th>Mechanisms of action</th>
<th>Main adverse effects</th>
<th>Increased adverse effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biguanides</td>
<td>Metformin</td>
<td>(i) Reducing hepatic glucose output. (ii) Increased peripheral utilization of glucose.</td>
<td>Nausea, anorexia, vomiting, abdominal pain</td>
<td>(i) Renal failure/renal failure. (ii) Sepsis. (iii) Lactic acidosis.</td>
</tr>
<tr>
<td>Long-acting sulphonylurea</td>
<td>Glibenclamide, Gliclazide, Glipizide</td>
<td>(i) Augment β-cell insulin secretion.</td>
<td>Hypoglycaemia</td>
<td>(i) Renal impairment. (ii) Severe hepatic impairment.</td>
</tr>
<tr>
<td>Short-acting sulphonylurea</td>
<td>Nateglinide, Repaglinide</td>
<td>(i) Augment β-cell insulin secretion.</td>
<td>Hypoglycaemia</td>
<td>(i) Renal impairment. (ii) Severe hepatic impairment.</td>
</tr>
<tr>
<td>Thiazolidinediones</td>
<td>Rosiglitazone, Pioglitazone</td>
<td>(i) Reduce peripheral insulin resistance.</td>
<td>GI disturbance, oedema, anaemia, headache.</td>
<td>(i) Hepatic impairment. (ii) Heart failure.</td>
</tr>
<tr>
<td>DPP-IV inhibitors</td>
<td>Sitagliptin, Vildagliptin, Saxagliptin</td>
<td>(i) Inhibit DPP-IV increase native GLP-1 resulting in increased insulin secretion and lower hepatic glucagon secretion.</td>
<td>Stagliptin: peripheral oedema, URTI. Vildagliptin: nausea, oedema, headache.</td>
<td>(i) Renal impairment. (ii) Severe hepatic impairment (for vildagliptin).</td>
</tr>
</tbody>
</table>

Summary of the mechanism of action and potential adverse effects associated with the use of oral hypoglycemic agents in the treatment of type 2 diabetes in terminal illness.

Target for blood glucose

Outside terminal illness, targets for capillary blood glucose concentrations are typically below 7 mmol/l. However, this may change during terminal illness, especially when there is renal impairment. The practical challenge is to achieve tight glycaemic control while preventing hypoglycaemia.

Adverse effects of oral hypoglycemic agents

Hypoglycaemia is the most common adverse effect associated with the use of oral hypoglycemic agents. It is usually mild but can be severe, especially in patients with renal impairment.

Kidney function

Chronic kidney disease is associated with an increased risk of hypoglycaemia, particularly in patients with type 2 diabetes. The use of biguanides, sulphonylureas, and thiazolidinediones may be associated with a higher risk of hypoglycaemia in patients with renal impairment.

Sulphonylureas

Long-acting sulphonylureas (e.g., gliclazide, glipizide) may be associated with increased risk of hypoglycaemia in patients with renal impairment. Short-acting sulphonylureas (e.g., nateglinide, repaglinide) may be associated with a lower risk of hypoglycaemia compared to long-acting sulphonylureas.

Thiazolidinediones

Thiazolidinediones (TZDs) are associated with an increased risk of hypoglycaemia, especially in patients with renal impairment. The risk is lower withonzaglitazone and pioglitazone compared to rosiglitazone.

DPP-IV inhibitors

DPP-IV inhibitors (e.g., sitagliptin, saxagliptin) are generally less likely to cause hypoglycaemia than other oral hypoglycemic agents.
Managing glucose control

Outside the setting of terminal illness the treatment of diabetes typically follows well-defined algorithms [e.g. National Institute if Clinical Excellence (NICE) guidance in the UK]. However, treatment choices are dependent on many other factors such as age, co-existing morbidity, food intake, carer support and risk of hypoglycaemia. T1DM always requires insulin therapy, however, only when a significant reduction in beta cell function occurs do patients with T2DM require insulin therapy. The key aims of managing hyperglycaemia are to reduce osmotic symptoms in the short-term and to reduce macrovascular and microvascular complications in the long-term. Meticulous control to avoid long-term complications is not required with terminal illness. With respect to the long-term comorbidities, patients are often treated with other therapies such as statins, ACE inhibitors and other antihypertensive agents, and aspirin. Consideration should be made to stopping these agents.

During terminal illness the management of diabetes will not only depend on the type of diabetes, but also on prognosis, oral intake and the presence of co-existing disease such as renal and hepatic impairment. One approach is to stratify patients into two distinct groups; those with constitutional symptoms associated with terminal illness, and those entering the later stages of terminal illness. There is no agreed consensus in the available literature in relation to the optimum blood glucose control, but anecdotally clinicians do not intervene with a blood glucose level up to 20 mmol/l. There is a clear balance between the risks of inducing hypoglycaemia in patients who are anorexic, cachectic, and generally unwell, against accepting a higher blood sugar level without unpleasant osmotic symptoms of thirst, lethargy and polyuria. A difficulty that commonly arises is precisely establishing the cause of symptoms in terminally ill patients. Distinguishing whether symptoms of fatigue are due to hyperglycaemia or advanced terminal illness can be complex. Given that the emphasis of treatment in the palliative setting is symptom-control it is important for the physician to not over-interpret these signs, and investigate beyond what is ethically and morally deemed acceptable.

Type 1 diabetes and Type 2 diabetes treated with insulin

During terminal illness the aim of therapy should be to avoid symptoms relating to hypoglycaemia and hyperglycaemia with a minimum number of injections. Patients with T1DM who are otherwise well should continue on their previous insulin regimens, but if there is reduced appetite then a dose reduction might be appropriate. To reduce the frequency of injections and potential treatment-associated post-prandial hypoglycaemia, long acting insulin analogues such as glargine or detemir may be appropriate, but there are no studies examining this in patients with terminal illness. There is also an argument to avoid the use of long-acting glucose monitoring in terminally unwell patients with days, weeks or months to live. Opinions from palliative care and diabetes specialists range from twice daily, to once every 3 days. However, there is a consensus that patients symptomatic with hypoglycaemia or hyperglycaemia should test more frequently until a safe range is achieved. Authors’ comment in the available literature that patients ‘suffer’ with regular finger-prick testing. Our experience is that most patients have become quite accustomed to this practice, and although this requires some consideration, the frequency of blood glucose testing should be tailored to the wishes of the patient and their families. In general, there may be reluctance to stop capillary blood glucose testing during terminal illness and there are reports where levels are monitored until the day of death. Within one study of patients with terminal illness, 29% (12/42) had blood glucose monitoring discontinued and only in a further 10% (4/42) was the frequency of monitoring reduced. Within this study, 76% (32/42) had blood glucose monitored up to and including the day they died. Of interest, patients and carers may be reluctant to reduce or stop glucose monitoring and may even regard a relaxed attitude to blood glucose levels in terminal illness as disinterest or neglect on the part of the medical and nursing staff. Within the above study only in 5% (2/42) of cases was there evidence of discussion regarding the change of management of diabetes with the patient or relatives.

With respect to T1DM, there is a general consensus that this is more challenging to manage in relation to glucose testing. Furthermore, although there is no agreement on the frequency of blood glucose monitoring; there is a consensus that this should be minimized to reduce discomfort associated with finger-prick testing. With respect to T2DM treated with OHA during the early phase of terminal illness, there is an overwhelming agreement that stopping blood glucose monitoring is a preferred course of action. With respect to the later stages of terminal illness, there is general consensus that blood glucose monitoring should be discontinued, but this is not always easily implemented.
preparations especially when appetite may be suppressed and there is little regular food intake. The management of T1DM during the later stages of terminal illness differs between specialists in palliative care and diabetes. Palliative care physicians are more likely to use ‘as required’ short-acting soluble insulin or rapid-acting human insulin analogues (aspart or lispro), whereas diabetes physicians favour the use of premixed and long-acting preparations.11 It may be that a flexible combined approach is required, for example, in patients with anorexia and vomiting a change to short-acting insulin may be initially required and subsequently a change to long-acting once a day insulin when symptoms have improved.

Type 2 diabetes
For patients with T2DM treated with oral agents, if there is hypoglycaemia, an obvious approach is to reduce the dose of the sulphonylurea. (e.g. 50% reduction). Metformin therapy may need to be stopped in this setting as they may contribute to anorexia. An alternative approach is to use a short-acting sulphonylurea (e.g. repaglinide, nateglinide). The shorter half-life of ~1 h of these agents may provide an advantage in that they may be administered if the patient is eating and withheld if the patient is unable to eat. In this way, the agents would be administered in a similar manner to a rapidly acting insulin analogue. Although there is no published literature on the use of such agents in the terminal phase of illness, this might be useful. For T2DM treated with OHA with blood glucose levels >15 mmol/l, then insulin therapy may be required. No consensus is available on the type of insulin, but twice-daily regime of short-acting insulin may be appropriate.

Education for patient and carer
The importance of patient education must not be overlooked, especially during the end of life. The role of the DSN is essential in this respect. The DSN may have already formed a bond with the patient and relatives during many years of outpatient care or during their hospital stay. The key role of the DSN is to provide support, education and advice in hospital or in the community to patients, relatives and health-care staff. They provide an important link with practice nurses, chronic conditions nurses and community and hospital palliative care staff. Their expertise with insulin delivery devices and home glucose monitoring is essential.

Patients and their relatives will have been previously educated to aim for good glycaemic control throughout the duration of the diabetes and may find it difficult to alter the practice. Furthermore, patients and relatives may also wish to follow the familiar routine. Sensitive discussion between familiar medical and nursing staff, the patient and family should occur to ensure that the avoidance of long-term complications is not the aim of diabetes management during terminal illness. This may, therefore, reduce the medication burden relating to both achieving glycaemic control and also to prevent other complications such as ischaemic heart disease and nephropathy. It may be necessary to provide education on the symptoms, detection and treatment of hyperglycaemia and hypoglycaemia. The range of acceptable blood glucose measurement will need to be explained to the patient and carer and a clear explanation of the reasoning behind this. Carers especially may need to be aware of the difficulty in balancing the risks of inducing hypoglycaemia against accepting a higher blood glucose level without unpleasant osmotic symptoms such as thirst, lethargy and polyuria. Dietetic advice and support may be essential particularly if enteral or parenteral feeding regimes are in use. The family and patients need to be aware that some concomitant medicines such as corticosteroids may increase blood glucose.

A proposed management algorithm
There is a clear paucity of guidelines and protocols available for managing patients with diabetes during the early and late stages of terminal illness. As already described there is also lack of agreement between medical specialists. Any algorithm for managing diabetes in terminal illness must differentiate between patients who are in the final terminal stages of an illness and those with weeks or months to live. Consideration is also required to the location of the patients, the carers, family nursing and medical staff.

We would suggest that all dietary restrictions relating to diabetes are relaxed or removed from the early stage of terminal illness. In both T1DM and T2DM, glucose monitoring should be reduced to an acceptable minimum. In the case of a patient treated with insulin, this may be 2–3 times per week and for a patient treated with oral agents blood glucose could be monitored 1–2 times per week, unless a circumstance arises that necessitates more frequent monitoring. This may include: hypoglycaemia, poor food intake, nausea and vomiting, enteral or parenteral feeding or corticosteroid use. We would recommend a target blood glucose range between 10 and 15 mmol/l in the early stage of
terminal illness with a more liberal range of 5–20 mmol/l in the later stages. The clear aim is to avoid hypoglycaemia and osmotic symptoms and other acute unpleasant problems such as oral or genital candida.

A proposed treatment algorithm for T2DM is shown in Figure 1. Early education, multidisciplinary planning with the patient and relatives are clearly important. The plan should be clearly explained to the patient and family and documented in the medical and nursing notes. Primary care and community palliative team involvement may also be crucial. A review of concomitant medication is essential with particular focus on the need for therapy with corticosteroids, statins, antihypertensive and aspirin. Metformin and TZD are best avoided due to potential adverse effects. During the early phase of terminal illness, the patient should be assessed in relation to the risk of hypoglycaemia. In those at high risk consider the use of a short

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**Figure 1.** Suggested algorithm for the management of patients treated with oral hypoglycaemic agents during terminal illness.  
"High hypoglycaemic risk: poor oral intake, nausea, vomiting, renal failure, hepatic failure. OHA: oral hypoglycaemic agent; SU: sulphonylurea.

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**Figure 2.** Suggested algorithm for the management of patients treated with insulin therapy during terminal illness.  
"High hypoglycaemic risk: poor oral intake, nausea, vomiting, renal failure, hepatic failure. Soluble insulin: Actrapid, Novorapid, Humalog."
acting SU or a DPP-IV inhibitor. There are no clinical trials or other studies looking at the use of any of oral agents or insulin in the management of diabetes with terminal illness. As with any medication, these agents should be avoided if there are contraindications to use.

A proposed algorithm for the management of T1DM is shown in Figure 2. Patients should be grouped by duration of terminal illness and hypoglycaemia risk. If there is a low risk then the current insulin treatment may be continued or a once a day long-acting preparation considered. If the patient is at high risk of hypoglycaemia, then consideration should be made to a reduction in the insulin dose or a switch to short-acting insulin analogue or soluble insulin with meals. An intravenous infusion of insulin would be best avoided.

**Conclusion**

The management of diabetes with terminal illness will become more common practice as the ageing population increases. There is a lack of consensus between physicians and this portrays a difficult and complex management dilemma. This results due to the lack of clinical research and clinical trials within this area of medicine. Much of the available literature is based on personal experience and peer opinions from specialists within palliative care and diabetes. We have reviewed the available published literature and suggest a set of treatment algorithms which are relatively simple, achievable and written as a collaborative effort between palliative care and diabetes. Underpinning these guidelines is the importance of tailoring treatment to individual patient needs. This requires flexibility, ongoing reassessment and full involvement of the patient and family throughout the process. The suggested algorithms are based on personal experience and views rather than evidence. They have been developed on current treatment strategies available in the literature, providing an up to date and easily usable aid to clinicians managing this group of patients. We acknowledge the limitations associated with such an approach, and encourage further research into approaching the management of diabetes at the end of life.

**Conflict of interest:** None declared.

**References**


