Review

Management of diabetes in patients with cancer

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Summary

Diabetes is common amongst patients with cancer. The co-occurrence of diabetes and cancer may lead to poorer prognosis and complications in patients undergoing cancer therapy. There is no randomized trial evidence that treating hyperglycaemia in patients with cancer improves outcomes, and therefore a pragmatic approach to managing hyperglycaemic in such patients is required. We discuss the management of hyperglycaemia in relation to cancer chemotherapy, glucocorticoids and enteral feeding. We also discuss management of glucose in diabetic patients with cancer approaching end of life care.

Introduction

Fuelled by rapid urbanization leading to changes in obesity, diet and physical activity on the background of genetic predisposition, rising levels of type 2 diabetes worldwide appear to show no sign of abating.1,2 Although it is widely recognized that diabetes is associated with vascular complications, it is less well known that the condition is also associated with an increased risk of cancer, independent of its association with obesity.3–6 Cancer and diabetes are both common conditions, but their co-diagnosis in the same individual occurs more commonly than might be expected. Consensus statements from the American and European Diabetes and Oncology Associations report that observational data suggest a strong link between diabetes and breast, colorectal, endometrial, liver and pancreatic cancers.7 They suggest that the likely pathogenesis of this association is through hyperinsulinaemia, hyperglycaemia, inflammation and possibly some diabetes therapies.

This article aims to review the management of diabetes in patients with cancer, discussing the challenges of anti-cancer therapies in patients with diabetes, the relative importance of glucose control in such patients, and the management of diabetes at the end of life.

The effect of cancer therapies on diabetes

Many cancer chemotherapeutic regimes include glucocorticoids which may induce diabetes or exacerbate pre-existing diabetes. Other therapies, such as androgen-deprivation therapy (ADT) with luteinizing hormone-releasing hormone agonists for prostate cancer, are linked with increased risk of the development of type 2 diabetes, possibly due to loss of insulin sensitivity.8 Use of ADT in patients with pre-existing type 2 diabetes and prostate cancer leads to worsening glycaemic control over 2 years, along with increased insulin requirements.9

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Chemoradiation may also induce hyperglycaemia.\textsuperscript{10} Platinum-based chemotherapy (e.g. cis-platin), 5-fluorouracil based chemotherapy,\textsuperscript{11} mTOR (mammalian target of rapamycin) kinase inhibitors (e.g. everolimus) and ABL (Abelson murine leukaemia) kinase inhibitors (e.g. nilotinib) have all been associated with hyperglycaemia.

**Does glucose control matter in people with diabetes and cancer?**

Observational studies suggest that the coexistence of diabetes increases mortality amongst patients with cancer, with a 30–50\% increased all-cause mortality for a variety of cancers.\textsuperscript{12–15} Pre-operative diagnosis of diabetes increases the risk of post-operative mortality for some cancers. In a meta-analysis, pre-existing diabetes was associated with increased risk of postoperative mortality across all cancer types (odds ratio 1.51 [1.13–2.02]), compared with non-diabetic patients undergoing operative cancer management.\textsuperscript{16} In vitro studies also show that hyperglycaemia reduces the efficacy of chemotherapy on breast cancer cells.\textsuperscript{17}

Although the co-diagnosis of diabetes may mean a poorer prognosis in patients with cancer, is there any evidence that improving glucose control improves prognosis? The value of very tight glycaemic control in people with type 2 diabetes has been called into question following the publication of a number of large randomized controlled trials (RCTs) in the last decade.\textsuperscript{18} Recent European and American Diabetes guidelines stress the need for individualized targets for glycaemic control, involving assessment of a patient’s age, co-morbidities and willingness to engage in managing glucose control.\textsuperscript{19} In patients with cancer, there is a lack of good RCT data to guide glycaemic targets. Observational evidence, however, suggests that poor glycaemic control may lead to poorer outcomes in cancer therapy.\textsuperscript{12}

Some anti-diabetic therapies may improve the prognosis of diabetic patients with cancer. In vitro studies of cancer cell lines suggest that metformin may inhibit cancer cell growth and proliferation,\textsuperscript{20} and inhibit cellular transformation in breast cancer.\textsuperscript{21} A number of population-based studies suggest that metformin has a protective role in the development of cancers in patients with diabetes.\textsuperscript{22}

In the absence of good RCT evidence of the potential benefits of managing hyperglycaemia in patients with cancer, a pragmatic approach to glycaemic control amongst diabetic patients with cancer should be taken.

**Practical management of hyperglycaemia in patients with cancer**

Managing pre-existing or newly diagnosed diabetes in patients with cancer can be challenging. Many patients undergoing treatment may be struggling with multiple co-morbidities and the adverse effects of their cancer therapy. Nevertheless, pragmatic management of hyperglycaemia appears to be important to reduce hyperglycaemia-related symptoms and perhaps to improve morbidity and mortality from cancer therapy.

**Cancer chemotherapies**

Patients with long-standing diabetes may have cardiovascular co-morbidities, renal or neuropathic disease which makes chemotherapy challenging. Many chemotherapeutic agents may exacerbate renal dysfunction or worsen neuropathic complications. Patients with diabetic co-morbidities should be carefully counselled about the risk and benefits of such agents. Avoidance of dehydration leading to acute kidney injury should be a clear priority in such patients.

**Glucocorticoid induced hyperglycaemia**

Glucocorticoids may be used in anti-emetics regimes, to reduce oedema, aid with nutrition or to help in pain management in patients with cancer. Haematological malignancies respond well to high dose glucocorticoids and these drugs are integral to the management of such malignancies. Glucocorticoids raise plasma glucose by increasing hepatic gluconeogenesis, increasing insulin resistance and reducing insulin secretion. Glucocorticoids are frequently administered in a high, once-daily dose. Splitting the dose into multiple smaller doses or administering the drug intravenously over a longer period may slightly mitigate the hyperglycaemic effects of glucocorticoids.\textsuperscript{23}

Patients without a diagnosis of diabetes should be screened for the disease prior to high dose glucocorticoid use (Table 1). Glycated haemoglobin (HbA1c) can be usefully employed as a screening test for pre-existing diabetes, although in patients with significant anaemia, accelerated red cell turnover or haemoglobinopathy, HbA1c may not be accurate. The World Health Organisation guidelines on the use of glycated haemoglobin for diagnosis of diabetes suggest that glucocorticoid use is a specific exclusion for use of HbA1c diagnostically, as glucocorticoids will induce acute hyperglycaemia, which may not be detected by HbA1c.\textsuperscript{24} This may make intermittent glucose testing necessary.
Capillary glucose testing can be performed on inpatients using a bedside glucometer. Such testing can also be carried out as an outpatient although this is probably necessary only in patients at high risk of developing diabetes (Table 2).

Patients with pre-existing diabetes should be made aware of the likely exacerbation of hyperglycaemia whilst on glucocorticoid therapy and should undertake more frequent capillary glucose testing. The cyclical nature of chemotherapy and glucocorticoid usage often needs a flexible approach to hyperglycaemia management. There are little published data in this area, but in the authors’ experience, use of intermittent oral or injectable hyperglycaemic therapy is not infrequently required. Careful self-monitoring of glucose levels, close liaison with the diabetes clinical team and education of the patient to anticipate commencement or escalation of therapy during chemotherapy are helpful in managing such patients. As glucocorticoid therapy often leads to significant post-prandial hyperglycaemia, use of agents targeting post-prandial glucose may be required (Table 3).

Some simple principles may be applied:

1. Intravenous sliding scale insulin regimes should be avoided unless the patient is unable to eat or drink fluids.
2. In patients with type 2 diabetes, metformin therapy should be encouraged. If the patient is already on metformin, this should only be discontinued if contrast media for imaging is being used, or if renal function deteriorates significantly (estimated GFR below 30 ml/min). To reduce the possibility of gastro-intestinal side effects, metformin should be commenced slowly—500 mg after evening meal and titrated if possible to 1000 mg twice daily.
3. If post-prandial hyperglycaemia is a significant problem, the use of short-acting sulphonylureas (e.g. gliclazide) can be considered.
4. If oral intake is unpredictable due to nausea and vomiting, prandial glucose regulators such as repaglinide may be helpful. These drugs are short-acting insulin secretagogues, which can be dosed variably according to food intake and may cause less hypoglycaemia.

Table 1 Diagnostic criteria for diabetes mellitus and abnormal glucose tolerance

<table>
<thead>
<tr>
<th></th>
<th>Fasting plasma glucose (mmol/l)</th>
<th>2 hour plasma glucose (mmol/l)</th>
<th>Random plasma glucose (mmol/l)</th>
<th>Glycated haemoglobin (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>≤6.0</td>
<td>—</td>
<td>≤7.8</td>
<td>&lt;.6.0 (&lt;42 mmol/mol)</td>
</tr>
<tr>
<td>Impaired fasting glucose</td>
<td>6.1–6.9 and ≤7.8</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Impaired glucose tolerance</td>
<td>&lt;7.0 and 7.8–11.0</td>
<td>—</td>
<td>—</td>
<td>Pre-diabetes: 6.0–6.4 (42–47 mmol/mol)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>≥7.0 or ≥11.1</td>
<td>≥11.1</td>
<td>≥11.1</td>
<td>≥6.5 (≥48 mmol/mol)</td>
</tr>
</tbody>
</table>

Table 2 Risk factors for the development of type 2 diabetes

<table>
<thead>
<tr>
<th></th>
<th>Ethnicity</th>
<th>Age</th>
<th>Family history</th>
<th>Previous gestational diabetes</th>
<th>Obesity</th>
<th>Medication</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>South Asians 6× increased risk, African Caribbeans 2× increased risk compared with White Europeans</td>
<td>Older age increases risk</td>
<td>In first-degree relatives</td>
<td>Increases risk by 50%</td>
<td>Body Mass Index &gt;30 kg/m² increases risk of diabetes 6-fold</td>
<td>Glucocorticoids, atypical anti-psychotics, beta-blockers, statins, thiazides</td>
</tr>
</tbody>
</table>

5. Insulin therapy may be necessary. Post-prandial glucose control can be achieved with prandial short- or rapid-acting insulin given prior to each meal. This will require input from a diabetes nurse specialist to train patients on insulin management and guide titration of insulin according to glucose levels.
6. Conversion to twice daily biphasic insulin (mixed prandial and intermediate insulin, e.g. humulin M3) may be useful for patients who are already on basal insulin with tablets.
7. Intensification of insulin therapy with a basal bolus (prandial insulin with separate basal dose) regimen may be necessary if hyperglycaemia is uncontrolled on the above regimes.
8. In patients on pre-existing insulin therapy, during high-dose glucocorticoid therapy, doses of insulin may need to be titrated to 2–3 times the original dosage. In addition, if glucocorticoids are tapered down or stopped suddenly, the dose of insulin will need to be reduced commensurately.

Type 1 diabetes

Patients with type 1 diabetes are at a particularly high risk of uncontrolled hyperglycaemia, and close liaison with the diabetes team is essential. Patients should be aware of ‘sick day rules’ with insulin administration but may need careful reminders at the initiation of therapy.
We are not aware of any guidelines aiding the management for type 1 diabetes and cancer. It may, however, be useful to consider the following:

1. Patients should continue to use their long-acting basal insulin each day (even if not eating) but may need a reduced dose if weight loss is a problem.
2. A higher than usual dose of insulin may be required if the patient suffers an intercurrent illness or complication (e.g., neutropenic sepsis).
3. If oral intake is variable or the patient is vomiting, it may be possible to administer prandial insulin immediately following a meal to allow a better estimate of the consumed carbohydrate load.

These patients should be issued with the contact details of their local diabetes team so that urgent advice can be given in the event of a deterioration in glycaemic control.

**Enteral feeding**

Enteral feeding may be needed in patients undergoing cancer therapy and this can pose a challenge in those with diabetes. Hyperglycaemia is common in patients on such feeding regimes and complex interventions may be required. Although there is little RCT evidence to help guide therapy in this

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**Table 3** Drugs used in the treatment of hyperglycaemia

<table>
<thead>
<tr>
<th>Drug class</th>
<th>Example</th>
<th>Mechanism of action</th>
<th>Normal dosage</th>
<th>Use in patients with cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biguanide</td>
<td>Metformin</td>
<td>Insulin sensitization leading to increased glucose uptake in muscle and reduced liver gluconeogenesis</td>
<td>500–3000 mg daily</td>
<td>Useful agent to continue if possible, although will need to be stopped if renal function deteriorates (estimated GFR &lt; 30) or iodinated contrast media required for imaging</td>
</tr>
<tr>
<td>Sulfonylurea</td>
<td>Gliclazide</td>
<td>Stimulation of insulin release from pancreatic islet cells</td>
<td>80–320 mg daily</td>
<td>Useful in acute hyperglycaemia due to glucocorticoid use</td>
</tr>
<tr>
<td>Prandial glucose regulator</td>
<td>Repaglinide</td>
<td>Stimulation of insulin release from pancreatic islet cells</td>
<td>4–16 mg daily</td>
<td>Useful in acute hyperglycaemia due to glucocorticoid use. Particularly useful if oral intake is unpredictable due to emesis</td>
</tr>
<tr>
<td>Insulin</td>
<td>Long acting (insulin glargine, detemir), intermediate acting (Humulin I, insulatard), biphasic (Novomix 30, Humulin M3) Short acting (actrapid) Rapid acting (Novorapid, Humalog)</td>
<td>Replacement of insulin deficiency</td>
<td>Variable between patients</td>
<td>Treatment of choice for acute hyperglycaemia especially associated with glucocorticoids (see text)</td>
</tr>
<tr>
<td>Alpha-glucosidase inhibitor</td>
<td>Acarbose</td>
<td>Inhibit disaccharidases to reduce glucose absorption in bowel</td>
<td>50–100 mg three times daily with meals</td>
<td>Not widely used, due to gastrointestinal side effects</td>
</tr>
<tr>
<td>Thiazolidinediones</td>
<td>Pioglitazone</td>
<td>Insulin sensitization through PPAR-gamma agonist effect</td>
<td>15–45 mg daily</td>
<td>Not useful in the acute setting as slow onset of action</td>
</tr>
<tr>
<td>Glucagon-like peptide-1 analogue</td>
<td>Exenatide, Liraglutide</td>
<td>GLP-1 stimulates insulin release and reduces appetite</td>
<td>10 μg twice daily 0.6–1.8 mg once daily</td>
<td>Not widely used, due to gastrointestinal side effects</td>
</tr>
<tr>
<td>Dipeptidyl-peptidase-4 inhibitor</td>
<td>Sitagliptin, Linagliptin</td>
<td>Inhibit DDP-4 thereby elevated endogenous GLP-1</td>
<td>25–100 mg daily 5 mg daily</td>
<td>May be a useful adjunct, but slow onset of action</td>
</tr>
</tbody>
</table>
circumstance, recent guidelines from the Joint British Diabetes Societies offer pragmatic assistance in such patients. These guidelines are more specifically for enteral feeding in patients following stroke, but may also be applied to enteral feeding in other circumstances.

The guideline suggest that a target glucose range should be around 6–12 mmol/l in patients on enteral feeding. Premixed human insulin or isophane insulin at the start and mid point of the feed is recommended as first line options in such patients. Use of metformin powder administered through the tube is recommended in appropriate patients, as glycaemic control can be significantly improved with metformin use. If the patient is already on basal insulin, then this may be continued, with bolus doses of short-acting insulin added at start and mid point of feed. Although it may be more convenient for the patient, frequent bolus feeds produce rapid excursions of plasma glucose which may not be easily managed with any regime.

Hypoglycaemia in patients on nasogastric feeds may be an issue. In this circumstance, giving 15–20 g of carbohydrate rapidly through the feeding tube should be feasible. Alternatively, intramuscular glucagon or buccal glucogel may be used.

Management of diabetes at the end of life

Managing diabetes in patients at the end of their life can be challenging. The aim is to facilitate a painless and symptom-free death, with the avoidance of hypo- or hyperglycaemic decompensation. To this end, Diabetes UK guidelines suggest a target glucose range of 6–15 mmol/l. In patients with stable disease and a prognosis of a year or more, the guidelines recommend review of prescription of drugs used to prevent vascular complications (angiotensin-converting enzyme inhibitors, statins, beta-blockers and aspirin) and consideration of their cessation or reduction in dose. Oral hypoglycaemic therapies and insulin regimes may need review to ensure that they are as simple as possible and that glycaemic targets are not too stringent.

As disease progresses and prognosis worsens, the guidelines suggest further simplification of regimes. Once daily long-acting insulin may be preferable to more frequent insulin regimes, or oral regimes, especially when given by a family member or when oral intake is poor. Use of short-acting prandial glucose regulators is encouraged especially when oral intake is erratic.

In the situation where the patient has days or hours to live, diabetes therapy should be kept to a minimum. In patients who are diet or metformin treated, glucose monitoring becomes an unnecessary burden. In patients on sulfonylurea, insulin, glucagon-like peptide-1 analogues or other drugs, consideration should be given to whether the treatment should be stopped altogether. If insulin is to be continued, the patient should be converted to once daily long-acting insulin. Occasional blood glucose monitoring may be required and 6 units of soluble insulin (e.g. actrapid) may be administered if glucose is above 20 mmol/l.

Conclusions

There is strong epidemiological evidence that diabetes is associated with an increased risk of a number of cancers. There is also growing evidence that the degree of hyperglycaemia and treatment modalities for hyperglycaemia influence the risk of cancer.

Managing glucose in patients with diabetes and cancer can pose a significant clinical challenge. As there is no clear evidence that tight glucose control improves outcomes in cancer, hyperglycaemia should be managed pragmatically, to ensure the patient is kept asymptomatic and at low risk of acute decompensation. Proactive management of glucocorticoid-induced hyperglycaemia may help reduce large fluctuations in glucose levels. An individualized management plan may help the patient manage their intermittent periods of cancer therapy proactively, so that they are able to anticipate glucose rises and respond to them quickly. Patients with type 1 diabetes or those requiring periods of enteral feeding will need careful liaison with the diabetes specialist team. Planning diabetes care at the end of life will need involvement of the patient and their family in setting realistic goals and avoiding distress in such circumstances.

The challenge of managing diabetes in patients with cancer is best approached using a multidisciplinary team of oncology and diabetes specialists managing the patient on an individualized basis.

Conflict of interest: None declared.

References