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Management of diabetes mellitus in terminally ill cancer patients

Abstract

Many patients not only with cancer cared for by palliative care services suffer of diabetes. Treatment of diabetes in palliative care differs markedly from general medicine. Patients in palliative care usually have short prognosis and treatment targets are related more to the possible symptoms of hyper- or hypo-glycaemia and less to prevention of long term complications. Therefore monitoring of plasma blood glucose can be done less often. In this article we discuss all aspects of plasma glucose control in terminally ill. We also discuss problem of hyperglycaemia induced by steroids. The use of oral hypoglycaemic agents and insulin, together or separately, is discussed in detail. For patients near the end of life and on insulin, we propose a scheme with once daily plasma glucose monitoring and once daily administration of long acting insulin.

Key words: diabetes mellitus, insulin, terminal illness, plasma glucose monitoring, steroid induced diabetes, oral hypoglycaemic agents

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Introduction

Diabetes mellitus is a common disease among the elderly. Approximately 10% of older patients have abnormal levels of blood glucose and/or abnormal glucose tolerance tests (GTT). Most of these patients (90%) will have regulatory, type II diabetes mellitus; only one in ten of the patients will be insulin dependent (type I diabetes mellitus).

There are no reliable statistics about the prevalence of diabetes among terminally ill cancer patients, but it is probable that the prevalence of diabetes is higher than in the elderly population. If tested using a GTT, approximately 37% of non-diabetic patients with advanced cancer would be classified as diabetics [1]. Important common features for both diabetes type II and cancer are:

- insulin resistance in the liver and increased hepatic glucose production;

- increased glucose recycling;
- reduced glucose utilization by the skeletal muscles;
- reduced skeletal muscle glycogen synthesis.

One important difference, however, is that in cancer there is a lack of hyperinsulinism [2]. The mechanism of cancer-related glucose intolerance is poorly understood, although it may be related to the onset of cancer cachexia. There may be tumour-specific factors that induce glucose intolerance by influencing the insulin receptors.

Patients with diabetes are also more likely to suffer from cancer [3, 4]. Insulin is a “growth factor” and may by itself stimulate the growth of diverse tumours. All of this results in a high frequency of cancer patients with diabetes on the palliative care wards. Patients with type II diabetes are reported to have a worse response to cancer chemotherapy, have more complications, and have a poorer prognosis than patients with cancer but without diabetes [5].

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The aim of the treatment

While with diabetes the aim of the treatment is normally to maintain blood glucose at nearly normal levels, the aim for diabetic patients in palliative care is different. Due to their marked insulin resistance, frequent infections and other symptoms, such as anorexia, nausea and vomiting, maintaining the blood glucose at “normal” levels is very difficult, if not impossible. Intensive treatment with anti-diabetics may increase the risk of hypoglycaemia. As in palliative care one tries to control symptoms without inducing adverse effects, wider ranges of blood glucose may be observed. The ranges between 8 and 15 mmol/L (150–250 mg/dL) are seen as safe and relatively symptom free [2]. Doctors and nurses need to realize that patients with long-standing diabetes and marked insulin resistance may experience hypoglycaemia much earlier and with blood glucose values which are in healthy people still seen as normal. The symptomatology of hypoglycaemia has much more influence on patients’ quality of life than hyperglycaemia. Mild hyperglycaemia by its diuretic effect may help to control some other symptoms in the terminally ill, such as heart failure and increased intracranial pressure. Maintaining blood glucose within narrow limits with a marked risk of hypoglycaemia is justified only in

cases of a long prognosis, where normoglycaemia can prevent some of the later consequences of diabetes (Table 1).

Dietary measures

It is often seen as cruel to limit patients with advanced cancer and diabetes with regard to their intake of sugar. However, if the occasional high intake causes hyperglycaemia and symptoms of thirst and lethargy, patients should be advised to change their habits. In most cases, if the intake of calories/sugar is regular, it is possible to allow the patient a higher sugar intake and increase the hypoglycaemic agents/insulin dose.

The choice of an oral hypoglycaemic agent

Metformin, a biguanide which increases the uptake of glucose by the muscles, can be used either as monotherapy or as an adjunct to sulphonylureas [6]. Metformin may contribute to an anti-cancer treatment effect by making less glucose available to the tumour [7, 8]. Traditionally, metformin has been seen as a not-such-a-good-choice in the case of heart failure, COPD or renal impairment, as it may increase the risk of lactic acidosis. This tradition is now being questioned because of the apparently

Table 1. Suggested scheme for managing patients with diabetes and advanced cancer (modified from [2])

Clinical condition	Intervention
Type II diabetes	
Patients on oral hypoglycaemic agents	
Weight loss, decreased appetite	Reduce oral hypoglycaemic drugs by 50%, monitor blood glucose 3 × week and when symptoms are apparent. In some patients, oral agents can be fully discontinued. Use preferentially short-acting drugs. Correct for poor renal function
Terminal phase	Discontinue all oral hypoglycaemic agents, do not monitor blood glucose unless symptoms are apparent
Patients with blood glucose values higher than 15 mmol/L	Consider starting with long-acting insulin, check blood glucose once daily at 6 pm. Use short-acting insulin to control symptoms, not blood glucose values
Type I diabetes	
Stable nutritional status	Maintain previous insulin regime, check blood glucose twice daily every 3 days
Reduced appetite	Reduce insulin, check fasting blood glucose daily
Severe anorexia, nausea and vomiting	Change to short-acting insulin on top of long-acting insulin
Terminal phase	Do not check blood glucoses unless symptoms are apparent. Reduce insulin. Administer only once daily low doses of long-acting insulin. Do not top up with short-acting insulin

beneficial effect on cancer as stated above [9]. Gliclazide and tolbutamide are short-acting drugs and can be prescribed when the fasting blood glucose is between 8–12 mmol/L. The dose should be reduced or discontinued in patients who are not eating or are vomiting. Other hypoglycaemic agents are long-acting and their kinetics may be changed in the case of progressing renal and/or hepatic failure resulting in long-lasting and potentially fatal hypoglycaemias. In many patients who have been using oral hypoglycaemics for a number of years, the dose in the terminal phase can be reduced or the drugs may be discontinued without danger of symptomatic hyperglycaemia.

The choice of insulin

Short-acting insulin SC injections have been used traditionally to control the brittle pattern of diabetes in the terminally ill. A sliding scale of insulin is usually attached to the prescription providing guidelines for the nurses and family members on how to handle it in case of hyperglycaemia. However, this approach needs many blood glucose determinations, which should be avoided as much as possible. An example of a sliding scale [2] is presented on Table 2.

However, these values may vary because of the insulin resistance which may differ from one patient to another. Be careful in patients with newly-diagnosed diabetes, as the insulin resistance may be low and they may be very sensitive, even to low doses of insulin.

In a patient not on antibiotics or changing doses of steroids, one can check the blood glucose once daily, usually at 6 pm, and administer long-acting insulin once daily, with or without oral hypoglycaemics. This regime may be maintained until the end, minimizing the number of blood glucose determinations.

The need for insulin can change rapidly when a patient recovers from an infection and starts to mobilize from bed with the aid of a physiotherapist.

Table 2. Sliding scale — an example

Fasting glucose	Insulin
10–15	6 U
15–18	8 U
18–22	10 U
> 22	12 U

At the same time, the appetite usually increases. This dynamic should be followed by more intensive blood glucose monitoring.

Steroid diabetes

Many patients previously unknown to be diabetics may develop diabetes after the administration of steroids. Glucocorticoids are prescribed to 30% of the palliative care population [10]. Dexamethazone prescribed to lower the intracranial pressure in the case of brain metastases is particularly notorious for this effect [11]. Hyperglycaemia may become apparent many days or weeks after commencing therapy and may become insidious. Hyperglycaemia is usually steroid dose-related. The doses of steroids should be reviewed as frequently as the doses of hypoglycaemic agents and insulin. Leaving the patient on a high dose of dexamethazone is frequently unnecessary and may precipitate diabetes earlier but may also induce many other complications. Patients with steroid diabetes who experience infections and are being treated with antibiotics may rapidly need less insulin and during such an instable period blood glucose should be determined 2–3 times a day.

Effects of other drugs on diabetes

Diuretics, which are often used to control ascites, may alter glucose control in diabetics. Thiazide diuretics and furosemide may produce hyperglycaemia [12]. Potassium-sparing diuretics such as Spironolactone may cause hyperkalemia. Diabetic patients are particularly predisposed to this effect and this drug may cause type IV tubular acidosis or hyporeninemic hypoaldosteronism.

The terminal phase

When the patient enters the terminal phase in the sense that dying is very close, he/she is usually not taking in any calories and drinking only a little. In many of these patients, the determination of blood glucose can be kept to a minimum and the dose of insulin can be markedly reduced. In the case of non-insulin dependent diabetes, drugs and insulin can be discontinued. In insulin dependent diabetes, insulin should be administered until the end, in reduced doses [13]. Some clinicians stop determinations of blood glucose and glucose is tested in a sample of urine, usually at 1 pm, providing the patient has an indwelling catheter. As steroids are frequently also discontinued at the same time, the

need for hypoglycaemic activity may be decreased. Hypoglycaemia can be difficult to recognize and may add to the symptoms of approaching death.

Conclusion

Dying with diabetes is not an easy clinical condition to manage. On the one hand, dying patients should experience the minimum burden of blood glucose monitoring and additional insulin injections; on the other, they should be free of the symptoms of diabetes. In general, hypoglycaemia is experienced as being much worse than hyperglycaemia. Too strict blood glucose control and the brittle course of diabetes may increase the risk of hypoglycaemia. Usually, hyperglycaemia should be treated when there are symptoms of dry mouth and dehydration. Some dehydration may be helpful in the terminal stages of increased intracranial pressure and heart failure. In general in palliative care, the symptoms should be treated rather than the blood glucose values.

References

1. Glicksman A.S., Rawson R.W. Diabetes and altered carbohydrate metabolism in patients with cancer. *Cancer* 1956; 9: 1127–1134.
2. Poulson J. The management of diabetes in patients with advanced cancer. *J. Pain Symptom Manage.* 1997; 13: 339–346.
3. Chodick G., Heymann A.D., Rosenmann L. et al. Diabetes and risk of incident cancer: a large population-based cohort study in Israel. *Cancer Causes Control* 2010; 21: 879–887.
4. Grote V.A., Becker S., Kaaks R. Diabetes mellitus type 2 — an independent risk factor for cancer? *Exp. Clin. Endocrinol. Diabetes* 2010; 118: 4–8.
5. Gallagher E.J., LeRoith D. Insulin, insulin resistance, obesity, and cancer. *Curr. Diab. Rep.* 2010; 10: 93–100.
6. Berstein L.M. Modern approach to metabolic rehabilitation of cancer patients: biguanides (phenformin and metformin) and beyond. *Future Oncol.* 2010; 6: 1313–1323.
7. Jalving M., Gietema J.A., Lefrandt J.D. et al. Metformin: taking away the candy for cancer? *Eur. J. Cancer* 2010; 46: 2369–2380.
8. Ben Sahra I., Le Marchand-Brustel Y., Tanti J.F., Bost F. Metformin in cancer therapy: a new perspective for an old antidiabetic drug? *Mol. Cancer Ther.* 2010; 9: 1092–1099.
9. Rachmani R., Slavachevski I., Levi Z., Zadok B., Kedar Y., Ravid M. Metformin in patients with type 2 diabetes mellitus: reconsideration of traditional contraindications. *Eur. J. Intern. Med.* 2002; 13: 428.
10. Mercadante S., Fulfaro F., Casuccio A. The use of corticosteroids in home palliative care. *Support Care Cancer* 2001; 9: 386–389.
11. Twycross R. The risks and benefits of corticosteroids in advanced cancer. *Drug Saf.* 1994; 11: 163–178.
12. Manrique C., Johnson M., Sowers J.R. Thiazide diuretics alone or with beta-blockers impair glucose metabolism in hypertensive patients with abdominal obesity. *Hypertension* 2010; 55: 15–17.
13. Quinn K., Hudson P., Dunning T. Diabetes management in patients receiving palliative care. *J. Pain Symptom Manage.* 2006; 32: 275–286.