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Management of colorectal cancer and diabetes

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Summary

Colorectal cancer is associated with diabetes mellitus and both of these common conditions are often managed together by a surgeon. The surgical focus is usually upon cancer treatment rather than diabetes management. The relationship between colorectal cancer and diabetes is a complex one and can raise problems in both diagnosis and the management of patients with both conditions. This literature review explores the relationship between diabetes, diabetic treatment and colorectal cancer and addresses the issues that arise in diagnosing and treating this patient group. By highlighting these difficulties, this review aims to improve understanding and to provide clearer insight into both surgical and non-surgical management.

Keywords

colorectal cancer, diabetes mellitus, colon cancer, rectal cancer, surgery

Introduction

Colorectal cancer is associated with diabetes mellitus and both of these common conditions are often managed together by a surgeon. The surgical focus is usually upon cancer treatment rather than diabetes management. Type II (non-insulin dependent) diabetes seems to increase colorectal cancer incidence[1,2] and certainly the incidences of both seem to increase with age. There are factors that surgeons should be aware of in the perioperative period if morbidity and mortality are to be minimised. Diabetic patients are a well-recognised group who fare less well following surgery in general, with surgical site infections[3] and myocardial ischaemia being two of the main causes of this morbidity. Factors discussed in this review are restricted to matters that colorectal cancer and diabetes have in common relevant to the oncology surgeon.

Methodology

A literature search was performed using PubMed, Embase, Ovid and Google search engine. The search included all articles up to and including 2012 and was limited to English language only. A combination of the following search headings was used: 'colorectal cancer', 'colon cancer', 'rectal cancer', 'diabetes' and 'surgery'. Exclusion criteria were technical reports, case reports and patients aged <16 years. There was manual cross-referencing of the yield. Any further articles identified were assessed against the inclusion/exclusion criteria before undergoing more detailed assessment.

Colorectal cancer and diabetes incidence

Colorectal cancer and diabetes are both common diseases in the Western World. Countries that have taken up a western lifestyle have also seen an increase in the incidence of both colorectal cancer and diabetes. Both case control and cohort studies have shown that type II diabetes increases the lifetime risk of colorectal cancer by up to three times the risk to the general population[4,5] and that diabetes is independently associated with greater mortality in colorectal cancers.[6] There is variability to the extent of the association between colorectal cancer and diabetes in these studies which may be explained by the different colorectal cancer stages included, differing follow-up, variable duration of diabetes and differing types of diabetes (insulin- and non-insulin-dependent/type II diabetes). The majority of studies have included only type II diabetes and so the variability of these results may also be explained in part by the natural progression of type II diabetes, where patients in the later stages of the condition have lower levels of insulin. The weight of evidence is that type II diabetes does increase colorectal cancer even when taking into consideration possible confounding factors including obesity, physical inactivity, screening patterns and diet.

Type II diabetes, glucose intolerance and obesity can be considered as on a spectrum which constitutes 'the metabolic syndrome'. Metabolic pathways involved in energy sensing, including AMP-activated protein kinase (AMPK) and mammalian target of rapamycin (mTOR) and insulin resistance and hyperinsulinaemia may at least in part link obesity, diabetes and cancer. Although the exact mechanism by

which AMPK and mTOR affects glucose control is still not, clear studies show that activation of AMPK inhibits the mTOR pathway and thus increases insulin sensitivity.[7,8] Metformin downregulates AMPK and thus activates the mTOR pathway which has been shown to affect cell proliferation; there is also evidence that mTOR activates tumour suppressors.[9] The action of metformin on AMPK may explain the epidemiological studies which indicate a reduced risk of colorectal cancer and other cancers in patients with type II diabetes who use metformin.[10,11] That metformin may be acting as a chemopreventative agent is supported by pre-clinical, clinical data and consideration of its mechanism of action. Pre-clinical studies have demonstrated a chemopreventative effect of metformin in rodent models of colorectal cancer,[12] for which a number of mechanisms have been proposed. In general, metformin treatment is well tolerated, low cost and may have other health benefits and this has encouraged clinical studies exploring its use as a chemopreventative drug in colorectal cancer and other cancers. Metabolic pathways involved in energy sensing and energy balance may also explain the observation that increased exercise is associated with a reduced risk of colorectal cancer recurrence following surgery combined with adjuvant chemotherapy.[13]

The mechanism by which diabetes increases the incidence of colorectal cancer is not clear though several possible mechanisms have been suggested. In particular, the insulin-like growth factor-1 signalling pathway has been shown to have a role in both cancer development and outcome.[14] Elevated levels of both circulating postprandial insulin and C-peptide have also been associated with an increase colorectal cancer risk in three large studies.[15,16]

The role of exogenous insulin in colorectal cancers is controversial as there are several studies that support the theory that exogenous insulin increases colorectal cancer[2,3] but others that refute this claim.[17] A recent systematic review concludes that while diabetes mellitus increases the risk of colorectal cancer, the use of insulin therapy may also increase this risk.[18]

However, many of the systematic reviews and meta-analysis studies supporting the premise that metformin reduces the mortality and incidence of colorectal cancer are based on observational studies of diabetic patients. There are currently few randomised controlled trials to support this hypothesis and in practice this would be difficult to carry out.[19,20]

Alteration in bowel habit in diabetic patients is common due to both medications and the disease process. The duration of diabetes and the age of the patient appear to affect the incidence of cancer and greater screening in this patient group may well be more appropriate. A recent study demonstrated that diabetic patients aged >45 years had a 1.20–1.45-fold greater risk than the non-diabetic population in developing colonic cancer.[21] Poor glycaemic control has also been associated with a greater risk of colorectal cancer; however, a Canadian study highlighted that it is this very group of patients who are less likely to undergo screening.[22] Indeed patients who are attend by their general practitioner (GP) less regularly are less compliant with medications and lifestyle advice and also are less likely to be involved in screening programmes.[23]

For poorly controlled diabetics, when GP referral to the colorectal surgeon is considered, controlling glucose levels may be the primary aim thereby delaying colorectal cancer investigation. As colonoscopy is currently the gold standard investigation to diagnose colorectal cancer, requiring a liquid diet and laxatives which can greatly alter glucose control, GPs would be understandably concerned in putting their patients forward for investigation until diabetic control is stable. Poor glycaemic control could also account for patient symptoms and therefore achieving good diabetic control prior to excluding colorectal cancer may become the short-term goal. One study demonstrated that patients with HbA1c $>5\%$ had a four-fold risk of incidence of colorectal cancer.[14] This may help to identify a patient group who may be considered for future colorectal cancer screening or at least a group where the threshold for investigating for colorectal cancer is low.

Diabetes mellitus and colorectal cancer diagnosis

Diarrhoea is one of the most common symptoms of colonic cancer but it is not uncommon to investigate this symptom only to eventually conclude that the diarrhoea is related to either the treatment or effects of diabetes. Diarrhoea, especially at night, is often a result of autonomic neuropathy, and diabetic neuropathy is one of the most common symptomatic complications of diabetes. Like colorectal cancer, diabetic neuropathy increases with age and the duration of diabetes. The possible underlying aetiological factors in diabetic neuropathy may include vascular, metabolic, neurotrophic and immunologic factors.

Diabetic diarrhoea is typically watery, nocturnal diarrhoea which may last many days or alternate with constipation. The pathogenesis of diabetic diarrhoea may include reduced gastrointestinal fluid absorption, bacterial overgrowth, pancreatic insufficiency and abnormal bile salt metabolism. Irrespective of previous diabetic control, the goal of perioperative treatment is to maximise diabetic control.

Patients with diabetes who have autonomic neuropathy are more likely to develop constipation.[24] However, patients with brittle diabetes are more likely to develop intermittent diarrhoea with chronic diarrhoea more commonly found in type I diabetics.[25] It is well known that metformin can result in diarrhoea[26]; however, presuming this is the case in all patients presenting with this high-risk symptom of colorectal cancer would be unwise. Given that patients with diabetes are at greater risk of developing colorectal cancer, investigation into bowel habit change is warranted and only after negative results can medication be implicated as the causative agent.

Diabetic patients are also more likely to develop faecal incontinence due to weakness in both internal and external anal sphincters.[27,28] Careful history taking and examination should help to clarify whether patients are experiencing a true recent increase in bowel habit or worsening anorectal function. Not uncommonly softer stool exposes a pre-existing sphincter weakness prompting pelvic floor clinic referral for incontinence rather than the underlying diarrhoea.

Colonoscopy and diabetes

Studies have shown that both obesity and diabetes are also associated both adenomas and hyperplastic polyps, again the exact mechanism for this is uncertain.[29,30] The increased presence of polyps results in a greater number of procedures and biopsies therefore potentially increasing the risk of endoscopy-related morbidity.

The main risk in diabetic patients is the need for bowel preparation prior to carrying out colonoscopy. The responsibility of glucose control is largely in the hands of the patient and for patients who have a background of difficult control the potential consequences can be costly and even life-threatening.[31] Alternatives have been investigated to try and identify those patients where colonoscopy is most justified, for example, tissue inhibitor of metalloproteinase 1 and carcinoembryonic antigen levels; however, diabetes (type I and type II) can falsely elevate both of these and so are of little diagnostic use.[32]

Preoperative factors in diabetes

Preoperative carbohydrate loading has become part of enhanced recovery programmes in recent years. Preoperative carbohydrate loading has been shown to be safe and recommended in non-insulin-dependent diabetic patients. In diabetic patients, preoperative carbohydrate loading has not been shown to result in adverse effects such as hyperglycaemia or delayed gastric emptying. However, it is suggested that monitoring of blood glucose levels is carried out at regular intervals perioperatively.[33]

Operative factors to consider in diabetes

Mortality rates of CRC and diabetes

There is evidence of increased short-term perioperative mortality in patients with colorectal cancer and diabetes.[1,34] A recent meta-analysis demonstrated that long-term all-cause mortality in patients with diabetes was 32% higher than in non-diabetics (95% CI: [1.24, 1.41]).[35] When stage 2 and stage 3 colonic cancer were studied in a large cohort it was surprising that the median survival was only 6 years for diabetics but nearly double this for non-diabetics.[1]

As diabetes results in more short-term postoperative complications as well as higher long-term cancer recurrence, it impacts upon risk calculations prior to offering surgery to unfit diabetic patients. In addition, this should prompt inclusion of diabetic status when assessing a colorectal surgeon's short- and long-term postoperative results.

Rectal cancer surgery and diabetes

Impotence and both urinary and faecal incontinence following rectal surgery is certainly technique dependent in addition to factors including diabetes, smoking, alcohol and the use of medications. The relative cause of impotence following a combination of radiation, chemotherapy and surgery for rectal cancer are complex. Emphasis upon autonomic nerve preservation may not have a great impact upon postoperative continence if the autonomic nerves are already affected by diabetes.

Faecal incontinence in diabetes may be due to anal sphincter incompetence or reduced rectal sensation in combination with diabetic diarrhoea. Low anterior resection especially in relation to adjuvant radiotherapy risks 'anterior resection syndrome'. It is likely that diabetic patients are more likely to suffer this complication which should be considered by the operating surgeon preoperatively when the options of permanent stoma *versus* aiming for long-term gut continuity are discussed.

Early postoperative recovery in diabetes

A recent study showed that diabetes also increased the risk of postoperative urinary infections which

not only increases in patient stay postoperatively but significantly increased the risk of in hospital mortality.[36] In the long term, after cancer treatment, diabetes affects patients both physiologically and psychologically with a greater perception of poor health following treatment.[37]

Bowel motility

Gastroparesis is abnormal gastric motility leading to impaired gastric emptying. This condition is often associated with diabetes but can also occur after surgery and certainly it has been noted anecdotally that patients with diabetes have slower gut recovery. This has become more apparent perhaps since the advent of enhanced recovery programmes where patients gut function is expected to return within a few days. Recently, it has been shown that cholinesterase inhibition accelerates colonic transit and improves bowel function in diabetic patients with chronic constipation[38]; however, the safety of such agents has not been well studied in the postoperative period. In the postoperative phase, patients with prolonged ileus may require parenteral feeding, unfortunately this can exacerbate glycaemic control and impair wound healing.[39]

Anastomotic factors

Anastomotic leak is the largest risk of mortality following colorectal surgery and most surgeons agree that diabetes is a risk factor in rectal surgery.[40,41] An anastomotic leak carries a high mortality, so it would appear sensible to consider a temporary stoma to defunction particularly low anterior resections in diabetics. A temporary loop stoma may reduce the consequences of a leak; however, it appears not to significantly change the leak rate *per se*.[42] Diabetes itself has been shown to be an independent risk factor for anastomotic leaks which has a high contributing factor to both morbidity and mortality postoperatively.[43]

A recent large study of patients undergoing colonic resections showed that the presence of diabetes did not seem to relate to colonic anastomotic leak rate, but diabetic patients who had a leak had more than a four-fold higher mortality compared with non-diabetic patients.[44] It was noted that diabetics on steroids did have an increased anastomotic leak rate.

Surgical risk reduction

A large study from Taiwan, where patients were followed for up to 12 years after diagnosis again demonstrated that diabetes is associated with a greater mortality associated with colorectal cancer. This was greatest in the working age group (25–54 years) but no significant difference was found with insulin usage. This study emphasises the need for greater postoperative care of diabetic patients. The commonest cause for increased mortality in type II diabetes patients is cardiovascular disease,[45] with this in mind there may be benefits to optimising patients preoperatively with specialist cardiology advice.

Simple blood glucose testing is routinely carried out in patients prior to major colorectal surgery and may identify such high-risk patients who may benefit from perioperative intervention and higher dependency recovery settings. In common with obese patients, those with diabetes have more difficult surgical access and delayed wound healing. By taking this into consideration when planning colorectal resection and managing not only surgical aspects but also the diabetic factors, morbidity may be reduced.[46]

Adjuvant treatment factors in diabetes

At present, 5-fluorouracil (5-FU)-based chemotherapy regimes are the main treatment for colorectal cancer.[47,48] While the side-effects of 5-FU have been well documented, the effects of this drug on glucose metabolism has rarely been investigated. A recent study by Feng *et al*. looks at these effects in detail.[49] Their retrospective study demonstrated that 5-FU increases the risk of hyperglycaemia in patients with initial normal fasting plasma glucose and that these effects can occur even after completion of treatment. In diabetic patients, there was the potential to increase insulin requirements and three patients in the study died from diabetic-related complications. This is the largest study specifically looking at diabetes as a complication of treatment. Other studies have highlighted the fact that cancer patients are more likely to develop chronic diseases[50]; however, the need to routinely monitor aspects of patients' health such as fasting glucose levels is becoming more apparent. The effects of 5-FU on glucose metabolism not only potentially increases the risk of recurrence in certain individuals but also has implications in patients who receive neoadjuvant chemotherapy. Patients not previously diagnosed with impaired glucose tolerance or diabetes may develop these problems following 5-FU treatment coinciding with surgical treatments thereby affecting wound healing and recovery. While the study by Feng *et al*.[49] was relatively small and further research needs to be carried out

to ascertain the spectrum of effects of 5-FU, the study will potentially affect how patients are managed both pre- and postoperatively with greater emphasis on glucose monitoring.

Oxaliplatin combined with a fluoropyrimidine currently represents a standard of care for stage 3 colorectal cancer. Oxaliplatin is associated with peripheral neuropathy and so for patients with diabetes this drug should be used with caution.

Radiation effects in diabetes

Toxicity following radiation to the pelvis is more common in diabetics[51] and certainly when assessing sphincter function, diabetes in addition to surgery and radiation may accumulate risk in faecal incontinence. However, the postradiation cancer response appears to be comparable between diabetics and non-diabetics.

Chemotherapy effects in diabetes

Chemotherapy in diabetic patients is a complex challenge. Not only is the diabetic control an issue, but following resection patients are more prone to loose stool. A large randomized controlled trial showed that patients with diabetes and stage 2/3 disease were more likely to suffer severe diarrhoea as a result of chemotherapy than patients without diabetes.[1] Patients with diabetes are also more likely to suffer from cardiovascular disease, renal failure and neuropathy all of which can be exacerbated by chemotherapeutic agents.

Antidiabetic medication and colorectal cancer

As discussed previously, the impact of hypoglycaemics, including insulin usage, on colorectal cancer is complex. There are several trials that suggest insulin may increase the risk of colorectal cancer in diabetic patients. However, this effect may in part be due to the protective effects of metformin as trials have shown that the apparent increased risk of colorectal cancer in patients who use insulin is abolished if they also use metformin.[52] Recent research does suggest that metformin may have antineoplastic properties[13,14] and patients receiving metformin appear to have a better overall survival compared with type II diabetics who are not taking metformin.[55] A recent meta-analysis appears to support the theory that metformin is protective against colorectal cancer in diabetics.[22] However, many of the studies are not clear if the results seen are due to beneficial effects of metformin or deleterious effects of insulin.[56]

Summary

It would be unwise to assume that diarrhoea in a diabetic patient is due to diabetes alone. The possibility of colorectal cancer in a diabetic should always be prevalent in a clinician's mind in view of the increased incidence of cancer associated with diabetes. The complications of investigating diabetic patients should not prevent instigating tests with the same haste as for non-diabetic patients assuming diabetic control is stable. As patients with colorectal cancer and diabetes have an increased risk of both short- and long-term mortality, it is important to recognize and address this at every stage of diagnosis and subsequent treatment. This is particularly true in low rectal surgery, where a defunctioning stoma should be strongly considered in a diabetic patient given their elevated leak risk. Preoperative glucose testing may be a simple method of identifying a high-risk group whether improvement of diabetic control alone will improve long-term outcomes or reduce lifetime cancer risk for colorectal cancer patients still needs to be established.

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