People with diabetes may be more likely to develop cancer – and cancer can, in itself, lead to diabetes. The relationship between these two conditions is complex, but the latest research is beginning to unravel the connections as Dr Eleanor Kennedy explains.
The old saying that good news doesn’t sell newspapers appears to be having something of a renaissance. In a summer that has had the agony of a World Cup defeat, political turmoil and dangerously high temperatures smashing weather records, an analysis of around 20 million people which found that women with diabetes are 27 per cent more likely to develop cancer was also published. And the bad news didn’t stop there. For men, the risk increased by 19 per cent compared with those who do not have the condition leading the research team who undertook the study to predict that, with the diabetes epidemic continuing to spiral, this could lead to soaring cancer rates in the next few years.

For people already living with diabetes, this represents a fresh blow, as living with one long-term condition is challenging enough, without having to live with two. So what are the links between diabetes and cancer? And what should we be telling our patients? Well, this news is not as new as some believe. The Warburg Hypothesis demonstrated, as far back as 1931, that cancer cells exhibited increased glycolysis and decreased oxidative metabolism. The net effect of this is that cancer cells are primed to use glucose as their main fuel for metabolism. In tumours, the rate of glucose uptake increases dramatically and lactate is produced, even in the presence of oxygen and functioning mitochondrial respiration.

But, as always, that’s not the whole story.

**Diabetes and cancer**

There is now convincing evidence that being overweight or obese, which are two very familiar phenotypes in diabetes clinics, can increase the risk of 11 cancers: oesophageal, liver, kidney, stomach, colorectal, advanced prostate, postmenopausal breast, gall bladder, pancreatic, ovarian and endometrial. Other common risk factors that heighten this risk include non-modifiable factors like age, gender, race and ethnicity and modifiable ones like weight, physical inactivity, alcohol and tobacco consumption and diet.

Professor Tahseen Chowdhury, Consultant in Diabetes at the Royal London Hospital, says that it is important to acknowledge that these risk factors are not seen across the whole diabetes spectrum. “The epidemiological data is very strong that, for obese patients with Type 2 diabetes, there is a 30–50 per cent increase in the risk of cancer. However, that link is not nearly as strong or as convincing for people with Type 1 diabetes.”

However, the way in which diabetes causes cancer cannot be simply explained by obesity because, in patients who have undergone bariatric surgery and whose diabetes has been reduced or even reversed, the procedure does not have such a profound effect on the cancer risk.

The Swedish Obese Subjects study has shown a reduced risk of developing cancer but one that seems to favour women, the greatest cancer prevention effects from weight reduction being seen in post-menopausal breast and endometrial cancers. However, any reduction in obesity-related cancers, numerically more common in men, such as colon, rectal, and kidney, is much less marked.

So what else could lead to this link between Type 2 diabetes and cancer? Instead of obesity, it may be that metabolic dysfunction – the hallmark of diabetes and including hyperglycaemia, hyperinsulinaemia and insulin resistance, is to blame. *Diabetes and Cancer: A Consensus Report* recommends more research into the possible mechanisms that these factors, as well as inflammation, may play in linking diabetes and cancer.

**The underlying science**

Given insulin’s well-documented role as a growth factor, it is perhaps not surprising that the link between diabetes, obesity and cancer could be facilitated by insulin and the insulin-like growth factor (IGF) axis. One meta-analysis has shown significant excess risks of colorectal and pancreatic cancers are associated with high circulating levels of insulin or C-peptide.

The majority of cancer cells express both insulin and IGF-I receptors. The insulin receptor is capable of stimulating cancer cell proliferation and metastasis. Insulin may exert its mitogenic effects through IGF-1 receptors, as studies have indicated that people are at an increased risk of several, mostly epithelial, cancers like breast, prostate and colon if they have increased levels of circulating IGF-1.

And hyperglycaemia is known to lead of altered IGF-1 signalling in smooth muscle cells, which allows the cells to undergo a mitogenic response. Although the authors link this process to this process to the development of atherosclerosis, abnormal vasculature is also observed in cancer.

Hyperinsulinaemia may also have a role, by promoting changes in the IGF system that lead to increases in the levels of circulating, bioactive IGF-1. As human tumours often overexpress IGF-1 receptors, it is possible that hyperinsulinaemia is potently mitogenic.

While researchers wrestle with the molecular origins of the links between certain cancers and Type 2 diabetes, clinicians face daily decisions about prescribing drugs other than insulin to their patients.

**Diabetes drugs and cancer**

There are, of course, the oral antidiabetic drugs that are used to treat Type 2 diabetes to consider. Several years ago, the thiazolidinedione class of drug was linked to increased levels of various carcinomas in animal studies. Due to an increased risk of adverse cardiovascular events, rosiglitazone is no longer approved in Europe. There were subsequent studies linking pioglitazone with a higher risk of bladder cancer in...
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humans but this has largely been disproven in larger cohort analyses7.

Then, of course, there was the glargine story. In 2009, Hemkens et al. published observational data designed to investigate the risk of malignant neoplasms and mortality in patients with diabetes treated either with human insulin or insulin analogues. In this cohort study of 127,031 patients, the authors showed that the cancer incidence with glargine was higher than expected compared with human insulin8. Thanks to the ORIGIN study and others, this finding was largely thought to have been debunked, with no higher frequency of malignancies being found in glargine-treated patients.

However, those working in the cancer field think that the studies cannot be easily compared as there are many inconsistencies in the findings of these meta-analyses. There are caveats even to the interpretation of the ORIGIN study – which was supposed to be the definitive trial. There was a very rapid drop-off in patient numbers during the trial, meaning that only 14 per cent of the recruits were followed out to the seventh year. Epidemiologists consider that this is too short a lag period to define any meaningful associations between exposure and cancer incidence9.

The GLP-1 agonists and DPP-IV inhibitor classes of drug, now well-established as second and third-line therapies in the treatment of Type 2 diabetes, have also been of particular interest to investigators, following warnings of potentially increased risks of acute pancreatitis and pancreatic cancer and of thyroid cancer. However, as real world data becomes available to complement the results of the randomised controlled trials, it is becoming clearer that, certainly for the cases of pancreatitis and pancreatic cancer seen in clinical trials, this is now not of such concern in large patient populations10.

And, of course, there is now some evidence to suggest that metformin, the drug that keeps on giving, may not only protect against cancer but could also be beneficial in reducing the risks of a recurrence of cancer when added to the chemotherapy treatments. This antitumour adjuvant drug role may work via inhibition of the tuberous sclerosis complex and AMP-activated serine/threonine protein kinase, cytotoxic effects, and/or immunomodulation11.

Cancer and diabetes

Although only pancreatic cancer has been definitely linked to causing diabetes, in patients with cancer, there is an increased risk of getting diabetes. This is due to the administration of cancer therapies. Patients with cancer are at risk of hyperglycaemia during treatments. Many factors can contribute to this – nutritional imbalances, physical inactivity, high stress levels and infections – but the one most commonly cited is treatment-induced.

Dr Daniel Morganstein, Consultant Endocrinologist at The Royal Marsden Hospital, recognises that the treatment pathways are often the culprits. “People with cancer are regularly treated with steroids. Steroids are diabetogenic so can often either cause diabetes or exacerbate pre-existing diabetes and management of this can be very tricky,” he explains. “Steroids are often given at high dose but in short bursts leading to big fluctuations in glucose levels. Changing diabetes treatment effectively during this can be challenging.” Careful and frequent monitoring of blood glucose levels are key, as is clear guidance for the patient on how to adjust his or her diabetes treatment during and after chemotherapy.

One meta-analysis found that, although the findings were not consistent among the studies, there was evidence to suggest that certain agents...
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Dr Daniel Morganstein

used in chemotherapy regimens were more likely to increase the development of hyperglycaemia. As well as steroids, a number of other drugs used in the treatment of cancer could do this, including docetaxel, everolimus, and temsirolimus alone, or in combination with other agents.

Palliative care
In cases of terminal cancer, management of diabetes during the end of life can be difficult. In people with diabetes, failure of surgery and/or chemotherapy and radiotherapy protocols is often exacerbated by poorer outcomes related to co-morbidities of the condition and the fact that such patients are more prone to post-operative infections. Prof Chowdhury feels that, whether the diabetes has led to cancer or the cancer has led to diabetes, minimising prolonged periods of hypoglycaemia and hyperglycaemia are key. However, he does realise that in the later stages of life, this is not always feasible. “Patient education, including careful self-monitoring of glucose is important but the withdrawal of monitoring and therapies designed to manage hyperglycaemia in patients with advanced or incurable cancer, and who are undergoing palliative care, can be challenging, but can also be a relief to patients and to their families.”

Diabetes UK has produced clinical care recommendations about end of life diabetes care which emphasises the importance of involving individuals and their families in the decision-making process regarding diabetes management and the need to balance the benefits of any diabetes intervention with the cancer prognosis.

Conclusion
Data establishing links between certain types of cancer and Type 2 diabetes are becoming more significant as large cohort studies continue to report. However, despite the relationship being there the underlying understanding of exactly how the two conditions are related remains the topic of some debate.

Weight loss and diet remain key factors in reducing the risk of both but neither holds the individual key to the whole story. Larger studies on patients undergoing w require longer follow-up times to determine whether the gender bias that appears to favour women can be observed in men. But it may be the very molecular details at in vitro levels that may inform important preclinical and prospective clinical studies that could unravel the effect of diabetes on cancer risk and progression and vice versa.

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