Does diabetes mean worse outcomes for cancer patients?

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Diabetes is a known risk factor for developing cancer, but could it also predict how cancer patients respond to treatment?

In a recent study of thousands of cancer patients published in *Clinical Cancer Research*, Imperial researchers found that having Type 2 diabetes was strongly linked to worse outcomes among those receiving immunotherapy drugs called immune checkpoint inhibitors.

According to the researchers, more work is needed to establish and understand the links further, but it could offer important insights into the mechanisms by which diabetes disrupts a common treatment for a wide range of cancers.

Dr. David Pinato from the Department of Surgery & Cancer spoke to Ryan O'Hare to explain the links, and what it could mean for cancer care .

What's the link between diabetes and cancer?

David Pinato—We've known for a long time that diabetes is one of the major risk factors that predisposes people to cancer—so if you have diabetes, you are more likely to develop cancer. And anywhere from 15%–20% of cancer patients in the U.K. will have Type 2 diabetes.

We also know that some cancer treatments, like chemotherapy, cause nausea so patients may not want to eat. For patients with diabetes, this can be dangerous as their blood glucose levels can drop, leading to hypoglycemic attack.

Another reason why patients with diabetes have been traditionally felt as more vulnerable is the higher risk of side effects from chemotherapy such as infection or nerve damage from certain types of chemotherapies.

What has been less clear, so far, is that if someone with diabetes does develop cancer, what impact does their diabetes have on how they respond to immunotherapy treatment?

Why does diabetes affect cancer outcomes?

DP—Type 2 diabetes is a chronic inflammatory condition which can have widespread impacts on our metabolism and immune system, as well as a number of associated health complications, so patients can be more frail.

In terms of cancer treatment, this means diabetic patients are often more fragile. For instance, with chemotherapy we intentionally target rapidly-dividing cells—like those found in the immune system— but we induce a higher risk of infection. Diabetic patients are flagged as being more vulnerable than other patient groups receiving this kind of treatment.

But whether a patient has diabetes or not, they will receive cancer treatment the same way. This includes immunotherapy and a class of drugs called immune checkpoint inhibitors, which are widely used and can be used for elderly cancer patients, or those for who chemotherapy isn't suitable.

What does your work add to this picture?

DP—Before our study, it wasn't clear whether having diabetes led to worse outcomes with immune checkpoint inhibitors. Because we know that diabetes is an immunosuppressive condition, we wanted to find out if having diabetes before receiving this immunotherapy could change patients' response and survival.

We looked at outcomes in more than 1,400 patients, with and without diabetes, and with a range of tumor types, receiving immune checkpoint inhibitors. What we found was that those patients with diabetes, who were taking medications to reduce their blood sugar levels, tended to have worse outcomes from immunotherapy. Overall, diabetes was

associated with worse overall survival, independent of the type of cancer.

But we took the observations a step further and analyzed tumor samples from patients to look at what's going on at the local cellular level. This showed that the tumor microenvironment of those patients with diabetes was way more immune suppressed, and there was actually evidence of T cells within the tumor being less capable of mounting an immune response [against the cancer], compared to in tumors from patients who didn't have diabetes.

Finally, we looked at the patients' blood sugar levels—which is a simple way of measuring how well they are controlling their diabetes. We found that people with higher blood sugar levels had evidence of more aggressive features of the cancer.

Do these immunotherapy drugs not work as well in diabetic patients, or are existing diabetes medications having an impact?

DP—We don't fully understand why immunotherapy drugs are not working as well in patients with diabetes: our study is the first step to try and understand why. It could be for any number of reasons, such as their already compromised immune state.

One of the things that we had to address in our work was the role of metformin, which helps people to control their blood glucose levels. This is a really common diabetes medicine, taken as a pill, and often the first medication patients are prescribed.

We found that people on metformin had slightly worse outcomes compared to others, but it's unclear why. Is it that the medication worsens the outcome? Or is it that patients on metformin had poorer

control of their diabetes? It may be these patients are not just taking metformin, but also require multiple other glucose lowering drugs on top of that as well, and this may still not properly control their diabetes.

What could this mean for the care of cancer patients?

DP—I think this could change patient care dramatically. But we need further clinical studies to evaluate whether or not the severity of diabetes is directly linked with the outcomes, or what effect different diabetes medications may have.

Diabetes is for most people an irreversible medical diagnosis; once you have it, you have it. But the quality of diabetes control isn't so rigid, so whether or not you have high or low blood sugar strongly depends on how well your diabetes is controlled. I think this is really where the message becomes important.

If we imagine a typical cancer patient receiving treatment, they are likely to have nausea, pain, they may be vomiting, and they may not be eating very well. So perhaps the last thing we may want to do is to restrict their diet further and say, "You shouldn't be eating sugar" or "You should be injecting insulin more liberally."

But this is where I think the value is in our research. If we can show that caring for diabetes is important to preserve cancer outcomes for immunotherapy, then it begs the question of whether being stricter with diabetes control can abate the difference in outcomes we're seeing between diabetics and non-diabetics.

There's this term "pre-habilitation," the idea of helping patients to be fitter before surgery or therapy to maximize their outcomes. So could diabetes care be part of this pre-habilitation of patients?

For example, if a diabetic patient with cancer is due to come into hospital for immunotherapy in two weeks' time, do we need to look at the diabetes regimen before they start? Or is it already too late at that stage to have an impact? We can't really answer this from our study alone, so these are still open questions for the future.

More information: Alessio Cortellini et al, Type 2 diabetes mellitus and efficacy outcomes from imune checkpoint blockade in patients with cancer, *Clinical Cancer Research* (2023). DOI: 10.1158/1078-0432.CCR-22-3116

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