EDITORIAL (SEE ZHANG ET AL., P. 2323)

Metformin and Colorectal Cancer Risk in Diabetic Patients

There has been substantial interest in investigating whether the long-term administration of metformin to diabetic patients leads to a reduction in the incidence of malignancies in general or more specifically colorectal cancer. A number of studies have been published on this field with mixed results (1,2). In this issue of *Diabetes Care*, Zhang et al. (3) report the results of a meta-analysis of five observational studies including 108,161 patients with type 2 diabetes. As compared with other antidiabetic treatments combined, use of metformin was associated with a lower risk of colorectal cancer (relative risk 0.63 [95% CI 0.47–0.84]). There was no evidence of significant heterogeneity among the included studies or statistical evidence of publication bias.

Metformin is the first drug of choice for the management of type 2 diabetes (4,5). It has two main antidiabetic mechanisms of action, both of which have also been implicated as anticarcinogenic mechanisms. Firstly, metformin inhibits hepatic glucose production through an LKB1/AMP-activated protein kinase–mediated mechanism. Metformin-induced initiation of an LKB1-mediated AMP-activated protein kinase–dependent energy stress response has been shown to adversely affect the survival of cancer cell lines (6,7). Secondly, metformin improves insulin sensitivity in peripheral tissues reducing hyperinsulinemia. Insulin resistance and hyperinsulinemia have been associated with increased risk of several types of neoplasm (8,9) and specifically with colorectal cancer (10). These mechanistic pathways provide sufficient rationale for investigating the hypothesis that use of metformin is associated with reduced risk of selected malignancies.

It is worth emphasizing that the study by Zhang et al. is a meta-analysis of observational studies and not a meta-analysis of randomized controlled trials. Thus, all the limitations inherent in the original observational studies included in the meta-analysis are naturally also present when such study results are combined. Paramount among these limitations is the potential for incomplete adjustment for confounding. In this setting, factors influencing the decision to use metformin as opposed to another antidiabetic agent may simultaneously also be associated with cancer incidence, resulting in bias referred to as confounding by indication. Such confounding factors may be known or suspected medication contraindications or unknown influences on prescribing decisions. There are major differences in the baseline characteristics of patients on metformin as compared with other antidiabetic agents that make confounding highly likely. For example, in the U.K. General Practice Research Database metformin users had a higher BMI, a younger age, a lower systolic blood pressure, a lower prevalence of cardiovascular disease, and a higher proportion of aspirin and NSAID use as compared with second-generation sulfonylurea users at the start of these therapies (11). These differences may be partly explained by safety concerns of providers about the use of metformin in the elderly or in patients with renal, hepatic or cardiac disease, thus targeting metformin to the obese, healthier individual with diabetes. The authors of the meta-analysis are restricted to combining the fully adjusted hazard ratios or odds ratios presented in each included study without any control over what characteristics were adjusted for or how they were ascertained in each study. Thus, considerable concerns remain that the reason patients on metformin had a lower risk of developing colorectal cancer may not be due to a pharmacological effect of metformin but because of other characteristics that made them less likely to develop colorectal cancer. This problem is compounded by the fact that the included observational studies are all retrospective, thus raising further concerns as to whether the measurement of confounding factors was accurate, as inaccurate measurement impairs the ability to successfully remove bias through adjustment (12).

Another important limitation is that the follow-up time of the included studies is rather short for an outcome such as colorectal cancer. Serial studies of sporadic colorectal tumor patients (13) and comparative lesion sequencing studies (14) have indicated that the transition from large adenoma to carcinoma takes approximately 15 years. It is very difficult to explain mechanistically how use of metformin over a mean period of only 2.4 years, as in the included study by Currie et al. (15) (which contributed most of the weight in the combined relative risk), could have reduced the risk of developing colorectal cancer. Rather, it is possible that colorectal cancer was present or that the adenoma to carcinoma progression was well underway before metformin was started in these patients. In this respect, stratification of results by duration of exposure to metformin, as well as considering whether a dose-response association was present, would have been very helpful: if metformin use truly reduced the incidence of colorectal cancer, we would expect the protective effect to be greater with longer duration of metformin use. Conversely, we would expect the hazard ratio to be close to 1 for short durations of exposure that could not possibly have affected the development of colorectal cancer (assuming adequate adjustment for confounders). However, if "protective" hazard ratios were found with very short exposure to metformin, then this finding would be suggestive of confounding or other bias. These issues were not considered by Zhang et al. in their meta-analysis, presumably because the published study results did not permit this.

A crucial factor that should affect our interpretation of the results is that metformin treatment was compared with all nonmetformin treatments lumped together, including insulin, sulfonylureas, thiazolidinediones, and other oral medications. Presumably, groups of patients in which metformin was combined with another agent, not an uncommon scenario, were also lumped together in the comparison group, although this is not clarified by the authors. Therefore, it is possible that the protective effect observed in the metformin group is not real but rather due to a hazardous effect of the other treatments. This is plausible because insulin, insulin analogs, and sulfonylureas have been associated in some research with more frequent cancer outcomes (16,17).

Large, randomized controlled trials of metformin versus other antidiabetic agents are available and may have sufficient size

and length of follow-up to permit a secondary analysis focused on cancer as the outcome. Such analyses would overcome the problems of confounding inherent in observational studies listed above. In ADOPT (A Diabetes Outcome Progression Trial), diabetic patients were randomized to metformin ($n = 1,454$), rosiglitazone ($n = 1,456$), or glyburide ($n = 1,441$) for a median of 4 years. The hazard ratio for malignancy was 0.92 (95% CI 0.63–1.35) for metformin versus rosiglitazone and 0.78 (0.53–1.14) for metformin versus glyburide. The number of colorectal cancers was seven in the metformin group, four in the rosiglitazone group, and ten in the glyburide group. In the RECORD (Rosiglitazone Evaluated for Cardiovascular Outcomes and Regulation of Glycaemia in Diabetes) study, 2,225 patients who were on a sulfonylurea were randomized to the addition of either metformin or rosiglitazone. The hazard ratio of malignancy during 5.5 years of mean follow-up was 1.22 (0.86–1.74) when comparing metformin versus rosiglitazone (including 24 gastrointestinal cancers [2.1%] in the metformin group and 12 [1.1%] in the rosiglitazone group). In addition, in the RECORD study, 2,222 patients on metformin were randomized to the addition of either sulfonylurea or rosiglitazone. The hazard ratio for malignancy was 1.33 (0.94–1.88) when comparing sulfonylurea to rosiglitazone (with 21 [1.9%] gastrointestinal cancers in the sulfonylurea group and 17 [1.5%] in the rosiglitazone group). The results of these two randomized controlled trials suggest little difference between metformin and rosiglitazone in malignancy risk, whereas sulfonylureas appeared to be associated with an increased risk that did not reach statistical significance. A meta-analysis of more randomized controlled trials of antidiabetic agents looking at risk for malignancy in general or colorectal cancer specifically—and ideally having access to individual patient data—will be particularly informative and may provide a more definitive answer than a meta-analysis of observational studies.

Do the results of the study by Zhang et al. have any direct implications on the management of patients with type 2 diabetes? Since metformin is already recommended as first-line treatment by the American Diabetes Association and the European Association for the Study of Diabetes, the choice of antidiabetic treatment should not be affected by this study. Instead, whether metformin truly has antineoplastic effects against colorectal cancer or not is perhaps more relevant in the field of colorectal cancer treatment or secondary prevention of colorectal cancer. Future studies should evaluate whether metformin use reduces colorectal cancer recurrence or whether it reduces the incidence of colorectal cancer in patients with multiple colorectal adenomas.

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