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# For glioma, a sweet side to diabetes

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See the article by Seliger et al., on pages 340–349.

One of the most common questions patients with glioblastoma—or their friends and families—ask neuro-oncologists is whether they should be curbing their sugar intake. It is a sensible query, given the extensive body of claims posted on the Internet and elsewhere linking cancer to sugar. While some of these claims are overstated, this potential link between glucose metabolism and cancer legitimately remains of great interest. We have known for decades that cancers of most types have aberrant glucose metabolism. Otto von Warburg described aberrant aerobic glycolysis in cancer cells, later termed the "Warburg effect," and much recent research has sought to dissect this phenomenon.[1] Glioma—including its most aggressive form, glioblastoma—is no exception, and glucose metabolism in glioma has been connected to a number of fascinating recent discoveries. Mutant isocitrate dehydrogenase (*IDH)1* and *IDH2*) genes, which are present in most grade 2 and 3 gliomas (lower-grade gliomas), influence glucose metabolism.[2] Glioblastoma has also been found to have aberrant glucose metabolism. For example, glioblastoma cells undergo significant amounts of both aerobic respiration and glycolysis,[3] while the mesenchymal subtype of glioblastoma may be particularly prone to glycolysis and susceptible to its inhibition.[4] Interventions that modify glucose levels and metabolism are currently of great interest as potential adjuncts in glioblastoma therapy. These include the ketogenic diet and related dietary manipulations, which sharply limit carbohydrate intake, lower glucose levels, and reduced insulin and insulin-like growth factor (IGF) levels.[5] Another potential intervention is the antidiabetes biguanide medication, metformin, which has preclinical evidence supporting its antiglioblastoma potential.[6,7] Metformin has been found to inhibit mitochondrial oxidative phosphorylation and increase glycolysis in cancer cells. It also increases the activity of AMP-activated protein kinase and thus inhibits the activity of the oncogenic mTOR protein.[8]

Given the possible links of glucose to glioblastoma and other cancers, it might be expected that diabetes would increase glioma risk. Prior studies suggest, however, a protective effect however, and antitumor effects of metformin and possibly other antidiabetes medications have been invoked as a potential explanation for this.[9,10] While the connections between glucose and glioblastoma have been the subject of intense study, important fundamental questions in this area remain to be answered. Should we be exercising more control of glucose levels in our patients? Should we be more concerned about the hyperglycemia we induce in many of our patients with the corticosteroids necessary to control the edema around brain tumors? Recent studies have indicated that hyperglycemia may have adverse prognostic implications in glioblastoma.[11–13] Alternatively, the possible inverse association between diabetes and glioma incidence suggests that high blood glucose may not be problematic at all—and perhaps high blood glucose is a good thing in this case. It is also important to determine whether we should be making broader use of metformin and other diabetes medications in our patients with glioma and glioblastoma and perhaps even be prescribing them for patients with normoglycemia.

One potential window on these issues lies in retrospective, matched, case-control analyses comparing the risks of glioma and diabetes, with attention to issues such as age, sex, glycemic control, and usage of antidiabetic medications such as metformin. The report by Seliger et al[14] in this issue of *Neuro-Oncology* is just such a retrospective report and makes substantial contributions to our knowledge on this subject. The authors identified a very large set of 2050 glioma patients within the Clinical Practice Research Datalink (CPRD), matching each glioma patient with 10 controls for age, sex, and several other factors. There were a number of notable findings. Odds ratios supported the prior finding by others that diabetes was associated with a decreased risk of glioma, and this reduced risk was particularly strong for glioblastoma. Interestingly, the reduced risk was greater and only reached statistical significance in men; there was a trend toward reduced risk in women, but it was weaker. This reduced risk in men was strongest in men with diabetes over a longer period or with worse glycemic control. The reason for reduced risk in men is unclear, but the authors posit an interesting explanation. They note that men with diabetes have been found to have reduced androgen levels, and that this may eliminate the well-described increased risk of glioblastoma in males. This hypothesis is plausible but requires further study, including additional work on a role for androgens in glioma. That being said, it is difficult to imagine alternative explanations. If the authors are correct, it also

suggests that anti-androgenic therapies could be useful in preventing or treating glioma. With respect to a potential role for antidiabetic drugs, the authors also found that usage of none of the medications assessed—which included metformin, insulin, and sulfonylureas such as glyburide and glipizide—conferred a significantly reduced risk of glioma/glioblastoma.

The results further illuminate the complex relationship between diabetes and glioma, and they are also reassuring with respect to the issue of whether glucose intake or blood levels need to be curtailed in patients with lower-grade glioma or glioblastoma. But does this report also argue against therapies such as metformin and the ketogenic diet? A few factors suggest that this may not be the case, even if additional studies validate the findings of Seliger et al. Firstly, while the authors did not uncover a significant negative correlation between the use of any antidiabetic medications and risk of glioma/glioblastoma, there were trends suggesting possible protective effects. The trends might even be seen as promising, with relative risks of 0.70 to 0.79 for the 3 classes of medications. It is therefore possible that larger studies could demonstrate significantly reduced glioma/glioblastoma risk with the use of these medications. Secondly, there may be subsets of patients with greater vulnerability to interventions such as metformin and the ketogenic diet. As noted above, a prior report has indicated that mesenchymal glioblastoma may be more sensitive to inhibitors of glycolysis such as dichloroacetate.[4] In addition, a small subset of lower-grade glioma or glioblastoma with mutations and/or amplifications in insulin or IGF receptors may be especially vulnerable to interventions that reduce circulating insulin and IGF (such as the ketogenic diet). These findings suggest that identifying biomarkers and sensitive subsets will be needed to guide further trials of glucose-related therapies, as is so often the case with treatments beyond radiation and chemotherapy. Thirdly, therapies such as metformin and the ketogenic diet may synergize with other glioma therapies and be best used in combination, as suggested by a number of preclinical reports testing such combinations in glioblastoma models.[15,16] Taking all of this into account, it is clear that the report by Seliger et al adds to this important area within neuro-oncology and will help guide further studies, but critical questions still remain.

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