Metformin and cancer risk: A look at the evidence

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Metformin is widely accepted as the first-line oral antidiabetes agent for people with type 2 diabetes because, in addition to lowering blood glucose levels, it lowers cardiovascular risk (Holman et al, 2008). It is also relatively favourable in terms of weight change, does not promote hypoglycaemia, is relatively cheap and has a good safety record over a long period of time (Bailey and Turner, 1996). If these characteristics were not sufficiently impressive, recent reports that metformin may also lower cancer risk in people with diabetes have been noted with interest.

The first report of such a potential benefit came from analyses of the DARTS (Diabetes Audit and Research in Tayside Study) cohort, a study that also suggested a dose-related reduced cancer risk with metformin (Evans et al, 2005). Subsequent reports from other cohorts also demonstrated lower cancer mortality with metformin therapy when compared with sulphonylurea and insulin therapy in people with type 2 diabetes (Bowker et al, 2006), as well as better outcomes following chemotherapy for breast cancer in women with type 2 diabetes on metformin versus those not on metformin (Jiralerspong et al, 2009).

More recently, Landman et al (2010) have added further evidence to support a potentially beneficial effect of metformin on cancer risk. The investigators followed 1353 people with type 2 diabetes in the ZODIAC (Zwolle Outpatient Diabetes Project Integrating Available Care) study over a median of 9.6 years and reported two main findings: first, in line with a wealth of data, people with type 2 diabetes have a 47% higher mortality ratio from cancer compared with the general population, and second, among people with type 2 diabetes, cancer mortality was 57% lower in metformin recipients compared with those not taking metformin. Of further interest, this study also reported an apparent dose–response effect with larger metformin doses associated with lower cancer risk. The importance of this study included its ability to adjust for potential confounders such as gender, BMI, adiposity, smoking, diabetes duration, insulin therapy and sulphonylurea use. Furthermore, the investigators showed that the results were similar after exclusion of mortality in the first 3 years, an analysis that attempts to overcome the potential bias of undiagnosed cancer at study onset. In this way, Landman et al (2010) provide some of the strongest evidence to support the hypothesis that metformin protects against cancer. Additional supportive data has now also emerged in a study of insulin-treated people with type 2 diabetes (Monami et al, 2011), as well as a recent meta-analysis (Decensi et al 2010).

But if the findings are true, are there any credible mechanisms to explain lower cancer risk with metformin? Of course, metformin acts to lower insulin resistance and, linked to this, lowers insulin levels. This could be important since hyperinsulinaemia may promote carcinogenesis (van der Burg et al, 1988). In addition, metformin appears to influence signalling molecules including LKB1, a well-known tumour suppressor (Ben Sahra et al, 2008). The effect of metformin on weight loss, albeit modestly, may also play a role since adiposity is linked to increased cancer risk. Thus, several mechanisms may explain metformin's cancer-reducing effect.

While relevant reports appear consistent, and credible mechanistic explanations for a favourable effect of metformin on cancer risk exist, the totality of the data should be viewed as hypothesis generating rather than definitive. The possibility of residual confounding, whereby unmeasured differences between metformin recipients and those not taking or prescribed metformin leads to erroneous results, must always be borne in mind. The salient lesson of research into hormone replacement therapy and cardiovascular outcomes, where trial results were opposite to those expected on basis of epidemiological studies, should not be forgotten (Rosano et al, 2006). Even the evidence of an apparent dose–response association of metformin with cancer risk cannot confirm a causal association, since those on higher doses may seek greater doctor attention, or be more health

seeking, or differ in some other way. In reality, the only way to confirm a causal association linking metformin with lower cancer risk is by conducting randomised controlled trials. Ideally, such trials would also be best conducted in people without diabetes (or those at high risk) to avoid confounding by other diabetes therapies.

In the meantime, metformin will continue to be the first-line therapy for type 2 diabetes on the basis of its vascular and glycaemic benefits, and safety profile, but the possibility it can also reduce cancer risk is sufficiently intriguing to lead investigators to urgently consider randomised trials. ■

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