COMMENT ON BEZIN ET AL.

GLP-1 Receptor Agonists and the Risk of Thyroid Cancer. Diabetes Care 2023;46:384–390

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Diabetes Care 2023;46:e119 | https://doi.org/10.2337/dc23-0076

A recent issue of Diabetes Care included a population-based case-control study by Bezin et al. (1) that has set off an alarm for diabetologists around the world. Bezin et al. attempted to address the issue of whether glucagon-like peptide 1 receptor agonists (GLP-1 RAs) were associated with thyroid cancer (TC) by using data from the French nationwide health care insurance system database. They looked at risk for TC according to GLP-1 RA use and cumulative duration of use. They showed that use of GLP-1 RAs for 1–3 years was associated with increased risk of all TC (adjusted hazard ratio 1.58, 95% CI 1.27–1.95) and medullary TC (adjusted hazard ratio 1.78, 95% CI 1.04–3.05). The authors concluded that clinicians should carefully monitor patients on GLP-1 RAs for the present risk.

In an associated commentary, Thompson et al. (2) showed some limitations of the study by Bezin et al. (1) that must be taken into account before interpreting the data. *1*) Statistical significance was found only for the cumulative duration of GLP-1 RA use between 1 and 3 years. *2*) The design of this case-control study shows efficiency limitations and detection bias may have occurred, as patients on GLP-1 RAs were monitored closely for the appearance of TC and had undergone more imaging procedures.

Nevertheless, we think that there are further issues that should be considered.

Bezin et al. (1) matched each case subject to a maximum of 20 control subjects by age, sex, and duration of diabetes. Obesity was not considered in the Cox regression model as a confounding factor, and that could have compromised internal validity. Obesity prevalence was higher in subjects with TC (11.8%) than in control subjects (8.4%), which would have increased TC risk by approximately 40% (although a statistically significant difference was not shown). The association of obesity with TC is well-known. In a meta-analysis that included 12,199 patients, the presence of obesity increased TC risk by 55% (3).

This is biologically plausible due to the effects of obesity: insulin resistance with concomitant hyperinsulinemia and chronic inflammation (4,5).

As obesity is associated with increased TC risk and GLP-1 RAs are prescribed preferentially to individuals with obesity and type 2 diabetes, drug indication bias should have been considered and controlled for in the statistical analysis.

Epidemiological studies based on databases are a very useful complement to clinical trials. They permit exploring phenomena of low frequency, such as the association shown between GLP-1 RAs and TC; nevertheless, they have major limitations, such as a lack of controlling for variables that acts as a confounding factor and the questionable quality of collected data. Multivariate analysis techniques must be used to adjust for every potential confounding factor. As Bezin et al. have noted that obesity is one of the relevant factors in the database, we suggest the authors perform an additional analysis and estimate TC risk with GLP-1 RA use, including obesity as the important confounding factor that it is.

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

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