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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We read with great interest the article by Bezin et al. (1). Glucagon-like peptide 1 receptor agonist (GLP-1 RA) exposure in rodents is associated with thyroid C-cell hyperplasia, tumor formation, and calcitonin secretion. Using the French national health care insurance database, the authors conducted a nested case-control analysis to determine the risk of thyroid neoplasm among individuals with type 2 diabetes treated with a GLP-1 RA. A total of 2,562 case subjects with thyroid cancer and 45,184 control subjects were included. The use of GLP-1 RA for 1–3 years was associated with an increased risk of thyroid cancer with adjusted hazard ratio (HR) 1.58 and medullary cancer with HR 1.78 after adjustment for various confounders.

While the findings are interesting and alarming, we believe these results need to be accepted with great caution. First, details of body weight were not included in their logistic regression model. Obesity is a known risk factor for thyroid cancer. Using a national database including 457,331 participants in the U.S., Kitahara et al. (2) showed a 1.26-fold and 1.30-fold increased risk of thyroid cancer and 3-fold and >5-fold increased risks of large (>4-cm) thyroid cancers among the overweight (BMI 25.0–29.0 kg/m^2) and obese (BMI ≥30.0 kg/m^2) individuals, respectively, compared with the group without overweight or obesity (BMI 18.5–24.9 kg/m^2). Obesity resulting in chronic inflammation induced by adipokines, excessive secretion of insulin growth factor, and insulin resistance has been proposed as the pathophysiologic mechanism (3). Given the salutary benefit of GLP-1 RAs on weight reduction, it is highly likely the cohort on these agents had higher weights than control individuals. Thus, it is difficult to accept the study results without body weight included as a potential confounder.

Second, the case selection for medullary thyroid cancer (MTC) is problematic. As the authors appropriately noted, the diagnostic code to identify MTC was not available in this cohort. Hence, they used the presence of serum calcitonin and carcinoembryonic antigen as a surrogate marker. It is uncertain if these values were ever elevated. While these are indeed used to assist in the diagnosis and monitoring of MTC, it is also a nonspecific test that is used in other conditions. MTC case detection ideally should be completed using confirmatory surgical pathology.

Third, despite the large cohort, case participants had a disproportionately higher prevalence of thyroid diseases associated with the risk of thyroid cancer (4,5) at baseline. While these were included in the regression model, it is possible additional confounding factors associated with thyroid pathology were not included. One such example is radioactive iodine therapy. This therapeutic intervention commonly used to treat thyroid diseases is known to cause secondary malignancy, including thyroid cancer, even with low doses (5). Hence, this information should also be included in the regression model.

In summary, to best validate findings presented by the authors, we believe more information needs to be obtained.

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

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