COMMENT ON BEZIN ET AL.

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

Mark M. Smits[1,2,3] *and Daniël H. van Raalte*[1,2]

Diabetes Care 2023;46:e120 | https://doi.org/10.2337/dc23-0134

With interest, we read the article by Bezin et al. (1), where a case-control study was reported that demonstrated increased risk of thyroid cancer among users of glucagon-like peptide 1 receptor agonists (GLP-1 RAs).

This may be an important observation, as development of thyroid medullary cancer was related to GLP-1 RA treatment in rodent studies (2). Because of the relatively low incidence rate (global average incidence of 10.1 per 100,000 women per year [3]), even large cardiovascular outcome trials have insufficient power to address this potential adverse effect. The study by Bezin et al. (1) could help us move forward.

Unfortunately, there are a number of important caveats for their analysis that need to be taken into account. First, the authors used the World Health Organization's VigiBase to conduct disproportionality analyses. As noted previously (4), these databases likely suffer from notoriety bias. The authors state that as no warning had been given before the analysis period ended, this should not affect the current complementary pharmacovigilance analysis. We feel, however, this is an oversimplified view of how clinicians report potential adverse effects. A potential link between GLP-1 RA use and thyroid cancer was noted already in 2010 (5), and similar findings were found by several other studies. As endocrinologists treat both thyroid cancer and diabetes, it is quite likely that awareness was already raised before the official box warning. Second, from a biological point of view, it is difficult to understand how an increase in cumulative exposure is not associated with an increased risk. We ask whether the authors could show the risk for exposure time on a linear scale. Finally, while the authors corrected for several covariates (social deprivation index, goiter, hypo- and hyperthyroidism, and the use of other glucose-lowering drugs), we question the influence of other medications at the start of the lag time. When we perform odds ratio (OR) calculations using the numbers provided in Table 1, we find the following values: β-blocking agents OR 1.146 (95% CI 1.036–1.266, $P = 0.0087$), diuretics OR 1.173 (95% CI 1.078–1.276, $P = 0.0002$), calcium channel blockers OR 1.164 (95% CI 1.059–1.278, $P = 0.0018$), ACE inhibitors OR 1.143 (95% CI 1.046–1.249, $P = 0.0034$), angiotensin II receptor blockers OR 1.201 (95% CI 1.106–1.304, $P < 0.0001$), opioids OR 1.200 (95% CI 1.101–1.307, $P < 0.0001$), and nonsteroidal anti-inflammatory drug OR 1.201 (95% CI 1.115–1.309, $P < 0.0001$). As many of these medications are more frequently given to patients also receiving a GLP-1 RA, they could surely have confounded the findings. Additional sensitivity analyses correcting for this could be in order.

We commend the authors for their work but urge caution with respect to interpretation and clinical consequences. Thyroid cancer remains an uncommon condition with a low mortality rate (<1 per 100,000 people) (3), and an increase of 1.8× still yields low absolute numbers. Screening for thyroid cancer is complicated and involves ultrasound and fine-needle aspirations, and it would not be routinely advocated for people using a GLP-1 RA. Given the many (cardiovascular) benefits of GLP-1 RA treatment in a high-risk population, including those for people living with type 2 diabetes, a potential small increase in thyroid cancer cases should not hold back physicians from prescribing these drugs.

Duality of Interest. D.H.v.R. has acted as a consultant and received honoraria from Boehringer Ingelheim, Lilly, Merck, Novo Nordisk, Sanofi, and AstraZeneca and has received research operating funds from the Boehringer Ingelheim–Lilly Diabetes Alliance, AstraZeneca, and Novo Nordisk. All honoraria are paid to his employer (Amsterdam University Medical Center at Vrije Universiteit Amsterdam University Medical Center). No other potential conflicts of interest relevant to this article were reported.

References

1. Bezin J, Gouverneur A, Pénichon M, et al. GLP-1 receptor agonists and the risk of thyroid cancer. Diabetes Care 2023;46:384–390
2. Bjerre Knudsen L, Madsen LW, Andersen S, et al. Glucagon-like peptide-1 receptor agonists activate rodent thyroid C-cells causing calcitonin release and C-cell proliferation. Endocrinology 2010;151:1473–1486
3. Pizzato M, Li M, Vignat J, et al. The epidemiological landscape of thyroid cancer worldwide: GLOBOCAN estimates for incidence and mortality rates in 2020. Lancet Diabetes Endocrinol 2022;10:264–272
4. Faillie J-L. Case–non-case studies: principle, methods, bias and interpretation. Therapies 2019; 74:225–232
5. Parks M, Rosebraugh C. Weighing risks and benefits of liraglutide—the FDA's review of a new antidiabetic therapy. N Engl J Med 2010; 362:774–777

[1]*Department of Endocrinology and Metabolism and Diabetes Center, Amsterdam UMC location Vrije Universiteit, Amsterdam, the Netherlands*
[2]*Amsterdam Cardiovascular Sciences, Diabetes & Metabolism, Amsterdam, the Netherlands*
[3]*Department of Biomedical Sciences, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark*

Corresponding author: Mark Smits, mm.smits1@amsterdamumc.nl