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THYROID EYE DISEASE

Statin Use Associated with Lower Incidence of Developing Thyroid Eye Disease in Newly-Diagnosed Graves' Disease

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Review of: Nilsson A, Tsoumani K, Planck T 2021 Statins decrease the risk of orbitopathy in newly diagnosed patients with Graves disease. J Clin Endocrinol Metab **106:**1325–1332. PMID: 33560351.

SUMMARY

Background

Thyroid eye disease, also known as Graves' orbitopathy (GO), is one of the extrathyroidal autoimmune manifestations of Graves' disease. It is thought to be due to thyrotropin (TSH) receptor autoantibodies and T-cell effects impacting the orbital fibroblasts, resulting in inflammation, adipogenesis, and extraocular muscle enlargement (1). 3-Hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor medications, colloquially known as statins, are thought to potentially have antiinflammatory effects (2), and they were associated with a reduced risk of developing GO in one 2015 retrospective study (3). To further investigate this association, the study reviewed here (4) aimed to examine the association between the use of statins and other lipid-lowering agents on the development of GO in patients with newly diagnosed Graves' disease.

Methods

This was a retrospective cohort analysis of a Swedish national drug and hospital visit database over the period 2005–2018. The analysis included adults with at least one hospital visit for newly diagnosed Graves' disease. Individuals were followed from the time of Graves' disease diagnosis until their first visit for GO, or until the end of 2018. A "statin user" was defined as an individual who obtained at least two prescriptions for an HMG-CoA reductase inhibitor, starting 3 months prior to the diagnosis of Graves' disease. The incidence of GO was then compared between statin users and statin nonusers by applying Cox regression analysis with a time-varying exposure variable (time since Graves' disease diagnosis). Additional, separate analyses were conducted to compare the use of statins against that of other lipid-lowering agents and to compare the effects of different statins.

Results

The cohort included 5574 statin users and 34,409 nonusers with Graves' disease. Statin users were found to be older, male, and more likely to be treated with radioactive iodine than were nonusers; statin users were also more likely to be using other lipid-lowering agents. The most common statin used was simvastatin (77.1%), followed by atorvastatin (28.9%). The main analysis revealed an unadjusted hazard ratio (HR) of 0.74 (95% CI, 0.65–0.84) for the development of GO in statin users. The HR increased to 0.86 (95% CI, 0.74–0.99) when adjusted for age and sex; the main HR result was driven largely by effects in men (HR for men, 0.78; HR for women, 0.91). Investigating different types of statin use revealed that current use (for more than 1 year) was associated with the lowest unadjusted HR (0.62;

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95% CI, 0.45–0.86), while current use of less than 1 year had a smaller effect (HR, 0.77; 95% CI, 0.66–0.89). The HRs for recent and past use were nonsignificant.

Analysis for other lipid-lowering agents or for the combination of statins and other lipid-lowering agents revealed nonsignificant HRs.

Conclusions

In Swedish adults with a new diagnosis of Graves' disease, statin therapy (mostly atorvastatin and simvastatin) was associated with a small, but significant risk reduction in the development of GO, which was largely driven by the positive results found in men.

COMMENTARY

This retrospective analysis supports the findings of the 2015 study by Stein and colleagues that statin use is associated with a lower risk of GO (3). Both studies found the effect to be limited to statins as opposed to nonstatin lipid-lowering drugs, suggesting that the purported antiinflammatory effect of statins could be responsible for this result (5). It is interesting to note that randomized, controlled trials found atorvastatin to have an antiinflammatory impact in patients with rheumatoid arthritis (6,7). The mechanism responsible for these findings in GO might be even more complex. Cell culture data with preadipocytes and orbital fibroblasts indicate that statins have a strong inhibitory effect on the expression of genes related to adipogenesis (8).

How valid are the results of this study? There are several limitations. Without access to laboratory or clinical data including smoking status or thyroid hormone levels, known risk factors for developing GO could not be easily adjusted for. Adherence to medications or severity of GO could not be assessed, and furthermore, surprisingly, radioactive iodine use did not appear to increase the risk of GO. However, the database provided a large set of patients for analysis, and the authors dissected the data in a thoughtful way in the attempt to capture the possible effects of statin use on GO. If the results are valid, the impact is small; based on the figure provided for a middle-aged woman, the risk of GO declines from 8% to 6.5% at 2.5 years after a Graves' disease diagnosis, implying that 67 Graves' disease cases would need to be treated with statins in order to prevent 1 case of GO, which would most likely be mild (4).

Overall, this study provides interesting findings suggestive of a possible benefit of statin therapy in reducing the risk of GO. Using the GO animal model might be the best next step to better understand these findings and to inform further prospective investigations.

REFERENCES

1. Taylor PN, Zhang L, Lee RWJ, Muller I, Ezra DG, Dayan CM, Kahaly GJ, Ludgate M 2020 New insights into the pathogenesis and nonsurgical management of Graves orbitopathy. Nat Rev Endocrinol **16:**104–116.

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2. Jain M, Ridker P 2005 Anti-inflammatory effects of statins: Clinical evidence and basic mechanisms. Nat Rev Drug Discov **4:**977–987.

3. Stein JD, Childers D, Gupta S, Talwar N, Nan B, Lee BJ, Smith TJ, Douglas R 2015 Risk factors for developing thyroid-associated ophthalmopathy among individuals with Graves disease. JAMA Ophthalmol **133:**290–296.

4. Nilsson A, Tsoumani K, Planck T 2021 Statins decrease the risk of orbitopathy in newly diagnosed patients with Graves disease. J Clin Endocrinol Metab **106:**1325–1332.

5. Ridker PM, Danielson E, Fonseca FAH, Genest J, Gotto AM Jr, Kastelein JJP, Koenig W, Libby P, Lorenzatti AJ, MacFadyen JG, et al. 2008 Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. N Engl J Med **359:**2195–2207.

6. Mowla K, Rajai E, Ghorbani A, Dargahi-Malamir M, Bahadoram M, Mohammadi S 2016 Effect of atorvastatin on the disease activity and severity of rheumatoid arthritis: Double-blind randomized controlled trial. J Clin Diagn Res **10:**OC32-6.

7. Li G-M, Zhao J, Li B, Zhang X-F, Ma J-X, Ma X-L, Liu J 2018 The anti-inflammatory effects of statins on patients with rheumatoid arthritis: A systemic review and meta-analysis of 15 randomized controlled trials. Autoimmun Rev **17:**215–225.

8. Shahida B, Johnson PS, Jain R, et al 2019 Simvastatin downregulates adipogenesis in 3T3-L1 preadipocytes and orbital fibroblasts from Graves' ophthalmopathy patients. Endocr Connect **8:**1230–1239.