Association of SGLT-2 Inhibitors with Thyroid Dysfunction: A Drug-Target Mendelian Randomization Study

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Abstract

Context: Diabetes and thyroid dysfunction are prevalent endocrine disorders. Diabetes substantially increases the incidence of thyroid dysfunction, and the concurrent presence of diabetes and thyroid dysfunction further heightens the risk of adverse events associated with diabetes. However, no studies have been conducted to investigate the impact of novel antidiabetic medications, particularly sodium-glucose co-transporter 2 (SGLT-2) inhibitors, on thyroid dysfunction.

Objective: This study aims to estimate the causal associations of SGLT-2 inhibitors with thyroid dysfunction.

Methods: We extracted single-nucleotide polymorphisms associated with SLC5A2 gene expression and glycated hemoglobin A1c levels from a genome-wide association study predominantly conducted in individuals of European descent. These genetic variants were utilized as tools to simulate the effects of SGLT-2 inhibitors. Subsequently, we conducted drug-targeted mendelian randomization (MR) studies to assess the impact of SGLT-2 inhibitors on thyroid dysfunction and captured the results demonstrating this effect.

Results: The inverse variance-weighted method served as the primary analysis technique in the MR study. Treatment with SGLT-2 inhibitors, predicted through genetic analysis, is strongly linked to a higher risk of thyroid disease (OR: 4.63, 95%CI: 2.94-7.28, \( p = 3.23 \times 10^{-11} \)), especially hypothyroidism (OR: 8.99, 95%CI: 5.31-15.25, \( p = 3.46 \times 10^{-16} \)). Furthermore, SGLT-2 inhibitors treatment substantially raises the occurrence of hyperthyroidism (OR: 1.01, 95%CI: 1-1.03, \( p = 0.02 \)). Conversely, immune dysfunction plays a significant role in the development of both hyperthyroidism and hypothyroidism, and SGLT-2 inhibitors treatment significantly increases the incidence of these related diseases (OR: 3.94, 95%CI: 2.74-5.67, \( p = 1.63 \times 10^{-13} \)).

Conclusions: Our study found that the use of SGLT-2 inhibitors significantly increases the incidence of thyroid dysfunction.

Introduction

Diabetes and thyroid dysfunction are significant areas of concern in the field of endocrinology and metabolism. There is a strong connection between thyroid dysfunction, specifically hyperthyroidism and hypothyroidism, and diabetes (1). The prevalence of thyroid dysfunction is higher in individuals with diabetes compared to the general population, ranging from approximately 10–24%. Among these disorders, hypothyroidism is one of the most common types in individuals with diabetes (2–4). Studies have reported that the coexistence of diabetes and thyroid dysfunction can worsen the progression of microvascular complications in diabetes, such as diabetic nephropathy and diabetic retinopathy, and also increase the risk of cardiovascular events, significantly impacting patients' prognosis (5, 6).

In addition to the inherent link between diabetes and thyroid dysfunction, it is important to acknowledge the potential influence of certain antidiabetic medications on thyroid function. Metformin, which is widely regarded as an outstanding antidiabetic drug, has been found to have a significant protective effect on the thyroid. Distiller et al. conducted a study on patients with type 2 diabetes and discovered a strong negative correlation between the use of metformin for treatment and the occurrence of hypothyroidism (7). Animal experiments have also demonstrated the effectiveness of metformin in reducing neurologically related complications caused by hypothyroidism in rats (8). On the other hand, the use of dipeptidyl peptidase 4 (DPP4) inhibitors, another
commonly prescribed oral antidiabetic medication, may also influence thyroid function. Long-term use of DPP4 inhibitors has been significantly associated with the worsening of Graves' disease(9). It should be noted, however, that research exploring the relationship between sodium-glucose co-transporter 2 (SGLT-2) inhibitors, a new generation of antidiabetic medication, and thyroid dysfunction is still lacking.

In 2013, the first SGLT-2 inhibitors were approved by the U.S. Food and Drug Administration (FDA) for the treatment of type 2 diabetes. In contrast to traditional hypoglycemic drugs, SGLT-2 inhibitors offer a broader range of benefits. In addition to lowering blood sugar, they have shown effectiveness in reducing blood pressure, improving heart function, and decreasing the incidence of major adverse cardiovascular events, thus providing cardiovascular protection(10). Moreover, SGLT-2 inhibitors have proven to be highly effective in managing diabetic kidney disease, leading to their designation as “the statins of the 21st century”(11, 12). However, there is presently a lack of research exploring the potential connection between SGLT-2 inhibitors and thyroid dysfunction, highlighting the significance of this matter. Notably, a case report documents the manifestation of thyrotoxicosis symptoms in one patient undergoing treatment with SGLT-2 inhibitors for type 2 diabetes(13). Regrettably, this unique case report appears to have received limited attention, possibly due to the rarity of the phenomenon and the limited number of related studies available. Additionally, given that diabetes itself poses a substantial risk factor for thyroid dysfunction, the impact of SGLT-2 inhibitors on thyroid function may be veiled. Given the widespread usage of SGLT-2 inhibitors, it is crucial to undertake thorough investigations to uncover the true causal relationship between these medications and thyroid function.

Due to the fact that individuals with diabetes are the primary users of SGLT-2 inhibitors, and diabetes itself is considered a significant risk factor for the development of thyroid disease, traditional observational studies face challenges in obtaining reliable results due to the presence of this crucial confounding factor. Similarly, the implementation of randomized controlled trials (RCT), which are regarded as the gold standard for establishing causal relationships, is hindered by the substantial demands of human and material resources, as well as ethical constraints. In contrast, mendelian randomization (MR) offers a genetic approach that employs single nucleotide polymorphisms (SNP) as instrumental variables to evaluate causal relationships between two traits. Due to the independence of instrumental variables from other confounding factors, MR enables the effective assessment of causal associations between previously observed exposures and outcomes. Moreover, MR helps mitigate common confounding biases inherent in traditional epidemiological research, ultimately enhancing the reliability of findings.

The purpose of this study is to utilize recently published genome-wide association study (GWAS) data and drug-target MR method to investigate the causal relationship between SGLT-2 inhibitors and thyroid dysfunction. Additionally, the study aims to uncover potential differential effects of SGLT-2 inhibitors on thyroid dysfunction, providing a foundation for further exploration of the mechanisms underlying the association between SGLT-2 inhibitors and thyroid diseases.

**Materials and methods**

1. **Study design**

Figure 1 illustrates the design of this study. Our aim is to assess the causal effect of SGLT-2 inhibitors on thyroid dysfunction using a two-sample drug-target MR method. The specific methodology includes: 1) Selecting genetic
variants related to SGLT-2 inhibitors; 2) Obtain research outcomes through UK Biobank and FinnGen databases; 3) Utilizing drug-target MR analysis to estimate the causal relationship between SGLT-2 inhibitors and thyroid dysfunction.

2. Selection and validation of SGLT-2 inhibitors genetic instrumental variables

The selection and validation of genetic instrumental variables for SGLT-2 inhibitors were conducted through four sequential steps, as previously described(14). Firstly, we identified genetic variants associated with mRNA expression levels of the SLC5A2 gene (the target gene for SGLT-2 inhibitors) in the Genotype-Tissue Expression (GTEx) and eQTLGen consortium databases, considering only variants with a significance level of \( P < 0.001 \). Additionally, functional variants with the potential for SGLT-2 inhibitors were also incorporated. Secondly, we assessed the association between each SLC5A2 variant and HbA1c levels (a marker for the glucose-lowering effect of SGLT-2 inhibitors) in a subpopulation of unrelated individuals of European ancestry without diabetes from the UK Biobank. We selected variants that showed regional association with HbA1c at a significance level of \( P < 1 \times 10^{-4} \). Thirdly, we employed a genetic colocalization approach to determine if SLC5A2 and HbA1c shared the same causal variants, with evidence of colocalization defined as a probability of colocalization between SLC5A2 expression and HbA1c exceeding 70%. Finally, we performed standard clustering procedures, removing variants with a pairwise correlation exceeding 0.8 to alleviate issues related to high correlation. After this rigorous screening and validation process, a total of 6 SNPs were identified as genetic instrumental variables strongly associated with both HbA1c and SGLT-2 inhibitors for subsequent MR analysis.

3. Study outcomes

The outcomes of this study are based on data derived from the two largest currently available GWAS databases, namely the UK Biobank database and the FinnGen study. In particular, the data for hyperthyroidism were obtained from the UK Biobank database, consisting of 3,545 cases. The data for thyroid disease (56,574 cases), hypothyroidism (40,926 cases), and immune-related diseases (96,150 cases) were obtained from the ninth release of the FinnGen study (Table S1).

4. Statistical analysis

We employed five main MR analysis methods to determine the results, namely inverse variance-weighted (IVW), MR-Egger, weighted median, simple mode, and weighted mode methods. Among them, the IVW method was used as the primary approach. In order to ensure the accuracy of the experimental results and avoid violating the three assumptions of MR, we conducted sensitivity analysis using tests for pleiotropy test, heterogeneity test, and leave-one-out sensitivity analysis.

In this experiment, we utilized the MR-Egger and the Mendelian randomization pleiotropy residual sum and outlier (MR-PRESSO) global tests to confirm the presence of horizontal pleiotropy. A \( p \)-value greater than 0.05 indicates the reliability of the obtained results. Simultaneously, the MR-PRESSO outlier test was performed to identify and eliminate outlier SNPs in the final result analysis.

For heterogeneity analysis, the main approaches used were the IVW and MR-Egger analysis methods, based on the evaluation of Cochran's Q statistic. An observed \( p \)-value greater than 0.05 indicates the absence of
heterogeneity among the utilized tools, affirming the robustness and reliability of the findings. Additionally, we visualized the heterogeneity of causal estimates through forest plots and funnel plots.

To assess the robustness of the results, we utilized the leave-one-out method for conducting sensitivity analysis. The method entails the sequential exclusion of individual SNPs. If all the curves on the leave-one-out plot align consistently on one side of 0, it suggests that omitting any SNP will have no fundamental impact on the research results, thus demonstrating the robustness of the findings.

All analyses were performed using the TwoSampleMR and MendelianRandomization packages in R (version 4.3.0).

**Results**

1. **The selected SNPs in MR analysis**

   We identified 6 SNPs as pharmacological targets for SGLT-2 inhibitors, all of which have F-statistics greater than 10, indicating no evidence of weak instrument bias (Table S2). Additionally, we conducted confounding factor correlation tests on the selected SNPs using the PhenoScanner database and found no SNP that needed to be excluded from the analysis due to potential confounding factors.

2. **Primary two-sample MR analysis**

   In our article, we employed the IVW method as the primary statistical approach for presenting the outcomes, as shown in Figure 2. The MR analysis results showed a significant association between genetically predicted SGLT-2 inhibitors treatment and an increased incidence of thyroid disease (OR: 4.63, 95%CI: 2.94-7.28, \( p = 3.23 \times 10^{-11} \)). Among many thyroid diseases, there is a close relationship between thyroid dysfunction (hyperthyroidism and hypothyroidism) and the occurrence and development of diabetes. Therefore, we verified the causal relationship between SGLT-2 inhibitors and the occurrence of hyperthyroidism and hypothyroidism. The study found a strong positive causal relationship between SGLT-2 inhibitors and the increased incidence of hyperthyroidism (OR: 1.01, 95%CI: 1.01-1.03, \( p = 0.02 \)) and hypothyroidism (OR: 8.99, 95%CI: 5.31-15.25, \( p = 3.46 \times 10^{-16} \)). On the other hand, immune dysfunctions are the main causes of hyperthyroidism and hypothyroidism, so we hypothesized whether the use of SGLT-2 inhibitors affects immune-related diseases and conducted verification. The research results revealed that the use of SGLT-2 inhibitors significantly increased the incidence of immune-related diseases (OR: 3.94, 95%CI: 2.74-5.67, \( p = 1.63 \times 10^{-13} \)). Furthermore, the MR-PRESSO process verified the positive results (Table 1). The four results mentioned above were illustrated using five MR analysis methods (Figure S1-S4). Additionally, the stability of the results was further verified through MR-PRESSO, and no outliers were found, indicating statistical significance in all four outcomes (Table 1).

3. **Sensitivity analyses for MR analysis**

   To assess whether the results have heterogeneity, we conducted Cochrane’s Q test. The test results showed no heterogeneity in the causal relationship between exposure and all outcomes (Table 2). Additionally, no evidence of horizontal pleiotropy was found in any of the four sets of results (\( p > 0.05 \)) (Table 2). This indicates that the results are not influenced by potential confounding factors, making our study results reliable and robust. The leave-one out analysis showed that no individual SNP had effect on the overall causal estimate (Figure S1-S4).
Moreover, we presented forest plots and funnel plots to visually display the distribution balance of the single-SNP effects in the four sets (Figure S1-S4).

**Discussion**

This is the first drug-target MR study investigating the causal relationship between SGLT-2 inhibitors use and thyroid dysfunction. Its objective was to evaluate the causal relationship between the use of SGLT-2 inhibitors and various thyroid dysfunctions. The study resulted in two main findings: firstly, the use of SGLT-2 inhibitors significantly promotes the occurrence of thyroid diseases. Secondly, SGLT-2 inhibitors significantly increase the incidence of hyperthyroidism and hypothyroidism.

The new antidiabetic drug SGLT-2 inhibitors have become one of the most effective treatment methods for type 2 diabetes patients, due to its significant glucose-lowering effect and remarkable cardiovascular and renal protection benefits\(^{(15–17)}\). Extensive research has found that SGLT-2 inhibitors have significant effects in improving cardiac function and structure\(^{(10,18)}\), reducing blood pressure\(^{(19)}\), decreasing the occurrence of adverse cardiovascular events\(^{(17)}\), and reducing proteinuria\(^{(20)}\). However, some side effects of SGLT-2 inhibitors still cause concerns, such as diabetic ketoacidosis\(^{(21)}\), genital and urinary tract infections\(^{(22)}\), fractures, and amputations\(^{(23–25)}\).

Currently, there is no existing foundational or clinical research on the relationship between SGLT-2 inhibitors and thyroid dysfunction. Therefore, clarifying the causal relationship between the two has theoretical significance and can help draw attention to the role of SGLT-2 inhibitors in thyroid diseases and thyroid dysfunction. We are highly concerned about a rare case report. According to a case report from 2022, one patient exhibited symptoms of thyrotoxicosis during the treatment of type 2 diabetes with SGLT-2 inhibitors\(^{(13)}\). Due to the rarity of such cases, we cannot determine whether SGLT-2 inhibitors affect thyroid function. Diabetes is widely considered a major contributing factor to thyroid dysfunction, so the adverse effects of SGLT-2 inhibitors on thyroid function may be masked by the influence of diabetes itself. Therefore, the true causal relationship between SGLT-2 inhibitors and thyroid disease is easily overlooked. To confirm the causal relationship between SGLT-2 inhibitors and thyroid disease, we conducted a MR study. The results of the study show that the use of SGLT-2 inhibitors significantly increases the incidence of thyroid disease. Additionally, the use of SGLT-2 inhibitors also significantly increases the incidence of hyperthyroidism and hypothyroidism.

Given the robust causal relationship between SGLT-2 inhibitors and the heightened occurrence of hyperthyroidism and hypothyroidism, coupled with the significant role of autoimmune abnormalities in the development of these conditions, we undertook a MR study to investigate the potential impact of SGLT-2 inhibitors on immune-related diseases. The findings from the study consistently indicate that SGLT-2 inhibitors exert a notable influence in promoting immune-related diseases.

Based on the research findings presented above, it is advisable for diabetes patients undergoing SGLT-2 inhibitors therapy to undergo regular monitoring of thyroid function in order to detect and prevent the occurrence of thyroid abnormalities. For diabetes patients with pre-existing thyroid dysfunction, it is recommended to avoid the use of SGLT-2 inhibitors to prevent exacerbation of their condition. It is worth noting that the current body of research remains limited, and further clinical and epidemiological studies are necessary to gain a deeper understanding of the complex relationship between SGLT-2 inhibitors and thyroid diseases.
Study Limitations

The results of our study have certain limitations. Firstly, the evaluation of the effectiveness of SGLT-2 inhibitors is based on the simulation of the genetic correlation between SGLT-2 inhibitors and HbA1c levels, rather than the direct effects of SGLT-2 inhibitors. Secondly, the results of the MR experiment are limited by the sample size of the database, and as the database continues to expand, the results may change. However, in this study, we used the largest available database and assessed the robustness of the results through various sensitivity methods, all of which indicate that the results are robust. Lastly, our analysis is limited to individuals of European ancestry, and we caution against generalizing our findings to other populations.

Conclusion

In conclusion, our MR study has revealed that SGLT-2 inhibitors have a significant promoting effect on thyroid diseases, particularly thyroid dysfunction such as hyperthyroidism and hypothyroidism. Considering the limitations of the MR design and the samples used, we should cautiously interpret the adverse effects of SGLT-2 inhibitors on thyroid function and further validate these findings through long-term follow-up clinical studies. The main objective of this article is to raise awareness about the causal relationship between SGLT-2 inhibitors and thyroid dysfunction. Despite these findings, we should not devalue the clinical utility of SGLT-2 inhibitors due to their strong effects in lowering blood sugar levels and providing cardiac and renal protection.

Declarations

Disclosure Statement: The authors declare no conflict of interest.

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Authors’ contributions

All authors made substantial contributions to the interpretation of the data and critically revised the manuscript. All authors have approved the submitted final version and are to be personally accountable for their own contributions. The authors’ contributions were as follows. CF wrote the paper taking into account the comments and suggestions of all the coauthors and had primary responsibility for the final content, conducted the literature search, and analyzed the data. XM MY DL WQ HP SF ZS BL advised on the analyses and drafted the paper. QL XH XW and JH designed the study, advised on the analyses and visualization, and supervised the study. All authors revised the paper, interpreted the results, and read and approved the final manuscripts. The authors report no conflicts of interest.

Ethics approval and consent to participate

All data used in the present work are publicly available and anonymized. All contributing studies had received appropriate ethical approval and patient consent at each original GWAS study site, and can be found in the original studies.

Consent for publication

Not applicable.
Funding

Not applicable.

Availability of data and materials

All summary statistics used in the present work are publicly available, and can be accessed and downloaded through websites. The genetic data for thyroid diseases, hypothyroidism, and immune-related diseases in this study were obtained from the 9th release of the FinnGen study (https://www.finngen.fi/en/access_results). The data for hyperthyroidism was obtained from the UK Biobank database (https://www.ukbiobank.ac.uk/).

Competing interests

The authors declare that they have no competing interests.

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References


Tables

Table 1 MR-PRESSO for causal effect between genetically proxied SGLT-2 inhibitors with outcomes.

<table>
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<th>Outcomes</th>
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<th>Outlier Corrected Estimates</th>
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Table 2 Pleiotropy and heterogeneity test for genetically proxied SGLT-2 inhibitors on outcomes.

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Figures
Figure 1

Study design

6 variants associated with expression level of SLC5A2 from GTEx and eQTLGen database

UK Biobank database:
- hyperthyroidism (3,545 cases)

FinnGen study (the 9th released):
- thyroid disease (56,574 cases)
- hypothyroidism (40,926 cases)
- immune-related diseases (96,150 cases)
Figure 2

Associations of genetically proxied SGLT-2 inhibitors with outcomes using different MR methods

Supplementary Files

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