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Glucagon-like peptide-1 receptor agonist use is associated with lower blood ferritin levels in people with type 2 diabetes and hemochromatosis: a nationwide register-based study

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INTRODUCTION

Hereditary hemochromatosis (HH) is most commonly caused by mutations in the HFE (High FE^{2+}) gene, leading to increased iron absorption in the intestines and iron accumulation especially in the liver, pancreas, and heart.[1] Usually, clinically apparent liver function abnormalities lead to the diagnosis after the age of 40 when the accumulated iron causes damage as the result of hemosiderosis. Among other consequences such as arthritis, cardiac arrhythmia, and hyperpigmentation of the skin, hemosiderosis may also lead to diabetes mellitus due to demise of insulin-producing β cells in the pancreas as well as reduced insulin sensitivity as the result of, for example, liver cirrhosis.[2]

Estimates suggest that 30%–60% of people with HH also have type 1 diabetes (T1D) or type 2 diabetes (T2D),[3] and alongside liver function abnormalities, diabetes mellitus may be the initial clinical manifestation of HH. Evidence has indicated that diabetes with clinical features similar to those of late-onset T1D may be an overlooked manifestation of HH-associated hemosiderosis.[4]

The diagnosis of HH is based on a combination of blood iron measurement using plasma ferritin levels as a validated proxy, clinical examination, and genetic testing.[1] The standard treatment for HH remains recurrent phlebotomy to reduce circulating iron levels and improve symptoms.[5] However, phlebotomy is an invasive procedure associated with side effects as well as regular use of healthcare personnel resources.

In this observational register-based study, we evaluated the effect of exposure to glucagon-like peptide-1 (GLP-1) receptor agonists (RAs) on circulating ferritin levels and on the frequency of phlebotomies in people with HH and T2D. GLP-1 RAs are widely used in the management of T2D, and preliminary evidence has indicated that these agents may lower ferritin levels.[6 7] Thus, we hypothesized that GLP-1 RA treatment could offer an alternative to or decrease the required frequency of phlebotomy. As comparator, we used exposure to another common T2D drug, sodium/glucose cotransporter-2 (SGLT-2) inhibitors, which to our knowledge do not influence ferritin levels or phlebotomy frequency in HH. Moreover, GLP-1 RAs and SGLT-2 inhibitors are usually introduced at a similar T2D disease stage.

RESEARCH DESIGN AND METHODS

A total of 4714 individuals with HH were identified in the Danish National Patient register (NPR; dataset ranging from 1994 to 2018, both inclusive; figure 1); linkage to the Danish Diabetes Register showed that 698 of these 4714 individuals also had a T2D diagnosis. Information on exposure to GLP-1 RAs and/or SGLT-2 inhibitors (filled prescriptions) was extracted from the Danish Register of Medicinal Products Statistics (DRMPS) using ATC codes (table 1); for the purpose of the present analyses, a person was considered exposed at a given time if a prescription had been recorded within the last 20 weeks. Duration of diabetes and duration of HH were calculated as the time between the date of first diagnosis to the date of the individual measurements, thereby accounting for the impact of duration of T2D and HH at each assessment of ferritin and phlebotomy.

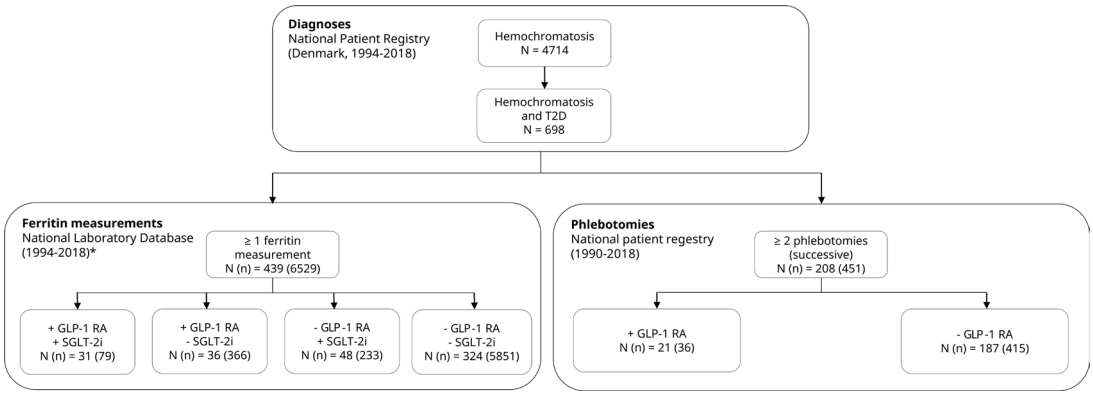

Figure 1 Cohort identification. People with a hemochromatosis diagnosis (ICD-10 codes 'DE831' and 'DE831A') were identified in the Danish National Patient Registry. Data on phlebotomies among people with hemochromatosis were derived from the National Patient Registry using treatment code 'BMBA01' and surgery code 'KTPH00'. Data on drug exposure were derived from the Danish Register of Medicinal Products Statistics using ATC codes A10BJ01, A10BJ02, A10BJ05, and A10BJ06 to identify GLP-1 RAs, and A10BD15, A10BD20, A10BD21, A10BK01, A10BK02, and A10BK03 for SGLT-2 inhibitors. *Data largely missing from administrative region Region Midt. Data set included data until April 2021, but only data until 2018 were used in alignment with the National Patient Registry. N, number of people; n, number of measurements. GLP-1 RA, glucagon-like peptide-1 receptor agonist; SGLT-2i, sodium/glucose cotransporter-2 inhibitor.

Ferritin data were collected from the Danish Laboratory Database (figure 1). For the period 2008 through 2021, the database contained 6529 ferritin measurements for 439 people with both HH and T2D. A total of 366 ferritin samples (36 people) were taken while exposed to a GLP-1 RA, 233 samples (48 people) while exposed to an SGLT-2 inhibitor, and 79 samples (31 people) and 5851 (324 people) were taken during exposure to both and none of these agents, respectively.

Data on phlebotomies (dates) were collected from the Danish NPR (between 1990 and 2018, both inclusive). Among persons with both HH and T2D, 7361 phlebotomies were recorded; of these, 451 phlebotomies in 208 people were successive, allowing for assessment of time between procedures.

While data points on ferritin measurements and phlebotomy are inherently irregular by time, because any procedure received by Danish citizens via the public healthcare system are recorded in the used registers, there are little or no missing data and no loss to follow-up.

Table 1 Filled prescriptions by drug class

ATC code (drug class)	Number of filled prescriptions
GLP-1 RAs (prescription data cover 2008–2020)	*2442*
A10BJ01 (exenatide)	40
A10BJ02 (liraglutide)	1881
A10BJ05 (dulaglutide)	66
A10BJ06 (semaglutide)	455
SGLT-2 inhibitors (prescription data cover 2013–2020)	*1196*
A10BD15 (metformin and dapagliflozin)	31
A10BD20 (metformin and empagliflozin)	108
A10BD21 (saxagliptin and dapagliflozin)	4
A10BK01 (dapagliflozin)	338
A10BK02 (canagliflozin)	6
A10BK03 (empagliflozin)	709

GLP-1RA, glucagon-like peptide-1 receptor agonist; SGLT-2i, sodium/glucose cotransporter-2 inhibitor.

Outcomes

We assessed two quantitative outcomes: ferritin levels and time between successive phlebotomies; for each data point for each of the two outcomes, it was defined if the individual was concurrently treated with a GLP-1 RA or SGLT-2 inhibitor or both.

Statistical analysis

For both outcomes, we modeled the

(natural) logarithm of the outcome, using linear mixed models. Hence, the fixed-effect estimates are relative levels of the outcome variable and estimated SD of random effects are interpretable as coefficients of variation.[8] For the (log) distance between phlebotomies, a simple random person effect was used, and only a single exposure variable for GLP-1 was used as fixed effect.

For ferritin levels, we used a model with random intercept and random slope along duration of HH. For the fixed effects on ferritin, we used a non-linear spline effect of duration of HH. On top of this, for outcomes during exposure to either drug, we used linear effects for duration of GLP-1 RA and SGLT-2 inhibitor exposure, with slopes depending on duration of HH. Additionally, we included linear effects of date of ferritin measurement, birth, T2D diagnosis and HH diagnosis to control possible confounding by calendar time (suitably centered):

$$\begin{aligned}\log(\text{ferr}_{pt}) = {} & \mu + f(Hdur) + \alpha_d + \beta_d Hdur + \gamma_d ddur + \zeta_d ddur Hdur + \\ & \kappa_1(t2015) + \kappa_2(doBth2050) + \kappa_3(doDM2010) + \\ & \kappa_4(doH2010) + a_p + b_p Hdur + e_{pt}, \\ & (a_p, b_p) \sim N_2(0,), e_{pt} \sim N(0, \sigma^2), independent\end{aligned}$$

where p indicates person and t the time of measurement, and f a restricted cubic spline. $d \in$ {GLP-1, SGLT-2} is the current drug exposure, Hdur the current duration of hemochromatosis, ddur the current duration of drug exposure, doBth date of birth, doDM date of diabetes and doH the date of hemochromatosis. The terms $(a_p, b_p) \sim N_2(0, \Sigma)$ (Σ unrestricted) are random effects at the person-level, and e_{pt} mutually independent residuals independent of the random effects.

In the ferritin dataset, 85% had a duration of HH of 0–15 years, whereas duration of drug exposure was mostly less than 5 years. Thus, we showed relative

ferritin levels across a HH duration of 0–15 years, using ferritin levels at 5 years of HH duration for a person not exposed to either drug class as reference.

Ferritin levels by duration of HH are depicted by categorical drug (GLP-1 RA or SGLT-2 inhibitor) and by exposure duration (0–4 years) for initiation at different HH durations. Derived from these, we showed the relative ferritin levels for persons exposed to GLP-1 RA compared with levels in those exposed to SGLT-2 inhibitors as well as compared those not exposed to either drug class.

Results from the analyses are reported and interpreted visually.

All data processing and analysis was done on anonymized data at Statistics Denmark's server; SAS V.9.4 was used for data handling and R 4.1.0 with the Epi package was used for statistical analyses.

Table 2 Demographics by of the ferritin cohort

	Ferritin cohort (N=439; n=6529)
Sex, males/females (N)	328/111
Age, years	
At first ferritin measurement	65 (58–72)
At first GLP-1 RA exposure	60 (53–66)
At first SGLT-2 inhibitor exposure	63 (54–70)
Duration of diabetes, years	
At first ferritin measurement	4.8 (0.8–10)
At first GLP-1 RA exposure	6.1 (3.1–11)
At first SGLT-2 inhibitor exposure	6.8 (4.1–12)
Duration of HH, years	
At first ferritin measurement	3.7 (0.2–11)
At first GLP-1 RA exposure	3.8 (-0.3–8.2)
At first SGLT-2 inhibitor exposure	6.9 (2.6–13)
Date of diabetes diagnosis, month/year	10/2010 (08/2004–01/2015)
Date of HH diagnosis, month/year	03/2011 (06/2004–11/2015)
Date of first ferritin measurement, month/year	01/2016 (02/2014–03/2018)
Date of last ferritin measurement, month/year	12/2020 (08/2018–03/2021)

Age and durations are medians (IQR). Time (month/year) is medians (IQR).
GLP-1 RA, glucagon-like peptide-1 receptor agonist; HH, hereditary hemochromatosis; N, number of people contributing to the analysis; n, total number of ferritin samples or phlebotomies; SGLT-2i, sodium/glucose cotransporter-2 inhibitor.

RESULTS

Ferritin levels

The demographics of the 439-person ferritin cohort are presented in table 2.

The number of filled prescriptions by specific compounds among the two drug classes (GLP-1 RAs and SGLT-2 inhibitors, covering the periods from 2008 to 2020 and 2013–2020, respectively) are summarized in table 1. Overall, ferritin levels decreased during the first 5 years since HH diagnosis; in the following 10 years, levels increased (figure 2A).

In the simple, preliminary model with only linear effect of time on GLP-1 RA and duration of HH, exposure to GLP-1 RA for 1 year was associated with around 30% (95% CI 20% to 40%) lower estimated ferritin levels; at exposure start, the effect was 28% and after 2 years of exposure it was 32%, representing an estimated nominal change of −1.3% per year (95% CI −4.6% to 2.2%) as a result of GLP-1 RA exposure. In contrast, SGLT-2

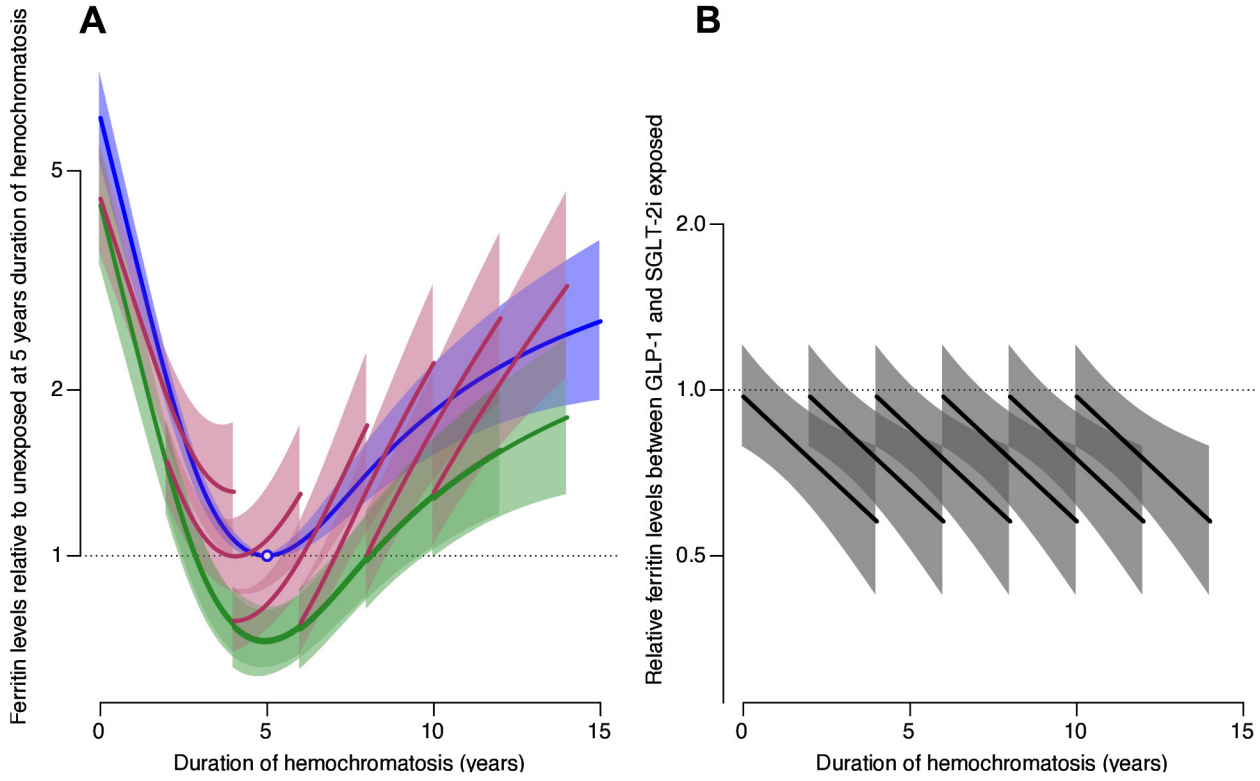

Figure 2 Relative ferritin levels by duration of hemochromatosis and by GLP-1 RA or SGLT-2 inhibitor exposure and no exposure. (A) Relative ferritin levels relative to levels for a person at 5 years after diagnosis of hemochromatosis by duration of HH. Blue line: Relative ferritin levels for a person not exposed to GLP-1 RA or SGLT-2 inhibitor. Green and maroon lines: Relative ferritin levels for a person exposed to GLP-1 RA (green) or SGLT-2 inhibitor (maroon). Shaded areas around lines represent 95% CI. (B) Ratio of ferritin levels between people exposed to GLP-1 RAs and people exposed to SGLT-2 inhibitor by time since hemochromatosis diagnosis and duration of exposure. Corresponds to the ratio between the green and maroon lines in panel A. Shaded areas around lines represent 95% CI. GLP-1 RA, glucagon-like peptide-1 receptor agonist; SGLT-2i, sodium/glucose cotransporter-2 inhibitor.

inhibitor exposure was associated with 23% increased ferritin levels per year (95% CI 13.1% to 33.7%).

In the more comprehensive non-linear model, changes in ferritin levels were estimated by time since HH diagnosis and time since GLP-1 RA or SGLT-2 inhibitor exposure and compared with estimated levels in those not exposed to either of the two drug classes (figure 2A). Estimated ferritin levels by time since HH diagnosis relative to a person with a HH diagnosis duration of 5 years is plotted in figure 2A, showing similar relative ferritin level at the time of start of GLP-1 RA or SGLT-2 inhibitor exposure. The effect of GLP-1 RA exposure compared with those not exposed indicated around 30% lower ferritin levels (95% CI 10% to 40%) (figure 2A, green line); this effect appeared largely independent of time since HH diagnosis and duration of GLP-1 RA exposure.

Comparing the effect of GLP-1 RA and SGLT-2 inhibitor exposure (figure 2B), ferritin levels were similar at exposure start between the two groups (ratio around 1); with increasing exposure time, the ratio between the GLP-1 RA and SGLT-2 inhibitor groups in terms of ferritin levels was markedly below 1, indicating a marked reducing effect of up to around 40% (at year 4 of HH duration) of GLP-1 RAs compared with SGLT-2 inhibitor exposure. This 10%-point greater treatment effect (ie, treatment effect of 30% comparing GLP-1 RA exposure or no exposure vs 40% effect comparing GLP-1 RA and SGLT-2 inhibitor exposure) reflected that ferritin levels increased with SGLT-2 inhibitor exposure to the level of that seen for persons not exposed to either GLP-1 RAs or SGLT-2 inhibitors (figure 2A, maroon lines).

Phlebotomy frequency

Because of the scarcity of data points on phlebotomies with concurrent SGLT-2 inhibitor exposure, SGLT2 inhibitor use was not considered in the analyses of the temporal distance between two successive phlebotomies. It should be noted that even for these two scenarios, data points were few (451 records with a previous one recorded for 208 individuals, of whom 93 had only one available record of a phlebotomy). The baseline mean duration between successive phlebotomies in people not exposed GLP-1 RAs was around 1 year. Analysis of these sparse data indicated that GLP-1 RA exposure was associated with a 50% longer duration between successive phlebotomies compared with not being exposed to GLP-1 RAs, although confidence intervals were wide, ranging from a 30% shortening to an around threefold prolongation of the duration between successive phlebotomies (95% CI 0.7 to 3.3). In two sensitivity analyses excluding

phlebotomies less than 1 or 2 months apart, the magnitude of the effect size did not differ markedly from that of the primary analysis (data not shown).

DISCUSSION

In this brief report, we provide evidence based on an analysis of real-world registry data in support of a potential effect of GLP-1 RA treatment on ferritin levels in people with T2D. Ferritin is a recognized surrogate of systemic iron levels, which is increased in HH to an extent that may cause organ damage, including to the pancreas and liver, resulting in or exacerbating diabetes. Further, our analyses show a trend towards a less frequent need of invasive phlebotomy—the current mainstay treatment of the disease—in people with T2D treated with GLP-1 RAs. Of note, ferritin levels appeared to increase towards the end of the 5-year observation period, likely reflecting the chronic and progressive nature of HH and the inability of available treatments to fully suppress the iron accumulations in the longer run. Consequently, even though a favorable effect of GLP-1 RA was identified, the present results underline that the drug class is not a curative intervention in HH. Further, this aspect also highlights the need for early invention to attenuate the rate of iron accumulation as soon as possible.

In the absence of curative interventions to correct the genetically determined abnormal iron absorption and considering the inadequacies of invasive and healthcare recourse intensive phlebotomy, an unmet medical need exists for interventions that address the consequences of the excess iron levels in HH. Furthermore, early intervention is key to avoid development of diabetes mellitus (ie, secondary diabetes), notably diabetes resembling late-onset T1D due to loss of functional pancreatic β-cell mass. While HH is traditionally regarded as a rare disease, genotyping studies have suggested a more common prevalence, supported by the observation that less than 10% with HH-related gene mutations develop clinically manifest disease. This underscores the need to identify susceptible individuals via targeted screening programs and to develop non-invasive and efficacious interventions to avoid the morbidity and premature mortality associated with HH. This is especially relevant for people with both HH and diabetes, who often present with related conditions such as cardiovascular disease and obesity. For such individuals, agents that simultaneously address excess iron levels as well as poor glycemic control and increased cardiovascular risk and body weight are clearly desirable.

GLP-1 RAs are widely used agents that improve glycemic control and, for some of the members of the drug class, reduce cardiovascular risk in people with T2D.[9 10] Certain GLP-1 RAs are also licensed to reduce body weight. On this background, GLP-1 RAs may be valuable in the management of HH and comorbid diabetes. To our knowledge, SGLT-2 inhibitors - another widely used pharmacotherapeutic option in T2D – do not have a known effect on ferritin levels or phlebotomy frequency. Of note, treatment with SGLT-2 inhibitors has been shown to result in increased hematocrit values as the result of decreased blood volume and/or increased renal production of erythropoietin[11] ; accordingly, use of this drug class in people HH may not be advisable.

The generalizability of our analyses is limited by the sparseness of the available data, especially on phlebotomies. Accordingly, the results of the present analyses are viewed as hypothesis-generating. Further, while we selected for T2D diagnoses only, misclassification of diabetes diagnoses across T1D and T2D and potentially 'secondary diabetes' may have been present in the databases used in this register-based study. However, the impact of this potential issue on the results of the analyses is considered minor. In this context, it should be noted that with the exception of dapagliflozin between early 2019 and late 2021, SGLT-2 inhibitors are not licensed in T1D in Denmark. Further, because this information was not available in the dataset, we did not account for use of other HH-specific interventions including the use of iron chelators in people, for whom phlebotomy may have been contraindicated; to our knowledge, however, the use of such drugs in HH is very rare in Denmark and countries such the UK. Further, because data extracted from the DRMPS are by definition data on filled prescriptions and not on actual use, the estimates may have been biased by the possibility that some individuals may have claimed a prescription but not actually taken the drug.

Future follow-on studies should preferably include data from more than one country to further extend the generalizability across regions and ethnicities as well as a broader range of drug prescription patterns. Other aspects that warrant further elucidation in new studies include the identification of the potentially most clinically useful GLP-1 RA in HH; this aspect could not be investigated based on the sparse data available in the present study. Finally, while the available information did not allow us to study these aspects in the present study, any potential effect modification of or mediation through the known marked effects of GLP-1 RAs and SGLT-2 inhibitors on glycemic control and body weight are also relevant to investigate in future studies. A previous report has suggested an association between high body mass index and hyperferritinaemia.[12]

Overall, the results of our analyses are in line with the early evidence that have indicated that GLP-1 RAs may have a ferritin-lowering effect.[6 7] Of note, a case report has suggested that GLP-1 RA treatment in people with HH (and cystic fibrosis) is associated with an increased risk of acute pancreatitis.[13] While this association has not been further substantiated, awareness of this aspect should be considered in the benefit/risk evaluation of GLP-1 RA treatment in HH.

In summary, the results of the present analyses support the hypothesis of a beneficial effect of GLP-1 RA treatment in HH. To further qualify and investigate the hypothesis, additional larger and more diverse studies are needed, for example, to explore the mechanisms

driving the potential benefit of GLP-1 RAs on excess iron levels in people with HH and T2D.

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