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Original article

SGLT2 inhibitors and incretin agents: Associations with alanine aminotransferase activity in type 2 diabetes☆

H.S. Bajaj [a,b,*], R.E. Brown [c], L. Bhullar [a], N. Sohi [d], S. Kalra [d], R. Aronson [c]

[a] LMC Diabetes and Endocrinology Brampton, 2979, Bovaird Dr. E, L6S0C6 Brampton, Ontario, Canada
[b] Leadership Sinai Centre for Diabetes, Mount Sinai Hospital, 60, Murray street, M5T3L9 Toronto, Ontario, Canada
[c] LMC Diabetes and Endocrinology Toronto, 1929, Bayview avenue, M4G3E8 Toronto, Ontario, Canada
[d] Royal College of Surgeons, 123, street Stephen's Green, Dublin, Ireland

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ABSTRACT

Aim. – The impact of new classes of glucose lowering medications on markers of non-alcoholic fatty liver disease (NAFLD) associated with type 2 diabetes (T2D) have been inconsistent in their magnitude and independence. This large retrospective study investigates changes in alanine aminotransferase (ALT) levels among subjects initiated on newer classes of T2D medications in comparison to a reference control group.

Methods. – We studied people with T2D from a large Canadian diabetes register, who had canagliflozin, dapagliflozin, liraglutide, sitagliptin or no further treatment added to their diabetes treatments. Stepwise multiple regression was used to determine the association of A1c and weight change on ALT. Propensity score weighting was used to balance baseline characteristics between treatment groups.

Results. – A total of 3667 subjects met study criteria. ALT levels (mean follow-up 4.8 months) were lower after treatment with sodium glucose co-transporter 2 (SGLT2) inhibitors, canagliflozin (−4.3 U/L, $P < 0.01$) and dapagliflozin (−3.5 U/L, $P < 0.01$), compared to incretin agents, liraglutide (−2.1 U/L, $P < 0.01$) and sitagliptin (−1.8 U/L, $P < 0.01$), each greater than the control group. Only the SGLT2 inhibitor treatment groups maintained a significant ALT reduction vs. control following multivariable adjustment and propensity score weighting. Greater ALT reductions were seen with higher baseline ALT for both the SGLT2 inhibitor treatment groups.

Conclusion. – SGLT2 inhibitors canagliflozin and dapagliflozin resulted in a weight and A1c-independent reduction of ALT levels compared to incretin agents, with a dose-response observed at higher baseline ALT levels. Further studies investigating the differential effects of these drug classes on NAFLD, and insulin/glucagon levels as potential mechanism explaining these differences, should be performed.

1. Introduction

Patients with type 2 diabetes mellitus (T2D) have a very high prevalence of non-alcoholic fatty liver disease (NAFLD). The prevalence of non-alcoholic steatohepatitis (NASH) in this population ranges from 60–88% and is associated with increased risk of developing liver fibrosis, cirrhosis and hepatocellular carcinoma [1–5]. There exists an unmet need to develop de novo hepato-protective medications as well as study the hepatic effects of existing glucose lowering medications used in T2D. Thiazolidinediones, such as pioglitazone, have, to date, been the only class of glucose lowering medications consistently shown to have beneficial hepatic effects [6–8].

Newer glucose lowering medications such as sodium glucose co-transporter 2 (SGLT2) inhibitors and glucagon like peptide-1 receptor agonists (GLP-1 RA), provide the added benefit of weight loss, which itself may have favourable effects on NAFLD parameters. Canagliflozin, dapagliflozin and empagliflozin are SGLT2 inhibitors with a mechanism of action related to glucosuria [9,10], with a known ancillary effect of increasing plasma glucagon levels [11–14]. SGLT2 inhibitors have been associated with reduction in alanine aminotransferase (ALT) levels, a biomarker for NAFLD, in limited studies [15,16] and change from baseline in the liver-to-spleen attenuation ratio on computed tomography in a recent, small, randomized trial comparing pioglitazone with

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* Corresponding author at: LMC Diabetes and Endocrinology, 2979, Bovaird Dr. E, L6S0C6 Brampton, Ontario, Canada.
E-mail address: harpreet.bajaj@lmc.ca (H.S. Bajaj).

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ipragliflozin [17]. GLP-1 RA and dipeptidyl peptidase-4 (DPP-4) inhibitors have similar mechanisms of action in T2D i.e. glucose-dependent insulin secretion together with inhibition of glucagon release. Additionally, GLP-1 RAs delay gastric emptying and lead to a reduction in appetite [18]. A meta-analysis of four observational studies suggested that sitagliptin and liraglutide similarly decreased ALT levels [19,20]. In a small, controlled trial of NASH patients with or without T2D – with 45 patients completing liver biopsies – liraglutide was associated with resolution of NASH, however these benefits were found to be proportional to the amount of weight loss [20]. By contrast, in a recently published controlled trial, 12 weeks of liraglutide or sitagliptin treatment did not reduce hepatic steatosis or fibrosis in patients with T2D [21].

Hence, the glucose – and weight-independent effects of newer glucose lowering medications (SGLT2 inhibitors and incretin agents) on markers of NAFLD have been equivocal – with no direct comparison to date. Thus, in the present large retrospective study, we investigate the effects of two SGLT2 inhibitors (canagliflozin and dapagliflozin), a DPP-4 inhibitor (sitagliptin) and a GLP-1 RA (liraglutide) on ALT levels among patients with T2D in comparison to a reference control group. We further investigate the independence of these effects from A1c and weight change using multivariable adjustment. Propensity score methods were also used to balance baseline covariates between treatment groups.

2. Material and methods

2.1. Study design

This retrospective study was conducted using an electronic registry of patients followed in seven Ontario-based LMC Diabetes & Endocrinology (LMC) centres. LMC is a multi-site, community-based, specialist-led, referral-based, multidisciplinary clinic group with a shared single electronic medical record. The LMC registry has been previously described [22,23].

The study population was chosen based on a pre-defined protocol, approved by an Ethics Review Board and registered on clinicaltrials.gov (NCT03233178). Inclusion criteria were patients:

- with type 2 diabetes who had previously provided consent for their registry data to be used for clinical research;
- who had started treatment with any one of the four glucose lowering medications (canagliflozin, dapagliflozin, sitagliptin and liraglutide) between January 1, 2012 and October 31, 2016;
- with medication persistence documented for >3 months on at least one follow-up clinic visit;
- with one or more ALT lab values obtained in Ontario within 6 months prior (baseline) and 6 months after (follow-up) starting the medication and;
- who had baseline values for HbA1c and body weight. Baseline ALT was the closest measurement prior to starting the medication.

Follow-up ALT was the last measurement, while the patient was still on the medication, within 6 months after starting. Control group included any patient with type 2 diabetes that did not have a glucose lowering medication added between June 1, 2014 and May 31, 2015. Patients were excluded if they had an A1c ≤7.0% at baseline, if they were enrolled in a research protocol with an investigational therapy, or if more than one glucose lowering medication was initiated simultaneously. Other exclusions were made for pregnancy, bariatric surgery, and known hepatic disorders, including hepatitis B, hepatitis C, history of liver transplant or documented history of alcohol abuse. Patients were only included in the final treatment groups if they had values for ALT, A1c and weight at baseline. All patients had complete information for demographic variables, duration of diabetes, and concomitant glucose lowering medications. The study was funded independently by LMC Diabetes & Endocrinology, with no external funding source. This study was carried out in accordance with the principles of the Declaration of Helsinki (2004 version).

2.2. Data analysis

Baseline characteristics were summarized as mean ± standard deviation or percentages for continuous variables and categorical variables, respectively. Baseline characteristics between the 5 patient treatment groups were compared using the population standardized differences, which is an appropriate criterion for assessing covariate balance between >2 treatment groups [24]. This was calculated as the difference between the mean of a covariate for a given treatment and the unweighted mean of a covariate for the pooled sample across all treatments, divided by the standard deviation of the covariate for the pooled sample across all treatments. For the purpose of this study, a standardized difference of < 0.20 was considered small and the variables between the groups were considered to be balanced [24].

To control for differences in baseline characteristics between the treatment groups, we applied the inverse probability of treatment weighting of the propensity score, defined as the probability of treatment assignment conditional on measured baseline covariates [25]. In our study, propensity scores were estimated for each treatment group by a multinomial logistic regression model, with treatment group as the dependent variable, and the following baseline variables as covariates: age, gender, ALT, A1c, weight, insulin use, and interaction terms for age and A1c, and age and weight. Treatment weights were calculated as the reciprocal of the probability that a patient received the treatment they received. Comparisons within treatment groups from baseline to follow-up for ALT, A1c, body weight and waist circumference were performed using paired *t*-tests. A regression model was used to assess differences in ALT change between the 5 treatment groups, using the SURVEYREG procedure in SAS to account for the weighting. Stepwise multivariable regression analysis was conducted with serial adjustment for A1c change, weight change and both combined.

Stratified analyses for baseline ALT were then performed within the weighted sample: stratifying by a clinical cut-off value of ALT < or ≥30 IU/L as well as stratifying by baseline ALT tertiles. All analyses were conducted using SAS version 9.4 (Cary, North Carolina).

3. Results

A total of 3844 patients met the study criteria. One hundrend and seventy-seven patients with very small propensity scores (<0.001) were excluded. The final sample size of the five treatment groups analyzed was: canagliflozin = 1325, dapagliflozin = 730, sitagliptin = 661, liraglutide = 521 and control group = 430. Baseline characteristics, including background glucose lowering medications, as well as doses of the newly added SGLT2 inhibitor or incretin agent for each treatment group are listed in Table 1. Weighting the sample successfully balanced all the baseline characteristics (standardized difference <0.20), with the exception that the control group still had a higher mean age compared to the population. Mean times for follow-up ALT after drug initiation were similar across the treatment groups.

All four treatment groups showed a significant reduction in ALT on follow-up (Table 2): canagliflozin −4.3 ± 11.8 IU/L, dapagliflozin −3.5 ± 14.3 IU/L, sitagliptin −1.8 ± 15.6 IU/L, liraglutide

Table 1
Baseline characteristics of the canagliflozin, dapagliflozin, sitagliptin, liraglutide and control group.

	Canagliflozin	Dapagliflozin	Sitagliptin	Liraglutide	Control	Population
n	1325	730	661	521	430	3667
Age, (years)	60 ± 10	58 ± 10[a]	64 ± 11[a]	58 ± 90[a]	70 ± 12[a,b]	61 ± 11
Males, (%)	58	57	57	56	57	57
Diabetes duration, (yrs)	14 ± 7	13 ± 7	13 ± 8	14 ± 7	18 ± 9[a]	14 ± 8
ALT, (IU/L)	30.6 ± 17.2	31.4 ± 19.3	28.3 ± 17.4	31.7 ± 17.5	23.6 ± 12.8[a]	29.7 ± 17.4
A1c, (%)	8.5 ± 1.1	8.6 ± 1.2	8.4 ± 1.2	8.6 ± 1.2	7.9 ± 1.0[a]	8.5 ± 1.2
A1c, (mmol/mol)	69 ± 12	70 ± 13	68 ± 13	70 ± 13	63 ± 11	69 ± 13
Weight, (kg)	91 ± 20	88 ± 19	83 ± 18[a]	100 ± 21[a]	84 ± 20[a]	89 ± 21
BMI, (kg/m^2)	32 ± 6	31 ± 6	30 ± 6[a]	35 ± 6[a]	31 ± 6	32 ± 6
Waist circumference, (cm)	107 ± 14	105 ± 13	103 ± 14[a]	114 ± 15[a]	104 ± 15	106 ± 15
FPG, (mmol/L)	9.3 ± 2.8	9.3 ± 2.4	8.9 ± 2.7	9.3 ± 2.8	8.3 ± 2.6[a]	9.4 ± 2.9
Triglycerides, (mmol/L)	1.86 ± 1.46	1.91 ± 2.32	1.85 ± 1.51	1.99 ± 1.18	1.56 ± 0.98[a]	1.90 ± 1.60
Insulin, (%)	47	45	28[a]	50	74[a]	47
Metformin, (%)	96	96	97	96	63[a]	92
Sulfonylurea, (%)	45	46	39	47	22[a]	42
Dose of newly added glucose lowering medication, (%)	100 mg: 73 300 mg: 27	5 mg: 54 10 mg: 46	50 mg: 19 100 mg: 81	0.6 mg: 8 1.2 mg: 59 1.8 mg: 23		

Data is presented as mean ± SD or as a %. ALT: alanine amino transferase; BMI: body mass index; FPG: fasting plasma glucose.
[a] Standardized dfference ≥0.20 before weighting.
[b] Standardized difference ≥0.20 after weighting.

−2.1 ± 13.9 IU/L, (all $P < 0.01$), while ALT remained unchanged in the control group. A1c reduction was observed at follow-up in each of the 5 treatment groups. Canagliflozin, dapagliflozin and liraglutide were each associated with significant weight loss and waist circumference reduction, whereas the sitagliptin and control groups showed minimal changes in weight and waist circumference.

Unadjusted ALT change from baseline was similar for intra-class comparisons (Fig. 1): SGLT2 inhibitors (canagliflozin vs. dapagliflozin), and incretin agents (sitagliptin vs. liraglutide). After stepwise adjustment for A1C change, weight change separately or combined adjustment for A1C and weight change, only the SGLT2 inhibitors (canagliflozin or dapagliflozin) showed significant ALT change vs. all other treatment groups, (except for the dapagliflozin vs. sitagliptin comparison, which did not reach statistical significance). On the other hand, for the incretin agents (sitagliptin or liraglutide), the unadjusted mean ALT was reduced compared to the control group however, and even these comparisons lost statistical significance following adjustment for A1c change (Fig. 1). Notably, adjustment for weight change resulted in loss of significant differences for liraglutide vs. control, but not for sitagliptin vs. control comparisons (−2.3 IU/L, $P < 0.01$).

Propensity score weighting (Fig. 2) showed similar findings to multivariable adjustment. In weighted between-group comparisons, statistically significant comparisons of ALT change were observed only for the SGLT2 inhibitors: canagliflozin vs. sitagliptin −2.2 (SE 0.7) IU/L ($P < 0.01$), canagliflozin vs. liraglutide −2.9 (SE 0.8) IU/L ($P < 0.01$) and canagliflozin vs. control −4.9 (SE 1.6) IU/L ($P < 0.01$); dapagliflozin vs. liraglutide −1.9 (SE 0.9) IU/L ($P = 0.03$) and dapagliflozin vs. control −3.8 (SE 1.6) IU/L ($P = 0.02$).

Stratified analyses for baseline ALT were performed within the weighted sample in two ways: stratifying by a clinically-relevant cut-off value of ALT < or ≥30 IU/L (Fig. 3) and stratifying by baseline ALT tertile. Mean baseline ALT was 20.1 ± 8.4 IU/L and 44.9 ± 27.1 IU/L for the ALT < 30 IU/L and ALT ≥30 IU/L sub-groups, respectively. Mean baseline ALT levels were 15.7 ± 3.3 IU/L, 25.5 ± 3.1 IU/L and 47.9 ± 19.1 IU/L for each of the three tertiles. Among patients with low ALT at baseline (<30 IU/L), canagliflozin had significantly greater reductions in ALT compared to sitagliptin, liraglutide and the control group. Among patients with high ALT (≥30 IU/L) (Fig. 3) and patients in the highest ALT tertile, canagliflozin had significantly greater reductions in ALT compared to the control group and liraglutide, while dapagliflozin had significantly greater reductions in ALT compared to liraglutide. Among patients in the second ALT tertile, both canagliflozin and dapagliflozin had significantly greater reductions in ALT compared to the control group. There were no statistically significant differences in ALT change between treatment groups for the lowest tertile of baseline ALT.

4. Discussion

In this retrospective study, two novel findings have emerged. Firstly, subjects with T2D initiated on SGLT2 inhibitors had clinically and statistically significant reductions in ALT levels (especially in the sub-groups with high baseline ALT), with a comparatively smaller reduction in ALT levels for incretin-based treatments. Secondly, the beneficial effects of SGLT2 inhibitors on ALT levels are independent of the changes in A1C and weight, unlike the effects of incretin agents which appear to be mediated through the A1c and weight reduction.

To our knowledge, this report is the first published study to compare and contrast ALT levels between the newer glucose lowering medication classes (SGLT2 inhibitor, DPP-4 inhibitor and

Table 2
Within group three-six month changes in clinical outcomes.

	Canagliflozin	Dapagliflozin	Sitagliptin	Liraglutide	Control
ALT, (IU/L)	−4.3 ± 11.8[a]	−3.5 ± 14.3[a]	−1.8 ± 15.6[a]	−2.1 ± 13.9[a]	0.3 ± 11.1
A1C, (%)	−0.8 ± 1.0[a]	−0.8 ± 1.2[a]	−0.8 ± 1.2[a]	−0.8 ± 1.2[a]	−0.1 ± 0.8[a]
A1c, (mmoL/moL)	−8.7 ± 10.9	−8.7 ± 13.1	−8.7 ± 13.1	−8.7 ± 13.1	−1.1 ± 8.7
Body weight, (kg)	−2.5 ± 3.2[a]	−2.0 ± 2.9[a]	−0.6 ± 2.7[a]	−2.2 ± 3.6[a]	0.2 ± 2.6
Waist circumference, (cm)	−1.3 ± 4.2[a]	−1.8 ± 3.8[a]	−0.8 ± 4.2	−1.2 ± 5.3[a]	0.6 ± 3.8[a]

Data is presented as mean ± SD. ALT: alanine aminotransferase.
[a] Significant change from baseline ($P < 0.01$).

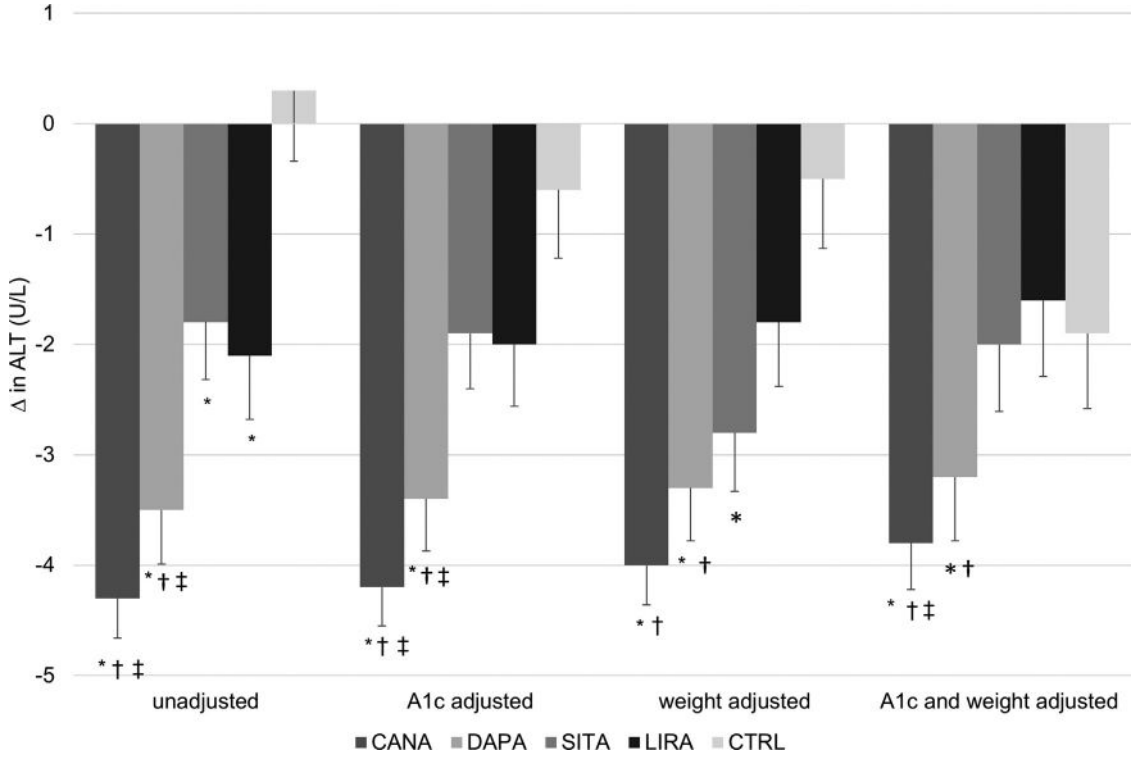

Fig. 1. Comparison of ALT change between canagliflozin, dapagliflozin, sitagliptin, liraglutide and control: unadjusted, A1c adjusted, weight adjusted and fully adjusted (A1c and weight adjusted) models. *: significantly different compared to control ($P < 0.05$); †: significantly different compared to liraglutide ($P < 0.05$); ‡: significantly different compared to sitagliptin ($P < 0.05$).

GLP-1 RA). Overall, our study results are consistent with the limited available literature, generally studying SGLT2 inhibitors and incretin agents separately, which has suggested a potential beneficial effect of these newer glucose lowering medications on biomarkers of NAFLD [15–17,19]. Similar to our study results, the beneficial hepatic effects associated with liraglutide were found to be proportional to the amount of weight loss in the Liraglutide Efficacy and Action in NASH (LEAN) trial [20]. Our study adds to this literature by suggesting that the reduction in ALT levels is higher for SGLT2 inhibitors compared to incretin agents – especially in the sub-group with higher baseline ALT. In addition, our finding of an independent ALT reduction effect with SGLT2 inhibitor initiation stands in contrast to a recent analysis of pooled phase 3 randomized control trial data, which attributed the

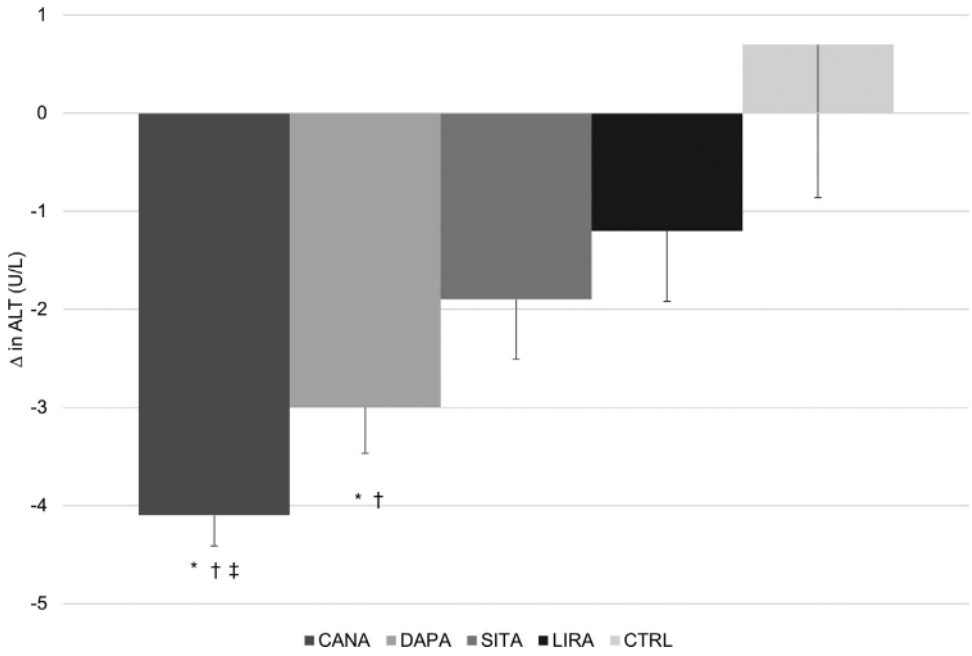

Fig. 2. Comparison of ALT change between canagliflozin, dapagliflozin, sitagliptin, liraglutide and control using inverse probability of treatment weighting. *: significantly different compared to control ($P < 0.05$); †: significantly different compared to liraglutide ($P < 0.05$); ‡: significantly different compared to sitagliptin ($P < 0.05$).

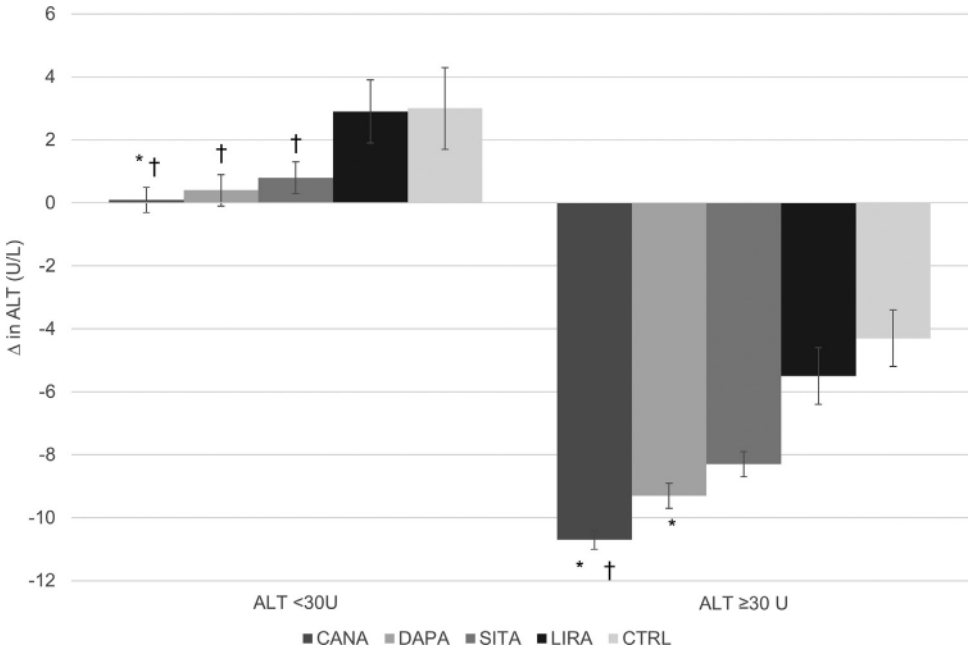

Fig. 3. Statistically significant differences in ALT change between study treatment groups using inverse probability of treatment weighting stratified by low (ALT <30 U/L) versus high (ALT ≥30 U/L) baseline ALT. In the low baseline ALT sub-group, there were significant differences in ALT change between canagliflozin and control ($P = 0.03$), canagliflozin and sitagliptin ($P = 0.02$), and between canagliflozin and liraglutide ($P = 0.02$). In the high baseline ALT sub-group, there were significant differences in ALT change between canagliflozin and control ($P = 0.03$), canagliflozin and liraglutide ($P < 0.01$), and between dapagliflozin and liraglutide ($P = 0.04$). * = significantly different compared to control ($P < 0.05$); † = significantly different compared to liraglutide ($P < 0.05$).

canagliflozin-associated decrease in liver enzyme levels entirely to weight and A1c changes [15]. Notably, patients with elevated levels of ALT had been excluded in these phase 3 trials – which could explain the different results compared to our study.

We did not study mechanisms that led to the apparent ALT reduction in this retrospective clinical data-based study. Nonetheless, the opposing effects of SGLT2 inhibitors and incretin agents on insulin: glucagon ratio are well established in the literature. SGLT2 inhibitors lead to glucagon stimulation leading to a fall in insulin: glucagon ratio in both pre-clinical and clinical studies [11–14]. Incretin agents lead to glucagon suppression and insulin stimulation, resulting in a rise in the insulin: glucagon ratio. Historically, insulin: glucagon ratio has been used as an index of anabolism, with insulin as the most potent anabolic hormone in the body, as opposed to glycogenolytic or catabolic activity of glucagon in the liver [26]. Hence, it is mechanistically plausible that these opposing glucagon effects may play a role in the differential liver effects of these two classes of glucose lowering medications. SGLT2 inhibitors, through glucosuria, may simulate calorie restriction by suppressing malonyl coenzyme A, thus allowing carnitine palmitoyl transferase 1 to distribute free fatty acids to β-oxidation instead of fat deposition [13,27,28] – which may explain their independent beneficial effect on NAFLD associated in T2D in addition to being a possible explanation for their protective effects documented in cardiovascular outcome trials [29–31].

Due to the growing epidemic of NAFLD, in association with T2D, there is an unmet clinical need for pharmacotherapy interventions that might be added to the lifestyle interventions currently recommended for management of these hepatic conditions [31,32]. The novel results of this study are hypothesis-generating, which should be further investigated in mechanistic studies as well as randomized trials comparing SGLT2 inhibitors and incretin agents in subjects with NAFLD associated with T2D. Depending on the results of future trials, it is plausible that medical management for patients with T2D may incorporate the presence of NAFLD as one of the clinical criteria for selection of appropriate glucose lowering medication.

Limitations of this study include those inherent to a retrospective observational analysis. We employed both multivariable adjustment as well as propensity score inverse probability of treatment weighting in two efforts to overcome the variations in background characteristics among the 5 treatment groups. Additionally, residual confounding and selection bias were limited in this retrospective analysis as unmeasured variables are unlikely to have influenced the choice of glucose lowering medication in our study. Another limitation of this study is that because of the clinical nature of this registry data, we were only able to use ALT levels as the sole surrogate marker for NASH. ALT has low sensitivity and predictive value as a biomarker in screening for NASH, and imaging or liver biopsy are preferred for liver categorization [33], but ALT has been independently and strongly associated with the presence of NAFLD and NASH on liver biopsy [4,34–36]. Notably, because we compared the ALT change from baseline (as a continuous variable) among the five study treatment groups, the limitation of ALT in clinical diagnosis of NAFLD/NASH does not detract from this study's contribution. Finally, the classification of a high ALT level has traditionally required adjustment for gender [37]. However, the low likelihood of gender-based treatment initiation in the study treatment groups as well as the tertile analysis performed in this study overcomes this limitation of use of an ALT level of 30 IU/L to define a clinically high level, irrespective of gender.

5. Conclusions

Initiation of SGLT2 inhibitors (canagliflozin, dapagliflozin) in a broad population of T2D patients was associated with a weight – and A1c-independent effect in reducing ALT levels (especially among those with higher baseline ALT levels); whereas the relatively smaller ALT reduction observed following initiation of

incretin therapies (sitagliptin, liraglutide) was found to be dependent on their weight and A1c reductions. Further research is needed to confirm and augment our study findings before a strategy of prescribing newer glucose lowering medications to patients suffering from NAFLD associated T2D can be applied to clinical practice.

Guarantor of the article

Dr. Harpreet S. Bajaj accepts full responsibility for the conduct of the study. He had access to all of the data and had control of the decision to publish.

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Contribution of authors

H.S. Bajaj, R.E. Brown and R. Aronson designed, planned the analysis and implemented the study.

R.E. Brown, L. Bhullar, N. Sohi and S. Kalra performed electronic registry data queries and cleaned the data generated.

H.S. Bajaj, R.E. Brown and R. Aronson interpreted the data.

H.S. Bajaj and R.E. Brown wrote the first draft of the manuscript.

R.E. Brown performed the statistical analyses.

All authors critically revised the manuscript for important intellectual content and approved the final manuscript.

Disclosure of interest

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R.E. Brown, L. Bhullar, N. Sohi and S. Kalra declare that they have no competing interest.

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