The effect of dapagliflozin on alanine aminotransferase as a marker of liver inflammation: updated results from the ABCD dapagliflozin audit

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Abstract

Introduction: People with type 2 diabetes are known to be at increased risk of non-alcoholic fatty liver disease (NAFLD). There is increasing evidence of diabetes treatments with benefits of also improving NAFLD. Although mostly focused on glucagon-like peptide 1 agonists, sodium-glucose linked transporter 2 inhibitors may also have some promise in improving markers of NAFLD.

Method: Data were extracted from the ABCD nationwide dapagliflozin audit tool. Alanine aminotransferase (ALT) was available in these data and was used as a marker of liver inflammation. Patients were stratified based on baseline ALT levels to see if this predicted response to treatment.

Results: 1,873 patients were included for analysis (mean±SD age 58.7±10 years, 60.8% male, median duration of diabetes 3.5 years (IQR 1.5–9)) and were followed up in this study for an average of 11.4 months. Where known (n=280), 60.8% of these were Caucasian. Baseline HbA1c was 7.8±17.2 mmol/mol, weight 102.1±22.5 kg and body mass index (BMI) 34.2±7.6 kg/m². Median ALT reduction overall was 4 U/L (95% CI 3 to 4; p<0.001). Reductions in weight (3.2 kg; 95% CI 2.9 to 3.5), BMI (0.9 kg/m², 95% CI 0.6 to 1.2) and HbA1c (10.8 mmol/mol, 95% CI 10.1 to 11.5) (0.9%, 95% CI 0.8% to 1.0%) were all significant (p<0.001). Where ALT was elevated at baseline (>19 U/L female; >30 U/L male), the median reduction in ALT was 5 U/L in women (95% CI 4 to 6; p<0.0001) and 10 U/L in men (95% CI 8 to 11; p<0.0001). Stratified into three groups by ALT using the male reference range and twice this, there were reductions in ALT in all groups, which was greatest (24 U/L 95% CI 20 to 27) in the subgroup with baseline ALT >59 U/L.

Conclusion: Our observational data suggest significant reductions in ALT as a possible marker of liver inflammation in those taking dapagliflozin. This appears to be greatest in those with the most elevated levels at baseline.

Key words: dapagliflozin, real-world, alanine aminotransferase (ALT), non-alcoholic fatty liver disease, SGLT-2

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Female and male, normal and raised ALT groups based on gender-specific reference ranges (female, ALT ≤ 19 U/L; male, ALT < 30 U/L). 

2. Normal (as defined by male reference range ALT < 30 U/L), mildly elevated (ALT 30–59 U/L) and markedly elevated based on twice the upper limit of the normal male reference range (ALT > 59 U/L).

The selection and stratification of patients is outlined in Figure 1.

Skewed data were analysed using Wilcoxon signed-rank tests (paired tests) and Friedman tests (difference between groups). For non-skewed data, paired t-tests were used for paired data whilst linear regression and Spearman’s correlation coefficients were calculated to express the relationship between the different variables (ALT, weight, HbA1c) and baseline ALT as well as between change in weight and change in ALT.

Any patients who discontinued dapagliflozin during the time frame of the audit to date were reviewed separately to describe their baseline characteristics and identify common reasons why the medication was discontinued as part of a sensitivity analysis.

Results

The baseline characteristics of the 1,873 patients included for analysis are shown in Table 1. The population had a mean±SD age of 58.7±10 years and 60.8% were male. Ethnicity data were available for only 208 of those included and 60.8% of these were British or Irish. The mean±SD baseline HbA1c was 9.2±1.57% or 78±17.2 mmol/mol. The mean±SD weight at baseline was 102.1±22.5 kg with a body mass index (BMI) of 34.2±7.6 kg/m². The average duration of diabetes at baseline was 3.5 years (IQR 1.5–9).

1. Female and male, normal and raised ALT groups based on gender-specific reference ranges (female, ALT ≤ 19 U/L; male, ALT < 30 U/L). 

The population was then stratified into groups using the following two methods and each method of stratification was analysed separately:

- Dapagliflozin is a sodium-glucose link transporter 2 (SGLT-2) inhibitor and there is much evidence to support its use with favourable outcomes in terms of HbA1c, weight, cardiovascular and renal outcomes, both alone and in combination therapy with other oral hypoglycaemic agents or insulin in randomised controlled trials and real-world data analyses. Evidence for its effect on NAFLD is more limited, especially compared with GLP-1 agonists such as liraglutide which are supported by large clinical trials specifically looking at NAFLD outcomes. Trial data from Korea suggest that SGLT-2 in combination with metformin is superior to dipeptidyl peptidase-4 inhibitors in improving ALT, and the significance of this improvement was maintained when adjusting for weight loss. There are further randomised controlled data showing improvements in liver fibrosis based on transient elastography as well as improvements in ALT and gamma-glutamyltranspeptidase with dapagliflozin compared with placebo, although the numbers were fairly small. Real-world data are also available, showing a significant reduction in ALT in 3,667 Canadian patients independent of weight loss and other variables and with greater reductions in ALT observed in those with higher baseline levels.

The dapagliflozin audit was initially launched in 2012 and collection ceased in 2018, although anonymised data from clinical commissioning groups (CCGs) continue to be integrated when they become available. The aim of this analysis of the ABCD dapagliflozin audit data is to establish whether the medication was discontinued as part of a sensitivity analysis.

Any patients who discontinued dapagliflozin at any point during the audit were also analysed to assess the reasons for discontinuing and to describe their baseline characteristics as part of a sensitivity analysis.

Methods

Data were obtained from the integration of ABCD UK and international audit data as well as data from CCGs. Patients were excluded if they did not have a minimum dataset of baseline ALT and follow-up (defined as 6-18 months after commencing) or if they discontinued dapagliflozin prior to having a repeat ALT measurement. Data for HbA1c and weight at baseline and follow-up (if available) were also extracted.

The population was then stratified into groups using the following two methods and each method of stratification was analysed separately:
The baseline characteristics of the male and female subgroups are shown in Table 2. This demonstrates similarities across the groups and, although the men with raised baseline ALT (>30 U/L) were heavier at baseline, the BMI of this group is comparable to that of the other groups.

Those who discontinued dapagliflozin were broadly similar in baseline characteristics to the above, other than having a longer duration of diabetes at baseline (median 12 years) and a greater proportion of those discontinuing were female (51.3%). The main reasons for discontinuing were efficacy (28%), followed by urinary tract infections (11%) and genital infections (usually candidiasis) (20%).

Over a mean follow-up of 11.4 months the median ALT reduction across the entire population was 4 U/L (95% CI 3 to 4; p<0.001). Reductions in weight (3.2 kg; 95% CI 2.9 to 3.5), BMI (0.9 kg/m²; 95% CI 0.6 to 1.2) and HbA1C (10.8 mmol/mol; 95% CI 10.1 to 11.5) (0.9%; 95% CI 0.8% to 1.0%) were all significant (p<0.001).

In the subgroups with elevated ALT at baseline (>19 U/L female; >30 U/L male) there was a median reduction in ALT of 5 U/L in women (95% CI 4 to 6; p<0.0001) and of 10 U/L in men (95% CI 8 to 11 U/L; p<0.0001). In women with normal baseline ALT there was a statistically significant increase in ALT of 1 U/L (95% CI ~2 to 0; p<0.0001) and in men there was a median decrease of 1 U/L (95% CI 1 to 2; p<0.0001); the clinical significance of such small

| Characteristic | Female Normal ALT | Female Raised ALT | Male Normal ALT | Male Raised ALT |
|---------------|------------------|------------------|----------------|----------------|
| Number        | 187              | 546              | 680            |                |
| Mean±SD age, years | 56.9±10.4       | 57.3±10.2       | 61.5±9.8       | 58.4±9.4       |
| Median (IQR) diabetes duration, years | 3.7 (1.7–10.3) | 3.5 (1.6–8)     | 3.9 (1.6–10.4) | 3.4 (1.4–7.8) |
| Caucasian, % (where known, n=51) | 41.2%           | 62.1%           | 68.9%          | 75% (n=100)    |
| Mean HbA1C, %±SD mmol/mol &%±SD | 9.2±1.8         | 9.2±1.5         | 9.2±1.85       | 9.5±1.55       |
| MeanSD BMI, kg/m² | 35.4±10.5       | 34.6±8.0        | 35.4±10.5      | 34.1±6.2       |
| MeanSD weight, kg | 92.7±20.4       | 95.0±20.0       | 92.7±20.4      | 109.5±20.8     |

ALT, alanine aminotransferase; BMI, body mass index; IQR, interquartile range; SD, standard deviation.

Figure 2. Bar chart showing median alanine aminotransferase (ALT) in each group at baseline and follow-up for normal (female ≤19 U/L; male <30 U/L) and raised ALT at baseline in patients commencing dapagliflozin. Error bars represent interquartile ranges. All results significant to p<0.0001
changes is unlikely to be of any relevance. The medians of each group with interquartile ranges are shown in Figure 2 and the changes in ALT with confidence intervals are shown in Figure 3.

When stratified into three groups based on baseline ALT as defined by the male reference range (<30 U/L) and twice the upper limit of normal, there were statistically significant (p<0.0001) reductions in ALT in all three groups with the greatest reduction (24 U/L; 95% CI 20 to 27) in the subgroup with markedly elevated baseline ALT (>59 U/L). The results are shown in Figure 4.

There were statistically significant differences between all groups in each analysis with the Friedman test (non-parametric analysis of variance) p<0.0001.

There was no correlation between baseline ALT and change in weight, but baseline ALT did significantly, though weakly, correlate positively with change in HbA1c and more strongly with change in ALT. There was no correlation between change in weight and change in ALT (p=0.16). Spearman’s coefficients and p values are shown in Table 3.

Table 3  Spearman’s rank correlation between baseline alanine aminotransferase (ALT) and metabolic and clinical outcomes in patients receiving dapagliflozin

| Metabolic/clinical parameter | Spearman’s rho | P value |
|-------------------------------|----------------|---------|
| Change in weight (n=1,847)    | ≤0.001         | 0.8     |
| Change in HbA1c (n=1,861)     | 0.004          | 0.003   |
| Change in ALT (n=1,873)       | 0.27           | <0.0001 |
| Change in weight vs change in ALT | <0.001 | 0.16   |
Discussion

Main findings

The subjects included in this analysis of the UK ABCD dapagliflozin audit had a median duration of diabetes of less than 5 years with raised BMIs and out-of-target HbA1c levels at baseline. Where the data are available, it suggests our dataset is generally representative of the UK population with 63.9% Caucasian ethnicity, albeit with a slightly stronger preponderance towards being male (60.8%).

Those discontinuing dapagliflozin were more likely to be female and, in view of urinary and genital infections being common reasons for the discontinuation, it is likely that the predisposition of women towards these infections is the likely explanation for this disparity. During the observed time period, dapagliflozin use was associated with significant reductions across the population in all parameters assessed in this audit: HbA1c, weight, BMI and ALT. Although the reduction in ALT appears to be fairly small across the entire population, the reductions in ALT in individual subgroups (ie, those with raised ALT levels at baseline) is large and may be of clinical significance. Perhaps most striking is the reduction of 24 U/L (95% CI 20 to 27; p<0.0001) observed in those with ALT levels at baseline more than twice the upper limit of normal. Additionally, Spearman's correlation reveals a positive correlation between baseline ALT and reduction in ALT. This suggests that those with the most elevated ALT levels at baseline are likely to see the greatest reduction in ALT and, by extension, potentially liver inflammation and NAFLD.

Baseline ALT did slightly predict the response of HbA1c to dapagliflozin therapy but did not predict weight loss or BMI. This study found no correlation between change in weight and change in ALT (p<0.001, p=0.16), suggesting that the effect of dapagliflozin may, in part, be independent of its effect in promoting weight loss.

Strengths and limitations

Using real-world data in an observational study such as this means the findings are likely to be generalisable to UK diabetes practice where off-licence use of medications may be encountered and users may have extremes of weight, HbA1c or other factors compared with the strict inclusion criteria often used in randomised controlled trials. All data, test results and measurements included will have been taken as part of routine diabetes care. For this reason, it was not possible to provide a suitable control group. Additionally, we were only able to access specific information and were lacking other information on potential confounding factors such as other concomitant medications or alcohol use – either of which could have some impact on ALT readings.

ALT has certainly been found to be reflective of histological scores and imaging findings in previous studies, although concerns are noted on its use in NAFLD.4 It is difficult to incorporate such tests which are invasive or not part of routine care in observational data collection. Further studies are needed using multimodality assessments of liver fibrosis and NAFLD (eg, magnetic resonance imaging, biopsy, transient elastography) to confirm that dapagliflozin is exerting a positive effect on liver outcomes beyond the scope of observational data.

Interpretation

There are not many studies for comparison assessing the impact of dapagliflozin on ALT. The randomised controlled trial which included multiple methods of assessment carried out by Shimizu et al18 showed more marked reductions in ALT from a similar baseline as well as improvement in other parameters including transient elastography score (which was the primary outcome measure). This study, however, had patients with markedly different BMIs compared with our observational dataset – 73.9 kg at baseline compared with 102.1 kg in our study.

The Canadian observational data presented by Bajaj et al19 provide perhaps the closest equivalent to our dataset, with similarities across all baseline characteristics including age, ALT and BMI although with a long duration of diabetes at commencement. They reported a similar decrease in ALT of 3.5±14.3 U/L across their entire population from baseline with statistical significance (p<0.01). Additionally, they found very little change in their normal baseline ALT subgroups, with large changes observed in those with elevated ALT at baseline. This remained the case even when adjusting for weight and improvement in HbA1c, which made minimal if any change to the outcome (fitting with our data entirely).

Furthermore, both dapagliflozin and canagliflozin were found to be superior to liraglutide in achieving reduction in ALT, although only canagliflozin achieved a statistically significant difference. Our similar observational dataset from the UK ABCD liraglutide audit showed smaller reductions in ALT compared with those seen with dapagliflozin in this study.

Implications for future research, policy and practice

Although, including this study, there are two large observational studies suggesting an association between dapagliflozin use and reduction in ALT, trial data are somewhat limited, especially when compared with the large-scale randomised controlled trials that have been conducted to support the use of other therapies, such as liraglutide.16

Most trials conducted on dapagliflozin include liver function tests as a measure of safety and not of efficacy in possibly treating NAFLD and, ultimately, more data are needed to confirm that dapagliflozin, and other SGLT-2 inhibitors, offer this additional benefit. If proven to do so, it may be that they are considered superior to liraglutide due to additional benefits accompanied by an easier mode of administration (ie, oral versus subcutaneous injection).

Additionally, it is not clear whether SGLT-2 inhibitors such as dapagliflozin have a weight loss-independent mechanism of action on NAFLD. Some animal-based experimental evidence suggests that SGLT-2 inhibitors may have a direct effect on alpha-cells in the pancreas, with subsequent glucagon secretion being a possible mediator of any direct effect on the liver.21,22 Ultimately, more evidence in human subjects is needed in this regard.
Conclusions
This observational study demonstrates the potential benefits of dapagliflozin in reducing ALT levels. These are real-world data so they are likely to be more generalisable than randomised controlled trial data. Due to a lack of large-scale trial evidence using multimodal assessments of liver function and markers of NAFLD, it is not clear whether this reduction in ALT represents true improvements in underlying liver pathology. Ultimately, more evidence is needed to confirm this relationship and affirm the potential role of dapagliflozin in the management of people with diabetes and co-morbid NAFLD.

Conflict of interest
TC, MY, IG, SP, AE, AR, AB, SR, II have nothing to disclose. REJR has received speaker fees, and/or consultancy fees and/or educational sponsorships from AstraZeneca, BioQuest, GI Dynamics, Janssen and Novo Nordisk. DS has received speaker fees/honoraria from Novo Nordisk, Sanofi, Boehringer Ingelheim, AstraZeneca and Merck.

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