

ORIGINAL ARTICLE

Effects of Canagliflozin on Abnormal Liver Function Tests in Patients of Type 2 Diabetes with Non-Alcoholic Fatty Liver Disease

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Abstract

Introduction: Canagliflozin, a second line OHA is well known to reduce weight. Patients of type 2 diabetes with non-alcoholic fatty liver disease (NAFLD) frequently have abnormal liver functions. We evaluated role of canagliflozin in reducing weight and improving liver function tests (LFT) in type 2 diabetes with NAFLD.

Aim: Effects of canagliflozin on abnormal liver function tests in patients of type 2 diabetes with non-alcoholic fatty liver disease.

Methods: We selected type 2 diabetes patients who were having comorbid NAFLD with abnormal LFT. Subjects were prescribed canagliflozin in dose of 100mg/day for 6 months. Dose adjustments of other drugs (oral hypoglycemics agents and insulins) was done to monitor glycemic target. Effects of canagliflozin was observed on LFT, vitals and HbA1c. It was an observational study. Subjects who developed major side effects were excluded and managed.

Results: One subject was lost to follow up during study and 31 completed the study successfully. Average HbA1c and weight differences were -0.46% and -1.86% respectively. Average ALT reduction was 36 U/L; $t = -9.153623$, p is < 0.00001 . Average AST reduction was 19.0 U/L; $t = -8.153600$; p is < 0.00001 . Average GGT reduction was 5.87 U/L; $t = -3.286677$, $p = 0.002588$. Average ALP reduction was 1.68 U/L; $t = -1.295661$, $p = 0.204973$. Serum Bilirubin was elevated by 0.04%; $t = 0.912$, $p = 0.368$. With 0.46% reduction in HbA1c there is 37.5% reduction in ALT levels ($R = 0.1424$) and with 1.86% weight reduction there is 37.5% ALT reduction ($R = 0.3448$).

Conclusions: Canagliflozin controls HbA1c and reduce weight in type 2 diabetes. It also significantly improves LFT in co-morbid NAFLD.

Introduction

Background

Non-alcoholic fatty liver disease (NAFLD) is considered as the hepatic manifestation of the metabolic syndrome – a condition related to type 2 diabetes, insulin resistance, hypertension, central obesity, “and” hyperlipidemia (low high-density lipoprotein cholesterol, hypertriglyceridemia). NAFLD is presumed to be the most common cause of chronic liver disease in western countries. Depending on the populations studied, estimates of current prevalence range from 5% to 30%.¹ India has the largest number of people with type 2 diabetes in the world and with increasing obesity and

type 2 diabetes, there is a miserable possibility of prevalence of NAFLD increasing further.²

Rational for this Study

Treatment for type 2 diabetes and NAFLD has several similarities. Life style modification, Weight reduction, Alcohol and Tobacco abstinence, Anti-Oxidants, Metformin, Thiazolidinediones “and” Liraglutide are the mainstay treatment for both conditions. Till date, the only FDA-approved agents that in controlled studies have shown to significantly improve liver histology in patients of type 2 diabetes with NAFLD are Pioglitazone³ and Liraglutide.⁴

Canagliflozin, a Sodium-glucose co-transporter 2 (SGLT2) inhibitors is a new oral hypoglycemic agent

(OHA) which controls blood sugar by producing glycosuria.⁵ Besides managing sugar the drug is proved to significantly reduce the weight among obese patients with type 2 diabetes⁶ and improves insulin sensitivity.

Objective of this Study

To evaluate Canagliflozin as first or second line in the treatment of type 2 diabetes with NAFLD and quantify its effects in improving LFT in above clinical setting.

Material and Methods

Study Type

Post marketing Observational study of pleotropic effects of Canagliflozin. Study design was made as per guidelines laid in STROBE STATEMENT.

Study Design and Subjects Selection

Study was conducted at Sarojini Naidu Medical College, Agra, India from August 2015 to July 2016. Subjects were selected from General Medicine OPD and Diabetes specialty clinic. During the above period, all patients with type 2 diabetes who were attending the above clinic were evaluated clinically for eligibility. Patients with type 2 diabetes, with NAFLD and abnormal liver function tests (LFT) were considered eligible to be enrolled for the study. 32 subjects of type 2 diabetes, having clinical suspicion of NAFLD were extensively investigated by means of pathological tests and radiological scans to confirm the diagnosis and enrolled further.

All patients were investigated for liver functions including Alanine aminotransferase (ALT or SGPT) and Aspartate aminotransferase (AST or SGOT), total serum Bilirubin, alkaline

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phosphatase (ALP) “and” Gamma Glutamyl transpeptidase (GGT).⁷ Normal values considered are ALT= 7-41 U/L, AST= 12-38 U/L, GGT= 9-58 U/L, ALP= 33-96 U/L, “and” Bilirubin= 0.3-1.3 mg/dl. A higher ALT or AST above normal value (ie ALT > 41U/L and AST > 38 U/L) with or without rise of other tests was considered as an abnormal LFT. Exclusion of other causes of abnormal LFT including viral, alcohol, autoimmune, metabolic, drugs “and” toxins etc. were done. Strong clinical suspicion along with an abnormal LFT (with exclusion of other causes) and radiological evidences are used to confirm diagnosis of NAFLD. Although liver biopsy is the gold standard for diagnosing NAFLD we did not incorporated it in this study because (i) it needs high level of motivation for repeated biopsy before and after observation period, (ii) high possibility that subject may left the study in between and, (iii) combining ultrasound to LFT have good sensitivity to diagnose NAFLD. Our center has medium resources to investigate NAFLD.¹³ The test we used to confirm NAFLD are tabulated in table 1. Patients with non-alcoholic steatohepatitis (NASH) and cirrhosis were not included in the study. Patients

Table 1: Modalities used to confirm NAFLD (combination of two or more¹³)

- 1 Medical and family history and history of alcohol intake
 - 2 General physical examination to evaluate for risk factors, BMI, and waist-hip ratio
 - 3 Test serum liver aminotransferases
 - 4 Imaging evaluation: ultrasound
 - 5 Serology to exclude viral hepatitis: HBsAg, HCV Ab
 - 6 Fasting blood sugar, lipid profile, HbA1c
 - 7 Screening for insulin resistance
 - 8 Rule out other chronic liver diseases: optional/additional lab tests (Hereditary hemochromatosis, Wilson’s disease, alpha-1-antitrypsin, deficiency, polycystic ovary syndrome, Autoimmune liver diseases (ANA, ASMA, AMA, anti-LKM Ab)
 - 9 Liver biopsy and histology
- HBsAg= hepatitis B surface antigen; HCV Ab= hepatitis C antibody; ANA=antinuclear antibody; ASMA=anti smooth muscle antibody; AMA= anti mitochondrial antibody; anti- LKM Ab= anti liver kidney microsomal antibody.

Table 2: Demographic and clinical profile of 31 subjects

Characteristics	Before	After	Data
Weight (Kg)	Mean= 83.61 SD= 9.53	Mean= 82.04 SD= 9.47	Difference 1.56
BMI Kg/Mtr ²	Mean = 30.16 SD= 2.68	Mean = 29.59 SD = 2.63	Difference 0.57 (Fig. 1)
HbA1c %	Mean = 7.6 SD = 0.73	Mean = 7.1 SD = 1.07	Difference -0.46

with NAFLD and type 2 diabetes with normal LFT were also excluded. Weight, vitals and LFT were observed before start of the study and repeated just after completion of observation period.

Procedure

Subjects who were on OHA or Insulin were prescribed Canagliflozin 100 mg daily with dose adjustments of other drugs to maintain glycemic targets and monitoring of possible side effects. Patients were informed about the beneficial effects of Canagliflozin for their better sugar control and weight reduction as well. Its side effects were also explained in detail. Canagliflozin used was available commercially. Self-monitoring of blood sugar was done by subjects to monitor blood sugar fluctuations and HbA1c was done in the mid of observation period to maintain glycemic targets. Frequency of subject’s visits were individualized as per the blood sugar levels. Total observation period was 6 months. Other necessary investigations were done during observation period as on required basis to prevent any complication or side effects and to monitor rapid deterioration of liver functions. Minor side effects were managed as on required. Subjects who developed major side effects were excluded immediately and managed.

Study Endpoints and Statistical Analysis

Change in the averages of subject’s Weight, HbA1c, AST, ALT, Bilirubin, GGT “and” ALP were observed before and after the observation period. Subjects who completed the follow up observation period of 6 months were considered eligible to be included in observation. Marked decrease or increase in blood sugar values, marked changes in HbA1c levels, rapid deterioration in liver function or vitals of subject or development of any known or unknown fatal side effect of Canagliflozin developed during observation period were considered

to exclude subjects immediately from the study. Repeated measure student’s *t* test was used to calculate statistical difference in LFT values before and after observation period and its significance. Pearson’s correlation coefficient calculator was used to evaluate relationship between HbA1c and Weight with LFT changes before and after observation period. All calculations and graphs generated using SPSS version 16 statistical calculator.

Results

Demographic and Clinical Profile

Clinical characteristics and pathological data are presented in table 2. One subject was excluded during observation period due to development of recurrent urinary tract infection and genital candidiasis. Twenty out of 21 new subjects and all 11 old subjects (total 31) completed the observation period with minimal side effects. Ratio of males and females was 2.1:1.

Average age of females was 44.8 years, whereas of males was 47.3 years (overall average age was 46.54 years; SD 10.58). HbA1c reduced by -0.46%, whereas average weights loss was 1.56 Kg before start and after completion of study.

Changes in LFT: (Students *t* test)

Changes in LFT displayed in table 3. Average reduction in ALT was 35.9 U/L; $t = -9.153623$; $p < 0.00001$. Average reduction in ALT was 19.0 U/L; $t = -8.153600$; $p < 0.00001$. There was 7.82% reduction in GGT level; $t = -3.286677$; $p = 0.002588$). There was 2.01% reduction in ALP levels; $t = -1.295661$; $p = 0.204973$; the result was not significant at $p \leq 0.05$. There was 3.41% rise in serum bilirubin levels; $t = 0.912519$; $p = 0.368771$; the result was not significant at $p \leq 0.05$.

Relationship between HbA1c reduction and changes in LFT

Presented in Table 4 and Fig. 2 the relationship between changes in HbA1c

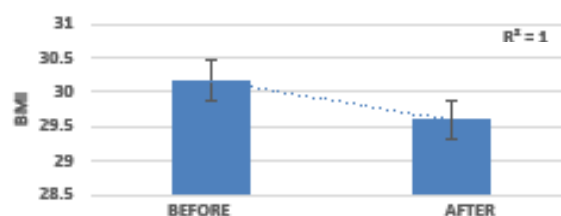


Fig. 1: BMI changes before and after study duration

and LFT before and after the study. With 0.46% reduction in HbA1c there was statistical significant reduction in ALT, AST, GGT “and” ALP levels, where as insignificant rise in bilirubin levels. But the strength of association between HbA1c and variables of LFT was weak.

Relationship between Weight Loss and Changes in LFT

Presented in Table 5 and Figure 3 the relationship between weight loss and

LFT before and after the study. With 1.86% weight loss there was statistical significant reduction in ALT, AST, GGT “and” ALP levels where as insignificant rise in bilirubin levels. But the strength of association between weight loss and variables of LFT was weak.

Relationship between weight loss and HbA1c

With a 1.86% reduction in weight of subjects there was 0.46% reduction in HbA1c levels. The relationship

was statistically significant but the association between the two variables was weak. (R=0.2344). The relation between the two variable is presented in Figure 4.

DISCUSSION

Lebovitz HE et al in their report that involved more than 5000 subjects of type 2 diabetes found 5.6% subjects with raised ALT level between 1 to 2.5 times the upper limits of normal.⁸ Further evaluation revealed that 98% of these asymptomatic subjects with mild raised ALT have fatty liver disease and chronic hepatitis.⁹ Among all liver disease NAFLD is the most prevalent among type 2 diabetes patients.¹⁰

Canagliflozin besides control the blood sugar level also reduces the weight of patients of type 2 diabetes. In this study we demonstrated that the weight reduction by Canagliflozin improves the LFT. The weight reduction was due to its glycosuric mechanism of reducing blood sugar. Besides glycosuria, osmotic diuresis,¹¹ a mild but usual side effect of Canagliflozin also reduce the weight. In a double blind placebo controlled study by Leiter LA et al on 1450 patients demonstrated that with 100, 300 mg strength of Canagliflozin, there was significant -4.1% and -4.2% reduction in body weight respectively.¹² The above study also proved effective and sustained reduction of HbA1c by Canagliflozin at 104 weeks. Reductions from baseline in HbA1C were -0.65% and -0.74% respectively. Our observation period was 6 months and also number of subjects were less but a sustained loss of weight of 1.86% was significant. Also, the HbA1c reduction was 0.46% from the baseline. Till date there is no evidence-based approved therapeutic drug available for managing or reversing NAFLD. Lifestyle change in the form of weight reduction and dietary modification is critical in any attempt to reverse the course of NAFLD.¹³ In the clinical setting of type 2 diabetes with NAFLD, Canagliflozin contribute to

Table 3: Difference in liver function tests before and after study duration (Students t test)

LFT	Before	After	Difference	T=	P=	Significance at P≤0.05
ALT (U/L)	96.0 SD = 18.69	60.0 SD = 17.58	37.5%	-9.153623	< 0.00001	Significant
AST (U/L)	72.0 SD = 16.7	53.0 SD = 10.3	26.38%	-8.153600	< 0.00001	Significant
GGT (U/L)	75.06 SD = 31.8	69.19 SD = 26.2	7.8%	-3.286677	0.002588	Significant
AP (U/L)	83.19 SD = 28.5	81.51 SD = 27.7	2.01%	-1.295661	0.204973	Insignificant
Bilirubin (mg%)	1.13 SD = 0.4	1.17 SD = 0.5	-3.53%	0.912519	0.368771	Insignificant

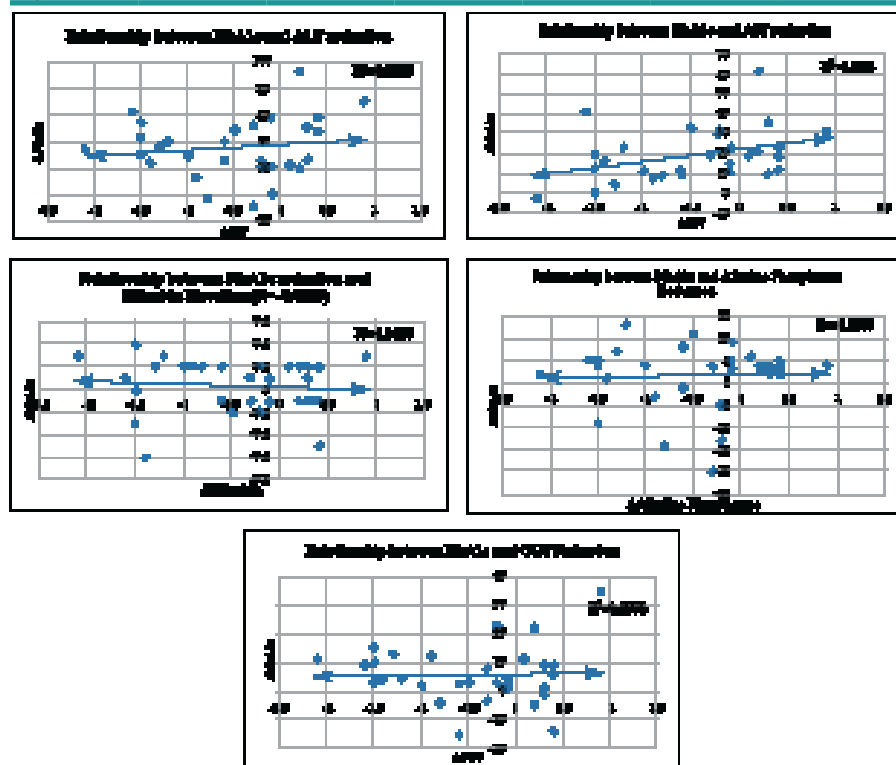


Fig. 2: Relationship between HbA1c and LFT

Table 4: Relationship between HbA1c change and LFT: (pearson R calculator)

LFT	% Change with 0.46% HbA1c reduction	Relation	Strength	R=
ALT	37.5	Positive	Weak	0.1424
AST	26.38	Positive	Weak	0.3484
GGT	7.8	Positive	Weak	0.0213
AP	1.9	Positive	Weak	0.0295
Bilirubin	2.65	Negative	Weak	-0.0823

Table 5: Relationship between weight loss and LFT: (pearson R calculator)

LFT	% change with 1.86% weight reduction	Relation	Strength	R=
ALT	37.5	Positive	Weak	0.3448
AST	26.38	Positive	Weak	0.1299
GGT	7.8	Positive	Weak	0.2295
AP	1.9	Positive	Weak	0.0782
Bilirubin	2.65	Negative	Weak	-0.2234

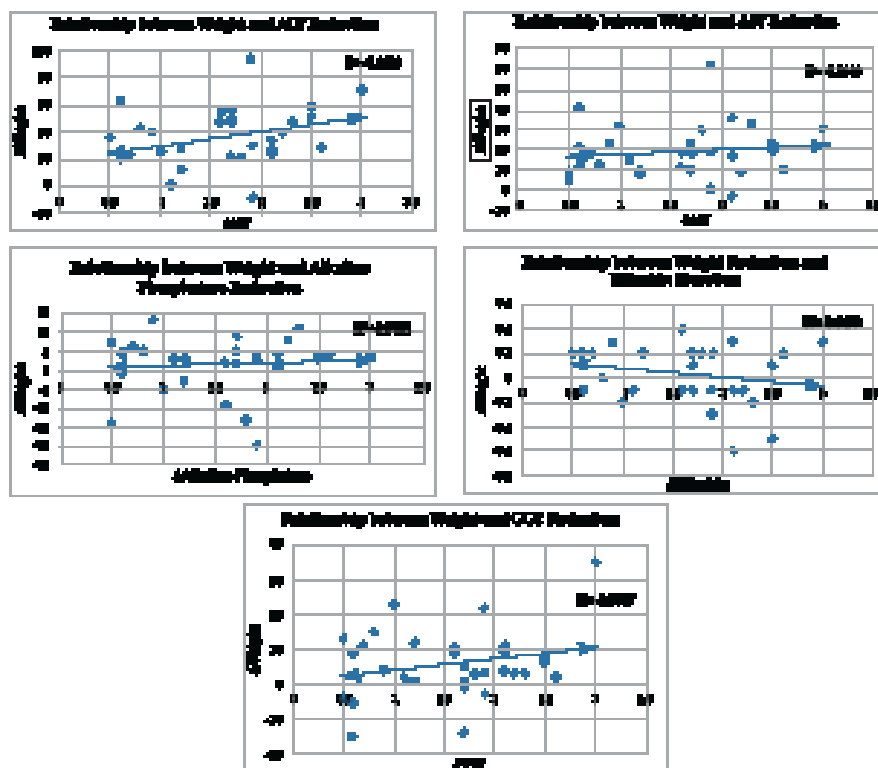


Fig. 3: Relationship between weight reduction and LFT

manage both the conditions by effective and statistically significant weight reduction. Weight reduction is also presumed to be due to osmotic diuresis or reduction in visceral fat mass and hepatic fat that has been proved in experimental studies on animal. Suzuki M et al also demonstrated that weight reduction was due to urinary glucose excretion and relative increase in fatty acid oxidation as compare to carbohydrate oxidation. The later mechanism prevents hepatic fat accumulation and reduction in inflammation in hepatic adipose tissue.¹⁴

As per the present literature, less than one third of patients having proven NAFLD have elevated LFT. In our study improvement in LFT was observed with weight reduction with slight increase in bilirubin level. In a landmark study done by John B. Dixon et al patients with biopsy proven NAFLD and NASH has significant improvement in liver histopathology with weight loss. Significant improvement in all parameters of LFT and HbA1c was also observed in this study.¹⁵ Study on type 2 diabetic mouse by Tahara A. et al demonstrated significant improvement in hepatic steatosis along with improvement in glycemic control and reduction in obesity with

use of other SGLT2 inhibitor.¹⁶ In a double blind randomized phase 3 placebo control trial, Cefalu WT et al demonstrated that Canagliflozin was well tolerated then metformin and provides greater and better HbA1c reduction than glimepiride.¹⁷ In a study by Nakano S et al, over obese mouse found markedly lowered both ALT (76%) and AST (48%) in a 4 week therapy with SGLT 2 inhibitor.¹⁸ In another trial by Okhi T et al, SGLT 2 inhibitors were found to be more effective in reducing weight and normalization of ALT levels then Incretin based therapy.¹⁹ Gautam. A et al in a controlled study on 30 cases and 32 comparators found remarkable weight reduction with use of Canagliflozin among patients of type 2 diabetes, having pioglitazone associated pedal edema. Thus, a co-prescription of Canagliflozin with pioglitazone can be promising results in NAFLD.²⁰ These findings support the use of Canagliflozin as a viable treatment option for patients who do not achieve sufficient glycemic control with metformin therapy. These evidences are putting firm strength for SGLT 2 inhibitor as potential agent in type 2 diabetes with comorbid NAFLD. Above evidences advocates SGLT2 inhibitors preferred over other OHA

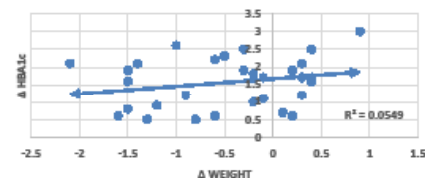


Fig. 4: Relationship between weight and HbA1c reduction

in the clinical setting of type 2 diabetes with NAFLD.

There are few limitations in this study. The sample size was less because the patients with above clinical conditions are relatively less in number. Also, definitive diagnose of NAFLD requires exhaustive investigations and invasive procedures which is not included in this study. The long-term safety profile of Canagliflozin are not elucidated. So, recommendation for its long-term use cannot be advocated with firm confidence.

Conclusion

Addition of Canagliflozin to the current treatment regimen of type 2 diabetes patients with NAFLD and deranged LFT, with simultaneous dose adjustment of previous OHA, not only favorably improves the HbA1c level but also helps in weight reduction. This also improves LFT significantly, with insignificant rise in serum bilirubin levels. Canagliflozin may have direct effect on improvement in liver function besides its indirect effect due to improvement in HbA1c levels and weight reduction.

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