

ORIGINAL ARTICLE

Efficacy of canagliflozin against nonalcoholic fatty liver disease: a prospective cohort study

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Summary

Background

Nonalcoholic fatty liver disease (NAFLD) is a common cause of chronic liver disease worldwide and is characterized by insulin resistance, hepatic steatosis and often prediabetes or diabetes. Canagliflozin, a selective sodium glucose cotransporter 2 inhibitor, is a new oral anti-diabetic drug that reduces hyperglycaemia by promoting urinary glucose excretion. Glycosuria produced by canagliflozin is associated with weight loss, mainly due to reduced fat volume and improve insulin resistance. Reduced body weight and improvement of insulin resistance by canagliflozin may be an effective treatment for NAFLD.

Methods

Thirty-five patients with NAFLD (17 men and 18 women) were enrolled and administered canagliflozin (100 mg). Body weight and serum levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transferase (γ -GTP), low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides (TG), blood sugar (BS), glycated haemoglobin (HbA1C), uric acid (UA) and ferritin, and fibrosis-4 (FIB-4) index values were measured at baseline and at 3-month and 6-month follow-up visits.

Results

Body weight and serum levels of AST, ALT, γ -GTP, TG, UA, HbA1C, BS and ferritin decreased significantly after 3 and 6 months of canagliflozin treatment. Serum BS levels and FIB-4 index values decreased slightly following 3 months of treatment; these results reached significance after 6 months. Reduced serum ALT levels at 6 months were significantly correlated with baseline HbA1C and ferritin levels. Moreover, a significant correlation between reduced body weight and serum ALT levels was observed at 6 months. Decreased serum ALT levels were significantly correlated with decreased serum ferritin at 6 months.

Conclusions

Canagliflozin significantly reduced the serum levels of BS, HbA1C, TG, UA and ferritin, as well as FIB-4 index values and body weight, with improved liver function. Sodium glucose cotransporter 2 inhibitors may be an important therapeutic modality for improving liver injury in NAFLD patients.

Keywords: canagliflozin, NAFLD, SGLT2 inhibitor.

Introduction

Nonalcoholic fatty liver disease (NAFLD) represents one of the most common causes of chronic liver disease

worldwide and is characterized by chronic liver inflammation and fibrosis leading to cirrhosis, with an increased risk of liver cancer in some patients (1). NAFLD is the hepatic manifestation of metabolic syndrome and is strongly

related to the features of this disorder (2). As such, most cases of NAFLD are closely related to obesity, impaired glucose tolerance, hyperlipidaemia and hypertension and are based on insulin tolerance and the hepatic manifestation of metabolic syndrome. The disease affects one-third of the population and two-thirds of patients with obesity or type 2 diabetes mellitus (T2DM).

Nonalcoholic steatohepatitis (NASH) is an aggressive form of NAFLD characterized by hepatocyte necrosis, inflammation and fibrosis; hence, the presence of fibrosis indicates a more aggressive course and may lead to cirrhosis. Premature mortality in NASH patients is related to both hepatic (cirrhosis and hepatocellular carcinoma) and extra-hepatic complications, largely cardiovascular disease (3). NAFLD pathogenesis is multifactorial and includes excessive inappropriate dietary fat intake combined with peripheral insulin resistance and oxidative stress (4). Thus, it is likely that insulin resistance and cellular stress, resulting from hepatic steatosis, act collectively to promote NAFLD, a pro-fibrotic state and progression to NASH (5). Canagliflozin is a sodium glucose cotransporter 2 (SGLT2) inhibitor developed for the treatment of adults with T2DM. It promotes urinary glucose excretion, resulting in decreased plasma glucose, mild osmotic diuresis and a net caloric loss (6). Canagliflozin is effective in improving glucose homeostasis, insulin sensitivity and beta cell function, as well as reducing body weight.

Since April 2014, ipragliflozin, dapagliflozin, luseogliflozin, canagliflozin, tofogliflozin and empagliflozin have been approved and are widely used in Japan (7). Improvement of insulin resistance by canagliflozin treatment may be effective in patients with NAFLD. Numerous previous studies using rodent demonstrated that SGLT2 inhibitors can ameliorate fatty liver with a significant loss in body weight, and the weight-reducing effects of various SGLT2 inhibitors have been documented in humans (8). However, reports evaluating the effects of SGLT2 inhibitors in clinical practice are limited. The aim of this study is to examine the clinical efforts of administering canagliflozin in patients with NAFLD.

Methods

Study design

This study was a prospective, open-label, uncontrolled pilot study between September 2015 and March 2017. All patients received 100 mg d⁻¹ of canagliflozin for 6 months. Body weight was monitored throughout the study, and body mass indexes were calculated. Serum levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transferase

(γ -GTP), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglycerides (TG), blood glucose (BS), glycated haemoglobin (HbA1C), uric acid (UA) and ferritin, and fibrosis-4 (FIB-4) index values were measured at baseline, as well as at 3 and 6 months after commencing the study. FIB-4 index values were calculated according to the following equation: FIB-4 index = $\{[\text{age (years)} \times \text{AST (IU L}^{-1})]/[\text{platelet count}(10^9 \text{ L}^{-1}) \times \text{ALT (IU L}^{-1})]\}$ (9).

Statistical analysis

Data are expressed as means \pm standard deviation. Differences between the means of two variables were evaluated using an independent *t*-test. Pearson's simple correlations were made between the data before the start of canagliflozin treatment and changes in variables after canagliflozin treatment. Statistical analyses were performed to compare the data before and after the study using an analysis of variance. $p < 0.05$ was regarded as statistically significant.

Patients

This study obtained informed consent from each patient and was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. Thirty-five patients with NAFLD (17 men and 18 women) were enrolled in the present study. All patients were screened for metabolic syndrome, diabetes mellitus, dyslipidaemia, hypertension and NAFLD, with all current medications recorded, and underwent abdominal ultrasonography. The inclusion criteria required that all patients had a fatty liver, did not have other causes of chronic hepatitis (alcoholism, drug-induced liver injury, viral hepatitis, hemochromatosis and autoimmune liver disease) and were older than 20 years. The main exclusion criteria were insulin use, current or potential pregnancy and an HbA1C value $> 5.5\%$. NAFLD was defined according to characteristic ultrasonographic findings, such as increased hepatorenal contrast or enhanced liver brightness (10). The mean patient age was 56.9 ± 14.3 years. The underlying disease was diabetes mellitus in 28 patients, hyperlipidaemia in 30 patients and hyperuricemia in five patients.

Results

All patients successfully completed the study protocol. Serum AST levels decreased significantly from 45.5 IU L^{-1} at baseline to 29.9 IU L^{-1} after 3 months and 28.6 IU L^{-1} after 6 months of canagliflozin treatment ($p < 0.05$). Serum ALT levels decreased significantly from 74.2 IU L^{-1}

at baseline to 42.0 IU L⁻¹ after 3 months and 40.4 IU L⁻¹ after 6 months of canagliflozin treatment ($p < 0.05$).

Serum γ -GTP levels decreased significantly from 80.6 IU L⁻¹ at baseline to 57.5 IU L⁻¹ after 3 months and 56.2 IU L⁻¹ after 6 months of canagliflozin treatment ($p < 0.05$). Serum TG levels decreased significantly from 225.1 mg dL⁻¹ at baseline to 172.1 mg dL⁻¹ after 3 months and 180.7 mg dL⁻¹ after 6 months of canagliflozin treatment ($p < 0.05$). Serum HbA1C levels significantly decreased from 7.45% at baseline to 6.58% after 3 months and 6.36% after 6 months of canagliflozin treatment ($p < 0.05$). Serum BS levels decreased slightly from 138.2 mg dL⁻¹ at baseline to 134.5 mg dL⁻¹ after 3 months; the decrease in serum BS levels reached significance after 6 months of canagliflozin treatment, with a value of 112.9 mg dL⁻¹ ($p < 0.05$). Serum UA levels significantly decreased from 5.67 mg dL⁻¹ at baseline to 5.02 mg dL⁻¹ after 3 months and 5.11 mg dL⁻¹ after 6 months of canagliflozin treatment ($p < 0.05$). Body weight significantly decreased from 73.3 kg at baseline to 70.7 kg after 3 months and 69.6 kg after 6 months of canagliflozin treatment ($p < 0.05$). Serum ferritin levels decreased significantly from 184.9 ng mL⁻¹ at baseline to 143.8 ng mL⁻¹ after 3 months and 117.3 ng mL⁻¹ after 6 months of canagliflozin treatment ($p < 0.05$). FIB-4 index values decreased slightly from 1.42 at baseline to 1.31 after 3 months; the FIB-4 index value was 1.27 after 6 months of canagliflozin treatment ($p < 0.05$), which was a significant change. Serum LDL-C and HDL-C levels remained

Table 1 Changes in the examined variables after 3 and 6 months of canagliflozin treatment

	Pretreatment	3 months	6 months
AST (IU L ⁻¹)	45.5 ± 30.4	29.9 ± 15.6*	28.6 ± 15.8*
ALT (IU L ⁻¹)	74.2 ± 68.5	42.0 ± 31.7*	40.4 ± 37.3*
γ -GTP (IU L ⁻¹)	80.6 ± 78.2	57.5 ± 54.9*	56.2 ± 52.6*
LDL-C (mg dL ⁻¹)	126.3 ± 37.4	119.9 ± 32.3	120.3 ± 31.1
HDL-C (mg dL ⁻¹)	53.0 ± 18.6	53.8 ± 17.9	54.5 ± 19.7
TG (mg dL ⁻¹)	225.1 ± 166.1	172.1 ± 103.3*	180.7 ± 95.3*
UA (mg dL ⁻¹)	5.67 ± 1.50	5.02 ± 1.15*	5.11 ± 1.13*
BS (mg dL ⁻¹)	138.2 ± 51.5	134.5 ± 52.7	112.9 ± 39.5*
HbA1C (%)	7.45 ± 2.16	6.58 ± 1.25*	6.36 ± 1.10*
Body weight (kg)	73.3 ± 16.3	70.4 ± 16.7*	69.6 ± 16.8*
Ferritin (ng mL ⁻¹)	184.9 ± 149.1	143.8 ± 134.9*	117.3 ± 107.7*
FIB-4 index	1.42 ± 0.76	1.31 ± 0.67	1.23 ± 0.63*

Data are presented as mean ± standard deviation.

AST, aspartate aminotransferase; ALT, alanine aminotransferase; γ -GTP, gamma-glutamyl transferase; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglycerides; UA, uric acid; BS, blood sugar; HbA1C, glycated haemoglobin; FIB-4, fibrosis-4.

* $p < 0.05$ vs. before treatment.

unchanged throughout the study. These data are shown in Table 1.

The reduction in serum ALT levels after 6 months was negatively correlated with HbA1C levels at baseline ($R = -0.323$, $p < 0.01$) (Figure 1). Moreover, the decrease in serum ALT levels after 6 months was positively correlated with serum ferritin levels at baseline ($R = 0.271$, $p < 0.01$) (Figure 2). Furthermore, the reduction in serum ALT levels after 6 months was significant positively

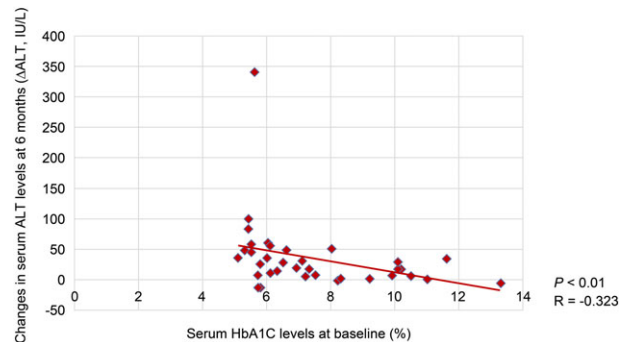


Figure 1 Correlation between decreased serum aminotransferase (ALT) levels and baseline serum glycated haemoglobin (HbA1C) levels.

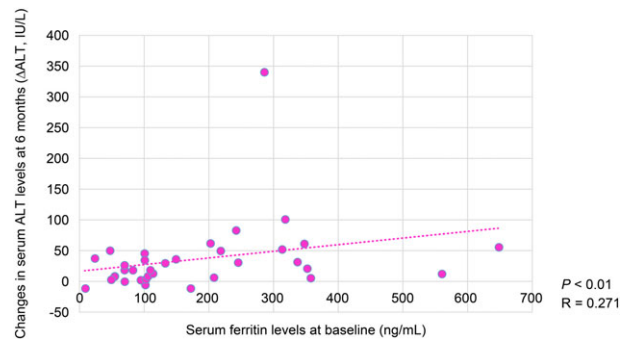


Figure 2 Correlation between decreased serum aminotransferase (ALT) levels and baseline serum ferritin levels at 6 months.

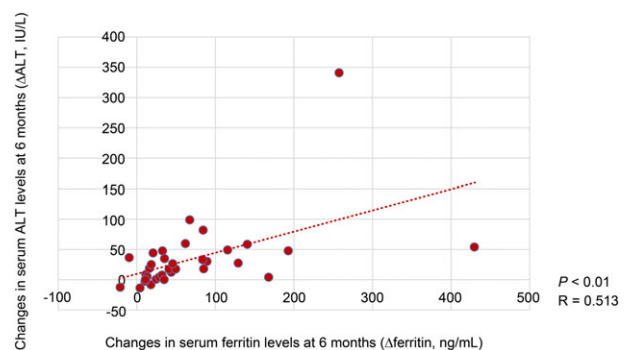


Figure 3 Correlation between decreased serum aminotransferase (ALT) levels and decreased serum ferritin levels.

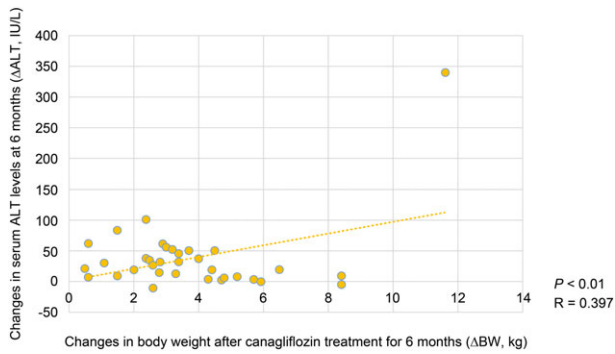


Figure 4 Correlation between reductions in body weight and serum aminotransferase (ALT) levels at 6 months.

correlated with the decrease in serum ferritin levels after 6 months ($R = 0.513$, $p < 0.01$) (Figure 3). The decrease in serum ALT levels after 6 months was positively correlated with the reductions in body weight observed after 6 months ($R = 0.397$, $p < 0.01$) (Figure 4).

Discussion

The aim of the present study was to investigate the efficacy of SGLT2 inhibitors for improving liver enzyme levels in patients with NAFLD. The results show that SGLT2 inhibitors improve glycaemic control and reduce body weight and serum AST, ALT and γ -GTP levels. Previous studies have reported that serum HbA1C levels were approximately 0.5–0.7% lower in patients treated with SGLT2 inhibitors than in patients administered a placebo. In this study, serum HbA1C levels decreased by 0.9–1.1%, which was a greater change than that reported in previous studies (11). Further, blood sugar levels decreased significantly after 6 months of canagliflozin treatment. These results suggest that the reductions in casual blood glucose levels attributable to canagliflozin treatment improve insulin resistance and postprandial blood glucose levels over time. In this study, a decrease in body weight was observed after 3 months, and was sustained over 6 months. Previous studies have reported that body weight was 2.5 kg lower in patients receiving SGLT2 inhibitors for 52 weeks than in patients administered placebo (12). Further, it has shown that SGLT2 inhibitors promote the renal excretion of glucose and decrease body fluid volume via osmotic diuretics. Consequently, the energy balance was negative, and a decrease in body weight was observed after 6 months. However, body weight reduction effects stagnate after approximately 3–6 months in patients receiving SGLT2 inhibitor treatment (13). These results suggest that long-term investigations are necessary to fully understand the body weight reduction effects of canagliflozin.

Serum TG levels were significantly lower in patients receiving canagliflozin than in patients administered placebo; serum LDL-C and HDL-C levels were almost unchanged. The mechanisms underlying the decrease in serum TG levels associated with SGLT2 inhibitor treatment are unknown at present. Further studies are needed to investigate the effects of SGLT2 inhibitors on serum lipid metabolism.

In this study, serum UA levels significantly decreased after canagliflozin treatment. It has suggested that glucose transporter-9 is involved in SGLT inhibitor-induced reductions in serum UA levels (14). These results suggest that the reduction in serum UA levels affords a protective effect on renal function and has a positive impact on blood pressure and carbohydrate metabolism disorders.

In this study, serum AST, ALT and γ -GTP levels significantly decreased after 6 months of canagliflozin treatment. Qing *et al.* reported that administration of the SGLT2 inhibitor luseogliflozin in a NASH rodent model resulted in weight loss and decreased serum ALT levels, as well as improved insulin resistance, liver fibrosis and fatty metamorphosis (15).

These results show that canagliflozin may improve hepatic steatosis and liver dysfunction in NAFLD patients. Moreover, the reductions in serum ALT levels were significantly correlated with baseline HbA1C levels at 6 months. The reductions in ALT levels were significantly correlated with reductions in body weight at 6 months. It further suggests that canagliflozin treatment may significantly improve liver dysfunction in NAFLD patients with mild carbohydrate metabolism disorders or in cases with significant weight loss after 6 months. The improvement in liver dysfunction observed in NAFLD patients may have been in conjunction with improvements in glycaemic control and insulin resistance in patients with T2DM and NAFLD (16). In studies of patients with NAFLD/NASH, weight loss is associated with improvements in liver dysfunction and other markers of NAFLD/NASH (17,18). Further, there is a relationship between NAFLD and T2DM (19), and in patients with NAFLD, weight loss can improve serum insulin levels, liver function and quality of life (20).

Furthermore, the reductions in serum ALT levels significantly correlated with baseline serum ferritin levels and a decrease in serum ferritin levels at 6 months. Hyperferritinemia with mild hepatic iron accumulation is observed in 20–30% of patients with NAFLD and is commonly referred to as dysmetabolic iron overload syndrome. Besides directly inducing liver damage, excess iron is also involved in the pathogenesis of metabolic syndrome by inducing adipose tissue and insulin resistance and modifying the release of adipokines. Furthermore, hyperferritinemia and increased iron stores have been

associated with greater severity of liver disease and hepatocellular carcinoma in patients with NAFLD (19). Abnormal iron metabolism in chronic liver disease is related to liver carcinogenesis. Hyperferritinemia has been observed in patients with NAFLD and is positively correlated with the severity of NAFLD (21). Further, hyperferritinemia is related to oxidative stress and mild hepatic iron overload. Increased iron stores are dependent on insulin resistance, which plays an important role in steatosis and steatosis hepatitis. Because iron plays a major role in liver damage and insulin resistance, phlebotomy, an iron-depleting therapy, has been extensively studied in recent years. It appears to be a safe and promising intervention that could ameliorate the harmful effect of iron (22). Calculations for serum ferritin include a simple, low-cost laboratory test that may be a good marker of hepatocellular aggression and liver fibrosis for the selection of patients who require hepatic biopsy (23). Moreover, ferritin may be an independent predictor of inflammation and liver fibrosis and may help in the decision of whether to perform a biopsy in individuals clinically diagnosed with NAFLD (24–29). Thus, in NAFLD patients, hyperferritinemia, hepatic steatosis and insulin resistance are related to each other via oxidative stress, which is likely involved in the onset and progression of NAFLD; however, it is necessary to elucidate the detailed mechanisms in future studies to establish a treatment regimen.

In recent years, a need for non-invasive diagnostic methods to assess liver damage has been noted, i.e. methods to identify symptoms of liver fibrosis that indicate possible development of advanced liver fibrosis or cirrhosis without the need for a liver biopsy (30). The FIB-4 scoring system is a non-invasive laboratory test to diagnose liver fibrosis in patients with NAFLD and is calculated using AST values, ALT values, platelet levels and age. The FIB-4 index significantly decreased after canagliflozin treatment. Canagliflozin may contribute to decreased serum ferritin levels and FIB-4 index values, as well as the suppression of hepatic fibrosis and development of liver cancer. This study showed a decrease in body weight, serum HbA1C, BS, AST, ALT, γ -GTP, TG, UA and ferritin levels, as well as FIB-4 index values in NAFLD patients administered canagliflozin for 6 months.

After administration of canagliflozin, excess glucose was excreted in the urine, which lowered blood glucose levels, reduced body weight and visceral fat and improved insulin resistance; further, impaired glucose tolerance and abnormal lipid metabolism were alleviated. These results suggest that liver dysfunction in NAFLD patients was improved. Decreased serum ferritin levels were also observed, likely attributable to improved glucose tolerance and liver dysfunction after administration of canagliflozin. Reduced iron liver stores attributable to

administration of SGLT2 inhibitors decrease oxidative stress and improve insulin resistance, which can also lead to decreased steatosis in NAFLD patients.

The present study has several limitations. First, other hypoglycaemic, anti-hypertensive, lipid-lowering or UA-lowering agents, as well as differences in food intake and/or exercise, may have influenced the study results. Second, the 6-month observation period was short. A study examining the efficacy and safety of canagliflozin treatment for more than 1 year is necessary.

In conclusion, administration of canagliflozin was an effective clinical treatment for NAFLD. Canagliflozin treatment during the early stages of NAFLD likely suppresses the development of diabetes mellitus, liver fibrosis and liver cancer. In future studies, it will be necessary to examine the long-term clinical efficacy of canagliflozin.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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