The Journal of Clinical Endocrinology & Metabolism, 2022, **107**, e2267–e2275
https://doi.org/10.1210/clinem/dgac138
Advance access publication 9 March 2022
Clinical Research Article

Dapagliflozin Improves Body Fat Patterning, and Hepatic and Pancreatic Fat in Patients With Type 2 Diabetes in North India

Amerta Ghosh,[1,2] Koel Dutta,[1] Surya Prakash Bhatt,[1,2,3,4] Ritesh Gupta,[1] Kanika Tyagi,[1] Irshad Ahmad Ansari,[1] Vasantha Kumar Venugopal,[5] Harsh Mahajan,[5] Ravindra Mohan Pandey,[6] Shivam Pandey,[6] and Anoop Misra[1,2,4,]

[1]Fortis C-DOC Center of Excellence for Diabetes, Metabolic Diseases, and Endocrinology, New Delhi 11048, India
[2]National Diabetes, Obesity and Cholesterol Foundation (N-DOC), New Delhi 110016, India
[3]Department of Pulmonary, Critical Care and Sleep Medicine, All India Institute of Medical Sciences, New Delhi 110029, India
[4]Diabetes Foundation (India), New Delhi 110070, India
[5]Mahajan Imaging Centre, New Delhi 110024, India
[6]Department of Biostatistics, All India Institute of Medical Sciences, New Delhi 110029, India

Correspondence: Anoop Misra, MD, Fortis-CDOC Center of Excellence for Diabetes, Metabolic Diseases and Endocrinology, B-16, Chirag Enclave, New Delhi 11048, India. Email: anoopmisra@gmail.com.

Abstract

Context: Excess hepatic and pancreatic fat may contribute to hyperglycemia.

Objective: The objective of this study was to examine the effect of dapagliflozin (an SGLT2 inhibitor) on anthropometric profile, liver, and pancreatic fat in patients with type 2 diabetes mellitus (T2DM).

Methods: This is an observational interventional paired study design without a control group. Patients (n = 30) were given dapagliflozin 10 mg/day (on top of stable dose of metformin and/or sulfonylureas) for 120 days. Changes in anthropometry (circumferences and skinfold thickness), surrogate markers of insulin resistance, body composition, liver, and pancreatic fat (as measured by magnetic resonance imaging (MRI)-derived proton density fat fraction [FF]) were evaluated.

Results: After 120 days of treatment with dapagliflozin, a statistically significant reduction in weight, body mass index (BMI), body fat, circumferences, and all skinfold thickness was seen. A statistically significant reduction in blood glucose, glycated hemoglobin A_{1c}, hepatic transaminases, fasting insulin, homeostatic model assessment of insulin resistance (HOMA-IR), and postprandial C-peptide was noted, while HOMA-β, postprandial insulin sensitivity, and fasting adiponectin were statistically significantly increased. There was no change in lean body mass. Compared to baseline there was a statistically significant decrease in mean liver FF (from 15.2% to 10.1%, $P < .0001$) and mean pancreatic FF (from 7.5% to 5.99%, $P < .0083$). Reduction in liver fat was statistically significant after adjustment for change in body weight.

Conclusion: Dapagliflozin, after 120 days of use, reduced pancreatic and liver fat and increased insulin sensitivity in Asian Indian patients with T2DM.

Key Words: dapagliflozin, hepatic fat, pancreatic fat, Asian Indians, diabetes, insulin resistance

Abbreviations: BMI, body mass index; DXA, dual-energy x-ray absorptiometry; FF, fat fraction; GGT, γ-glutamyl transferase; HbA_{1c}, glycated hemoglobin A_{1c}; HC, hip circumference; HOMA-IR, homeostatic model assessment of insulin resistance; MRI, magnetic resonance imaging; NAFLD, nonalcoholic fatty liver disease; PDFF, proton density fat fraction; ROI, region of interest; SGLT2i, sodium glucose cotransporter-2 inhibitor; SGOT, serum glutamic oxaloacetic transaminase;SGPT, serum glutamic pyruvic transaminase; TGs, triglycerides; T2DM, type 2 diabetes mellitus; WC, waist circumference; W-HR, waist-to-hip ratio; WhtR, waist-height ratio.

The prevalence of type 2 diabetes mellitus (T2DM) is high and continues to increase in India (1). As compared to White individuals, T2DM among Asian Indians is characterized by onset at a younger age, with greater subcutaneous and intra-abdominal obesity (at relatively lower body mass index [BMI]), insulin resistance, and faster decline in β-cell function (1, 2). Apart from abdominal fat depots, hepatic fat accumulation (nonalcoholic fatty liver disease [NAFLD]) is believed to be central to induction of insulin resistance in Asian Indians (3). More important, the presence of NAFLD with insulin resistance poses a roadblock to management of T2DM (4). Reduction of liver fat is possible with balanced or restrictive diets and appropriate physical activity. In the multicentric Look AHEAD (Action for Health in Diabetes) clinical trial (n = 5145 overweight adults with T2DM), hepatic fat reduction was seen after 12 months of intervention (5). In this context, a number of other studies have been conducted, and are well summarized by Perdomo et al (6).

Further, fatty pancreas (nonalcoholic fatty pancreatic disease) is an area of emerging interest but has been less investigated. Research on mice shows that adipocyte infiltration in the pancreas alters islet fatty acid composition, which

Received: 7 June 2021. **Editorial Decision:** 3 March 2022. **Corrected and Typeset:** 1 April 2022

may result in islet-cell dysfunction (7). We have previously reported ectopic fat deposition in the liver and pancreas (using pancreatic volume as a surrogate of pancreatic fat), in young, nonobese Asian Indians with T2DM (8). Specifically, in this study, we showed that the following magnetic resonance imaging (MRI)-derived volumes were higher in nonobese individuals with T2DM compared to nonobese, normoglycemic individuals: total abdominal fat (19.4%), total intra-abdominal fat (49.7%), intraperitoneal fat (47.7%), retroperitoneal fat (70.7%), and pancreatic volume (26.6%). Further, pancreatic volume index (21.3 %) and liver span (10.8%) were comparably higher in patients with diabetes than in controls (8). In addition to this, we have also reported statistically significant positive correlations for pancreatic volume with BMI, waist circumference (WC) and hip circumference (HC), waist-to-hip ratio (W-HR), subcutaneous and intra-abdominal fat, and increased liver span (as a surrogate of NAFLD) (8).

Previous research has shown that reduction of liver and pancreatic fat leads to metabolic benefits. Lim et al (9) showed that normalization of both β-cell function and hepatic insulin sensitivity in T2DM were associated with a decrease in pancreatic and liver triacylglycerol stores; all this was achieved by dietary restriction alone. Restrictive dietary protocols have shown a reduction of pancreatic fat content (10) along with improvement in pancreatic morphology (11).

The use of some antihyperglycemic drugs has led to weight loss and reduction of hepatic fat and fibrosis (12). Pioglitazone, sodium glucose cotransporter-2 inhibitors (SGLT2i), and glucagon-like peptide-1 receptor agonists analogues have been shown to be variably effective in this context; however, studies are limited. It is possible that, if excess fat in liver and pancreas is reduced with the use of a drug, normoglycemia may be achieved more efficiently in patients with T2DM.

We hypothesized that the usage of SGLT2 inhibitor dapagliflozin in patients with T2DM would statistically significantly decrease pancreatic and liver fat. To investigate this hypothesis, we recruited overweight/obese patients with T2DM, and treated them with dapagliflozin for 3 months to evaluate changes in anthropometry, hepatic, and pancreatic fat along with metabolic parameters.

Materials and Methods

Inclusion Criteria

Inclusion criteria included overweight and obese (BMI = 23.0-35.00 kg/m^2) patients aged 20 to 50 years with T2DM of less than 5-year duration and glycated hemoglobin A_{1c} (HbA_{1c}) 6.5% to 11%, on a stable dose of metformin and/or sulfonylureas over the last 8 weeks, and grade II or greater grade of NAFLD on abdominal ultrasound.

Exclusion Criteria

T2DM patients with poor glycemic control (HbA_{1c} > 11%), history of frequent hypoglycemia or ketoacidosis, type 1 diabetes mellitus, patients requiring major drug intervention (insulin) to maintain good glycemic control, pregnant or lactating women, women planning for pregnancy/gestational diabetes, patients with severe cardiac and renal disease, or undergoing immunosuppressive therapy, substantial alcohol consumption (> 20 g/day for women or > 30 g/day for men), Child-Pugh class B/C liver cirrhosis, other causes of liver disease, confounding concomitant drug use (including insulin, incretin mimetics, thiazolidinediones, vitamin E), and other disorders (pancreatitis, pancreatic lipomatosis or pancreatic calculi) were excluded. All contraindications to drug dapagliflozin as per label were also considered as exclusion criteria.

Sample Size Calculation

To determine the change in outcome with an α error of 5%, 97% power, pretest (15.16) and posttest mean (10.06), SD in pretest (7.7), SD in posttest (7.7), effect size (0.718) and 20% dropouts, the effective sample size was at least 31 participants. Therefore, to recruit 31 patients, 40 patients were screened.

Study Design

This is a prospective interventional study without a control group. After institutional ethics committee approval, a sample of 30 patients with grade II to III NAFLD and T2DM visiting Fortis C-DOC Hospital for Diabetes and Allied Sciences, New Delhi, were recruited. Informed, written consent was taken. All patients underwent 2 weeks' diet and exercise run-in using standard Indian guidelines.

We strictly maintained diet and activity logs in the following manner: a) once-weekly phone calls and b) during monthly visits of the patients. Medication compliance was also maintained in a similar manner.

Clinical details were measured from the case records of the patients. Blood pressure, circumferences (mid arm, neck, chest, WC, HC), and skinfold thickness at 6 sites (triceps, biceps, anterior axillary, suprailiac, subscapular, and lateral thoracic) were defined (13, 14). The sum of all skinfolds (Σ6SF, total skinfolds), ratios of subscapular and triceps skinfolds, central skinfolds (sum of subscapular and suprailiac), and peripheral skinfolds (sum of biceps and triceps) were computed. W-HR and waist-height ratio (WhtR) were calculated. Overweight and obesity were defined as BMI (kg/m^2) of 23 to 24.9 and greater than or equal to 25, according to guidelines for Asian Indians (15). Abdominal obesity was defined as a WC of greater than or equal to 90 cm in men and greater than or equal to 80 cm in women (15). Each eligible individual underwent ultrasonography of the liver and pancreas before recruitment for assessment of NAFLD (16). Following ultrasonography, patients fulfilling the inclusion criteria were randomly assigned to receive 10 mg of dapagliflozin daily as mentioned previously. Anthropometry, biochemistry, handgrip, dual-energy x-ray absorptiometry (DXA), and MRI were performed at baseline and at 120 days post intervention.

We administered a standard vegetarian Indian mixed meal in the morning meal between 8 and 8:30 am. The calories and nutrition composition of the mixed meal was as follows: total energy; 400 kcal with 55% carbohydrates, 20% protein, and 25% fat. This was given as follows: 2 pieces of whole bread (50 g),1 glass low-cream cow milk (200 mL), butter (5 g), and green moong (green gram) sprouts (100 g).

Blood glucose was analyzed by the spectrophotometry-based hexokinase method (Flex Reagent Cartridge, DF-40, SMN 1044971, Dimension Clinical Chemistry System, Siemens Healthcare Diagnostics). Serum insulin was analyzed using a chemiluminescence immunoassay (Immulite 1000 Insulin kit; Siemens catalog No. LKIN1, RRID: AB_2750939, Siemens

Medical Solutions Diagnostics https://antibodyregistry.org/search.php?q=AB_2750939). Estimation of C-peptide and adiponectin were performed by the enzyme-linked immunosorbent assay method (Millipore catalog No. EZHADP-61K, RRID:AB_2801457 https://antibodyregistry.org/search.php?q=AB_2801457 and Diagnostics Biochem Canada Inc catalog No. CAN-C-P-4380, respectively). HbA_{1c} was estimated by turbidimetric inhibition immunoassay (Roche Diagnostics). Postprandial insulin sensitivity index for glycemia was calculated with the formula: Insulin sensitivity index for glycemia [ISI (Gly)] = 2/[INSp × GLYp] + 1, where INSp and GLYp were insulinemic and glycemic areas, respectively, of individuals under study. In addition, the trapezoidal rule was used to calculate the area under curve for 0- and 120-minute blood glucose values (17). The Homeostatic Model Assessment of Insulin Resistance (HOMA-IR), HOMA–Quantitative Insulin Sensitivity Check Index (QUICKI) Index, and HOMA-β (%) were calculated. Lipids (serum triglycerides [TGs], total cholesterol, high-density and low-density lipoprotein cholesterol, and serum TGs, TG-glucose ratio), hepatic transaminases (serum glutamic oxaloacetic transaminase [SGOT], serum glutamic pyruvic transaminase [SGPT], and γ-glutamyl transferase [GGT]) were estimated.

The measurements of the handgrip strength were determined by means of the JAMAR-Dynamometer (JA Preston Corp). Patients were shown the correct handling and positioning of the instrument, they were asked to sit straight, with the upper dominant arm in a neutral position and a 90° flexion of the elbow. The forearm was held in neutral position and the wrist at a 0 to 30° extension. The instrument was held freely without resting the arm or instrument. Patients were asked to perform the handgrip strength thrice and the average value was taken. The instrument was regularly checked for damages and functioning and was calibrated (18).

Fat mass, fat free mass, and muscle mass were measured by DXA scans using a LUNAR Prodigy Advance DXA machine (GE Medical Systems) as mentioned in our recent study (8). Presence of fat in liver and its severity was assessed with ultrasound using a 3.5-MHz curvilinear probe (Siemens-G 60 S 2004) as previously described (19).

Estimation of Fat Fraction of Liver and Pancreas Using Magnetic Resonance Imaging

Single-breath-hold multipoint Dixon-based acquisition, IDEAL IQ sequences were performed by 3-T MRI (GE Healthcare) to estimate the liver and pancreas fat contents. Nine regions of interests (ROIs) for the liver (6 in the right lobe and 3 in the left lobe) and 3 ROIs for the pancreas (one each in the head, body, and tail regions) were carefully placed including as much as possible of parenchymal tissue while avoiding large vessels on image-generated parametric maps to measure hepatic and pancreatic fat fraction (FF). The average of these values was calculated. A single radiologist (V.K.V) who is trained in these methods of MRI analysis performed the measurements. The radiologist was blinded to clinical and ultrasound data.

Statistical Analysis

Data were entered in an Excel spreadsheet (Microsoft Corp). The distribution of demographic, clinical, medical history (personal and family), anthropometric, body composition, and biochemical parameters was confirmed for approximate normality. For quantitative variables, mean and SD, number (%), and difference (95% CI) were computed as measures of descriptive statistics. Comparisons of clinical, anthropometric, body composition, biochemical, liver, and pancreatic fat were performed by paired *t* test. The mean difference of the values at the end (120 days) and start (0 months) of the protocol was calculated for all the variables. We used multivariate linear regression to mutually adjust for liver and pancreatic fat and weight change. All statistical analyses were performed using Stata14 (StataCorp, College Station, TX, USA). For all the aforementioned values, a *P* value of less than .05 was considered statistically significant.

Results

Demographic and Clinical Profiles

The mean ± SD for age was 42.56 ± 7.05 years. Seventeen patients had diabetes duration of less than 1 year. Seven patients had a history of hypertension; 4 had dyslipidemia. The following are average (SD) values of some parameters; BMI 31.36 ± 4.44, WC 104.13 ± 9.72 cm, fasting blood glucose 180.50 ± 58.87 mg/dL, postprandial blood glucose 237.52 ± 87.34 mg/dL, and HbA_{1c} 8.98 ± 2.06%. On abdominal ultrasound, NAFLD grading was as follows: 80% of patients had grade III and 20% of patients had grade II.

All 30 patients were on metformin (dose 500-2000 mg/day), and 13 patients were on sulfonylureas (glimepiride in doses of 1-4 mg/day). Five patients required discontinuation of antihyperglycemic agents during the course of the study (2: metformin 500 mg and 3: glimepiride 2 mg).

All patients were encouraged to have meals according to Asian Indian guidelines that took into consideration weight, activity level, etc (20). All patients were told to perform physical activity as per guidelines for Asian Indians (21).

Changes in Parameters after 120 Days of Dapagliflozin Treatment

Anthropometry

Mean body weight, BMI, circumferences, and ratios (mid arm, neck, chest, waist, hip, thigh, and WhtR), skinfold thickness (biceps, subscapular, suprailiac, lateral thoracic, calf, central, peripheral, and total skinfolds) were statistically significantly decreased after 120 days of treatment. In addition, mean handgrip strength values were statistically significantly increased after 120 days of treatment (Table 1 and Fig. 1).

Biochemistry and metabolic variables

Mean fasting blood glucose, postprandial blood glucose, HbA_{1c}, serum TGs, serum TG glucose ratio, SGOT, SGPT, GGT, fasting insulin, HOMA-IR, and postprandial C-peptide were statistically significantly decreased after 120 days of treatment. In addition, HOMA-β, postprandial insulin sensitivity, and fasting adiponectin levels were statistically significantly improved after 120 days of treatment (Table 2).

Body composition on dual-energy x-ray absorptiometry

Mean values of body fat (% and in kg), trunk regional fat (%) and trunk fat (g), were statistically significantly decreased at 120 days, while total lean mass did not change (Table 3).

Liver and pancreatic fat fractions

Mean values of liver span statistically significantly decreased. Liver FF (ROIs right lobe, %LFFRL in 1, 2, 3, 4, 5 and 6 and

ROIs left lobe, %LFFLL in 1, 2, and 3, and mean %LFF) and pancreatic FF (%PFF head and tail and mean %PFF) were statistically significantly decreased after 120 days of treatment (Table 4 and Fig. 2).

Multivariate linear regression coefficients

We used multiple linear regressions to mutually adjust for liver and pancreatic fat and weight change. We found the liver fat (0.385 [0.15-0.61]; $P = .002$) reduction after dapagliflozin treatment was independent of weight loss (Table 5).

Discussion

In this study, use of dapagliflozin (10 mg/day for 120 days) in patients on stable doses of metformin and/or sulfonylureas led to a statistically significant decrease in body weight, subcutaneous fat, abdominal obesity, improvement in insulin resistance, postprandial insulin sensitivity and glycemic measures, and most important, a reduction in liver and pancreatic fat. The strength of the study is the comprehensive use of measurements of body fat patterning, liver, and pancreatic fat; changes in the latter have been measured for the first time with dapagliflozin therapy. Our study includes a few novel measurements: detailed body fat patterning by use of skinfolds and circumferences and use of handgrip strength.

Using multiple methods of measurements, many investigators have shown that SGLT2is improve liver fat and fibrosis (22).. Hitherto, the effect of dapagliflozin on liver fat has been measured in 6 studies (23-28). Among these, the use of dapagliflozin alone has been evaluated in only one study (26). Further, MRI–proton density FF (PDFF) was used for the evaluation of liver fat in 4 studies (23-26, 28) and liver biopsy was not conducted in any study. In a double-blind, placebo-controlled trial (n = 6 each arm), dapagliflozin treatment for 8 weeks led to statistically significant placebo-corrected decreases in liver PDFF (23.74%, $P < .01$) and liver volume (20.10 L, $P < .05$). Interestingly, using the hyperinsulinemic euglycemic clamp, Latva-Rasku and colleagues (25) showed that tissue-specific, insulin-stimulated glucose uptake did not change in skeletal muscle, liver, myocardium, or white and brown adipose tissues, and endogenous glucose production remained unaffected. In a study like ours by Kurinami et al (29), dapagliflozin compared to other antihyperglycemic drugs for 24 weeks led to decreased abdominal and visceral fat, transaminases, and hepatic fat. These authors assessed the liver/spleen attenuation ratio as an indirect marker of NAFLD. Overall reduction in liver fat after use of dapagliflozin as estimated by MRI PDFF was shown in 4 studies: –3.74% (8 weeks) (26); –13% (12 weeks) (28); –2.35% (24 weeks) (23); and more than 30% (baseline

Table 1. Anthropometry profile

Variables	Baseline, 0 d	Last visit, 120 d	Difference (95% CI)	*P*
Weight, kg	83.6 ± 10.23	79.81 ± 9.56	3.79 (1.23 to 4.23)	.002
Body mass index	31.36 ± 4.44	29.78 ± 4.56	1.58 (0.98 to 2.18)	.0001
Circumference, cm				
Mid arm	31.69 ± 2.89	30.9 ± 3.16	0.78 (0.26 to 1.31)	.004
Neck	38.51 ± 3.71	37.68 ± 3.85	0.83 (0.40 to 1.25)	.0004
Chest	108.02 ± 8.77	106.63 ± 9.21	1.39 (0.25 to 2.53)	.019
Waist	104.13 ± 9.72	100.1 ± 10.28	4.03 (2.75 to 5.31)	.0001
Hip	102.6 ± 8.64	99.53 ± 9.15	3.06 (1.85 to 4.27)	.0001
Thigh	56.51 ± 6.87	54.53 ± 6.72	1.98 (1.27 to 2.69)	.0001
Ratios				
Waist-hip	1.01 ± 0.03	1.00 ± 0.04	0.01 (–0.009 to 0.022)	.071
Waist-height	0.64 ± 0.06	0.63 ± 0.03	0.01 (0.005 to 0.06)	.001
Skinfold thickness, mm				
Biceps	14.30 ± 6.75	12.81 ± 6.40	1.50 (0.23 to 2.76)	.021
Triceps	21.76 ± 7.50	19.96 ± 7.15	1.80 (–0.12 to 3.72)	.06
Subscapular	31.90 ± 9.40	29.63 ± 8.68	2.26 (0.33 to 4.20)	.023
Suprailiac	34.06 ± 9.50	32.16 ± 8.54	1.9 (0.33 to 3.76)	.046
Lateral thoracic	34.43 ± 8.31	31.6 ± 7.98	2.83 (1.45 to 4.21)	.0002
Thigh	34.56 ± 9.87	32.6 ± 9.28	1.96 (–0.38 to 4.32)	.09
Calf	17.00 ± 5.30	15.7 ± 5.29	1.3 (0.07 to 2.52)	.03
Central	65.96 ± 18.90	61.79 ± 17.22	4.17 (2.65 to 5.21)	.002
Peripheral	36.06 ± 14.23	31.77 ± 13.55	4.29 (2.31 to 5.47)	.003
SS/TR ratio	1.47 ± 1.25	1.48 ± 1.20	–0.01 (0.008 to 0.03)	.08
Central/peripheral ratio	1.83 ± 1.32	1.94 ± 1.27	–0.11 (0.09 to 0.03)	.09
Total skinfolds	223.54 ± 67.16	207.39 ± 62.17	16.15 (13.25 to 19.65)	.004
Handgrip strength, J[a]	35.91 ± 6.56	38.62 ± 5.65	2.71 (1.54 to 3.86)	.05

Values are in ± SD. *P* value less than .05 is statistically significant.
Abbreviation: SS/TR, ratio of subscapular and triceps skinfolds.
[a]With Jamar handgrip dynamometer.

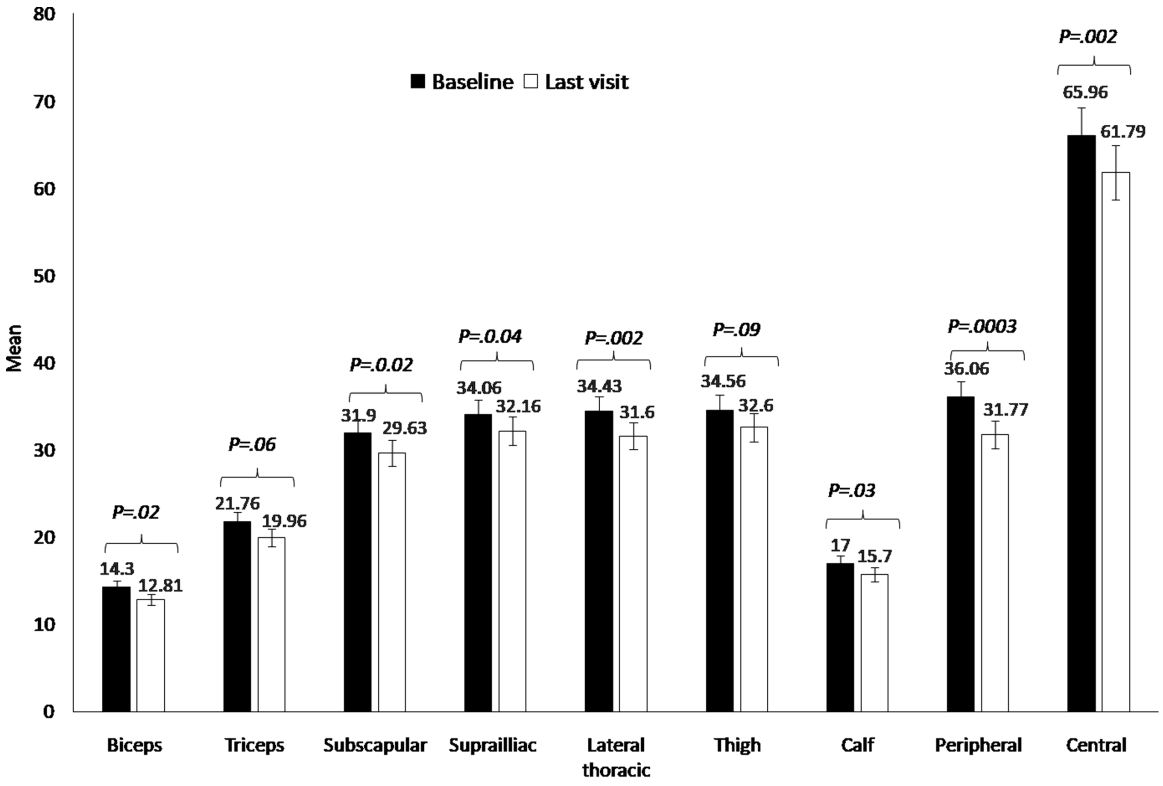

Figure 1: Changes of anthropometry profile from baseline to 120 days of treatment.

Figure 1. Changes in anthropometry parameters at baseline and at 120 days of treatment.

Table 2. Biochemical and metabolic profiles

Variables	Baseline, 0 d	Last visit, 120 d	Difference, 95% CI	*P*
Fasting blood glucose, mg/dL	180.50 ± 58.87	121.9 ± 33.16	58.60 (33.0 to 84.14)	.0001
PP blood glucose, mg/dL	237.52 ± 87.34	156.5 ± 52.72	81.02 (49.4 to 112.6)	.0000
Hemoglobin A_{1c}, %	8.98 ± 2.06	6.88 ± 1.19	2.10 (1.37 to 2.84)	.0000
Serum triglycerides, mg/dL	241.28 ± 178.42	157.4 ± 66.54	83.7 9 (21.41 to 146.17)	.0102
Triglyceride/glucose ratio	1.33 ± 0.06	1.29 ± 0.08	0.04 (0.009 to 0.06)	.05
Total cholesterol, mg/dL	181.93 ± 47.07	172.19 ± 30.61	9.74 (–6.74 to 26.22)	.2365
HDL-C, mg/dL	42.48 ± 19.32	41.11 ± 8.91	1.37 (–5.66 to 8.42)	.6917
LDL-C, mg/dL	106.81 ± 35.56	103.55 ± 26.68	3.25 (–11.19 to 17.71)	.6482
SGOT, U/L	31.29 ± 21.39	25.77 ± 13.16	5.51 (0.83 to 10.19)	.0224
SGPT, U/L	58.61 ± 36.68	44.48 ± 27.44	14.13 (6.07 to 22.18)	.0012
GGT, U/L	58.41 ± 37.20	43.33 ± 30.92	15.08 (5.08 to 25.08)	.0045
Fasting serum insulin, µIU/mL	31.29 ± 21.61	23.44 ± 16.42	7.76 (0.66 to 14.86)	.0332
PP serum insulin, µIU/mL	94.02 ± 288.76	50.53 ± 30.17	43.49 (–69.58 to 156.57)	.0043
HOMA-IR	13.95 ± 4.32	7.06 ± 2.21	6.89 (4.31 to 7.56)	.001
HOMA-QUICKI	0.27 ± 0.09	0.29 ± 0.07	–0.02 (–0.005 to 0.090)	.002
Fasting HOMA β, %	-0.032 ± 0.05	0.345 ± 0.09	–0.377 (–0.20 to 0.45)	.001
PP HOMA β, %	4.417 ± 2.35	2.960 ± 1.45	1.457 (0.009-3.32)	.003
PP insulin sensitivity	0.032 ± 0.001	0.64 ± 0.0532	–0.607 (–0.120-0.864)	.004
Fasting glucose-to-insulin ratio	5.77 ± 2.12	5.20 ± 1.96	0.57 (0.009-0.64)	0.05
Fasting C-peptide, ng/mL	7.02 ± 4.37	6.13 ± 2.51	0.88 (–1.03 to 2.80)	.3523
PP C-peptide, ng/mL	10.60 ± 5.07	7.46 ± 3.21	3.14 (1.10 to 5.17)	.0039
Fasting adiponectin, ng/mL	39.90 ± 64.54	91.12 ± 128.95	–51.21 (7.67 to 94.75)	.0228
PP adiponectin, ng/mL	51.75 ± 79.39	64.73 ± 65.36	–12.97 (–21.97 to 47.92)	.4527

Values are in ± SD. *P* value less than .05 is statistically significant.
Abbreviations: GGT, γ-glutamyl transpeptidase; HDL-C, high-density lipoprotein cholesterol; HOMA β; Homeostatic Model Assessment β; HOMA-IR, Homeostatic Model Assessment of Insulin Resistance; LDL-C, low-density lipoprotein cholesterol; PP, postprandial; QUICKI, quantitative insulin sensitivity check index; SGOT, serum glutamic oxaloacetic transaminase; SGPT, serum glutamic pyruvic transaminase.

Table 3. Dual-energy x-ray absorptiometry profile

Variables	Baseline, 0 d	Last visit, 120 d	Difference, 95% CI	*P*
Total body fat, %	42.14 ± 7.94	40.67 ± 7.83	1.47 (0.48 to 2.45)	.0048
Total body fat, kg	44.38 ± 9.65	42.89 ± 10.60	1.49 (0.40 to 2.57)	.0090
Total lean mass, g	45783.97 ± 9816.25	45407 ± 10285.62	376.96 (–521.7 to 1275.7)	.3980
Total regional fat, %	40.74 ± 7.75	39.06 ± 7.51	1.68 (0.64 to 2.71)	.0024
Arm regional fat, %	35.21 ± 10.34	34.41 ± 9.87	1.79 (0.87 to 2.71)	.0004
Arm tissue fat, %	36.60 ± 10.56	34.79 ± 10.12	1.81 (0.87 to 2.75)	.0005
Leg regional fat, %	37.21 ± 9.75	35.9 ± 9.59	1.31 (0.55 to 2.07)	.0014
Trunk regional fat, %	46.57 ± 8.09	44.38 ± 6.81	2.18 (0.46 to 3.90)	.0143
Arm tissue, g	8089.7 ± 1412.43	7780.13 ± 1702.04	309.26 (58.64 to 559.88)	.0173
Arm fat, g	2937.26 ± 883.53	2684.1 ± 914.10	253.1 (107.94 to 398.25)	.0013
Arm lean mass, g	5152.4 ± 1324.06	5096.43 ± 1409.94	56.7 (–70.75 to 182.75)	.3737
Arm total mass, kg	8.42 ± 1.45	8.11 ± 1.74	0.30 (0.05 to 0.55)	.0186
Leg tissue fat, %	38.79 ± 10.03	37.45 ± 9.88	1.34(0.56 to 2.11)	.0015
Leg tissue, g	23451.8 ± 5287.8	22820.07 ± 5279.59	631.73 (11.99 to 1251.47)	.0460
Leg fat, g	9205.33 ± 3453.01	8666.93 ± 3365.06	538.4(189.19 to 887.60)	.0037
Leg lean, g	14246.57 ± 3421.03	14153.1 ± 3366.36	93.46(–258.77 to 445.70)	.5915
Leg total mass, kg	24.46 ± 5.45	23.82 ± 5.45	0.64(0.01 to 1.26)	.0461
Trunk tissue fat, %	45.22 ± 10.72	45.38 ± 6.94	–0.16 (–3.74 to 3.41)	.9248
Trunk tissue, g	43462.2 ± 9532.41	41959.67 ± 10478.22	1502.53 (410 to 2595.06)	.0087
Trunk fat, g	20480.37 ± 5855.80	19202.83 ± 6158.90	1277.53 (495.5 to 2059.51)	.0023
Trunk lean, g	22981.8 ± 5153.66	22756.93 ± 5532.04	224.86 (–399.98 to 849.72)	.4676
Total tissue fat, %	42.15 ± 7.95	40.68 ± 7.84	1.47 (0.48 to 2.46)	.0048
Total tissue, g	79385.1 ± 15597.32	76905 ± 16922.94	2480.1 (967.50 to 3992.69)	.0022
Trunk/total, FMR	0.61 ± 0.04	0.61 ± 0.04	0.0003(–0.008 to 0.009	.9380
Legs/total, FMR	0.268 ± 0.038	0.27 ± 0.38	–0.002(–0.009 to 0.004	.4954
Arms + legs/trunk, FMR	0.58 ± 0.11	0.58 ± 0.11	–0.0003(–0.02 to 0.02)	.9770

Values are in ± SD. *P* value less than .05 is statistically significant.
Abbreviation: FMR, fat mass ratio.

to 52 weeks) (24). In our study, a 5.1% reduction in liver fat was achieved in 120 days.

Recently, research regarding pancreatic fat in diabetes has increased, and its importance is being realized. Pancreatic fat is linked to reduced insulin secretion, which is more likely in individuals with prediabetes, low BMI, and increased genetic risk of type T2DM (30) In a study of 296 individuals at increased risk for diabetes, pancreatic fat (measured with MRI) was shown to be negatively associated with insulin secretion in those with high genetic risk (31). Other investigators have differed from this conclusion. In 56 individuals of varied glucose tolerance, total ($r = 0.385$, $P < .01$) and intralobular pancreas adipose tissue infiltration ($r = 0.310$, $P < .05$) was positively associated with age only, and not with fasting or 2-hour glucose levels, BMI, or visceral fat content (32). However, there is a paucity of intervention data suggesting that pancreatic fat reduction leads to improvement in insulin secretion. In a recently published French study, the only previous study of effect of SGLT2i on pancreatic fat, the use of empagliflozin for 12 weeks (n = 56) led to no statistically significant reduction from baseline in pancreatic fat seen by magnetic resonance spectroscopy (33). In our present study, an average reduction of pancreatic fat by 1.53% was seen, significantly in the head and tail of the pancreas. In a study in which a calorie-restricted diet was given to 11 participants for 8 weeks, a reversal was seen of diabetes with a reduction of pancreatic triacylglycerol (8.0 ± 1.6% baseline to 6.2 ± 1.1% at 8 weeks ($P = .03$) (9). A reduction in pancreatic fat seen with a calorie-restricted diet and our intervention with dapagliflozin is similar, indicating the potential of this drug in the reversal of diabetes if used early in its natural history. Finally, it is often argued that weight loss with dapagliflozin leads to fat loss including in the liver and pancreas. We adjusted for weight changes and found that the change in liver fat after dapagliflozin treatment was independent of weight loss. Finally, it is interesting to note that in mice dapagliflozin enhances β-cell self-replication (promotes duct-derived β-cell neogenesis) and induces α- to β-cell conversion likely in response to α-cell glucagon-like peptide-1 release (34).

The effect of SGLT2is on skeletal muscle mass is important, especially because a substantial number of Asian Indians are sarcopenic (35). In a previous study, the use of bioelectrical impedance analysis and abdominal computed tomography showed that absolute changes in skeletal muscle mass and soft lean mass were not statistically significantly different between those treated with dapagliflozin vs nondapagliflozin drugs over 6 months (36). In the present research we also showed no statistically significant changes in various measures of lean mass with the use of dapagliflozin over 3 months. Interestingly, handgrip strength was shown to be statistically significantly increased after 3 months of treatment with dapagliflozin in our study. In a study conducted in Japan (n = 112), patients

Table 4. Liver span (on ultrasound) and liver and pancreatic fat fractions (on magnetic resonance imaging)

Variables	Baseline, 0 d	Last visit, 120 d	Difference, 95% CI	*P*
Liver span, cm	17.49 ± 1.92	16.68 ± 1.76	0.91 (0.41 to 1.40)	.0007
Liver fat fraction, %				
Right lobe				
LFFRL (1)	15.24 ± 7.28	10.60 ± 6.87	4.64 (2.61 to 6.66)	.0001
LFFRL (2)	15.74 ± 7.96	10.29 ± 6.40	5.44 (3.03-7.57)	.0000
LFFRL (3)	15.64 ± 7.82	10.24 ± 6.84	5.39 (3.06 to 7.73)	.0001
LFFRL (4)	15.27 ± 8.36	10.43 ± 7.02	4.83 (2.37 to 7.30)	.0004
LFFRL (5)	15.78 ± 8.33	10.42 ± 6.91	5.35 (2.73 to 7.97)	.0002
LFFRL (6)	15.73 ± 8.62	10.03 ± 6.73	5.7 (2.89 to 8.50)	.0003
Left lobe				
LFFLL (1)	14.44 ± 7.74	9.58 ± 6.27	4.86 (2.38 to 7.35)	.004
LFFLL (2)	14.52 ± 8.08	9.30 ± 6.12	5.21 (2.53 to 7.90)	.004
LFFLL (3)	14.26 ± 7.52	9.51 ± 6.43	4.74 (2.58 to 6.90)	.0001
LFF (mean)	15.16 ± 7.77	10.06 ± 6.51	5.10 (2.80 to 7.41)	.0001
Pancreatic fat fraction, %				
PFF (head)	7.65 ± 6.40	5.77 ± 3.72	1.87 (0.41 to 3.33)	.0135
PFF (body)	7.83 ± 5.63	6.81 ± 4.40	1.01 (–0.09 to 2.13)	.0726
PFF (tail)	7.12 ± 6.05	5.41 ± 4.24	1.71 (0.56 to 2.86)	.0049
PFF (mean)	7.52 ± 5.84	5.99 ± 3.98	1.53 (0.42 to 2.64)	.0083

Values are in ± SD. *P* value less than .05 is statistically significant.
Abbreviations: LFF (mean) %, liver fat fraction %; LFFRL (1) %, liver fat fraction right lobe (1) %; LFFRL (2) %, liver fat fraction right lobe (2) %; LFFRL (3) %, liver fat fraction right lobe (3) %; LFFRL (4) %, liver fat fraction right lobe (4) %; LFFRL (5) %, liver fat fraction right lobe (5) %; LFFRL (6) %, liver fat fraction right lobe (6) %; LFFLL (1) %, liver fat fraction left lobe (1) %; LFFLL (2) %, liver fat fraction left lobe (2) %; LFFLL (3) %, liver fat fraction left lobe (3) %; PFF (body) %, pancreas fat fraction (body) %; PFF (head) %, pancreas fat fraction (head) %; PFF (mean) %, pancreas fat fraction (mean) %; PFF (tail) %, pancreas fat fraction (tail) %.

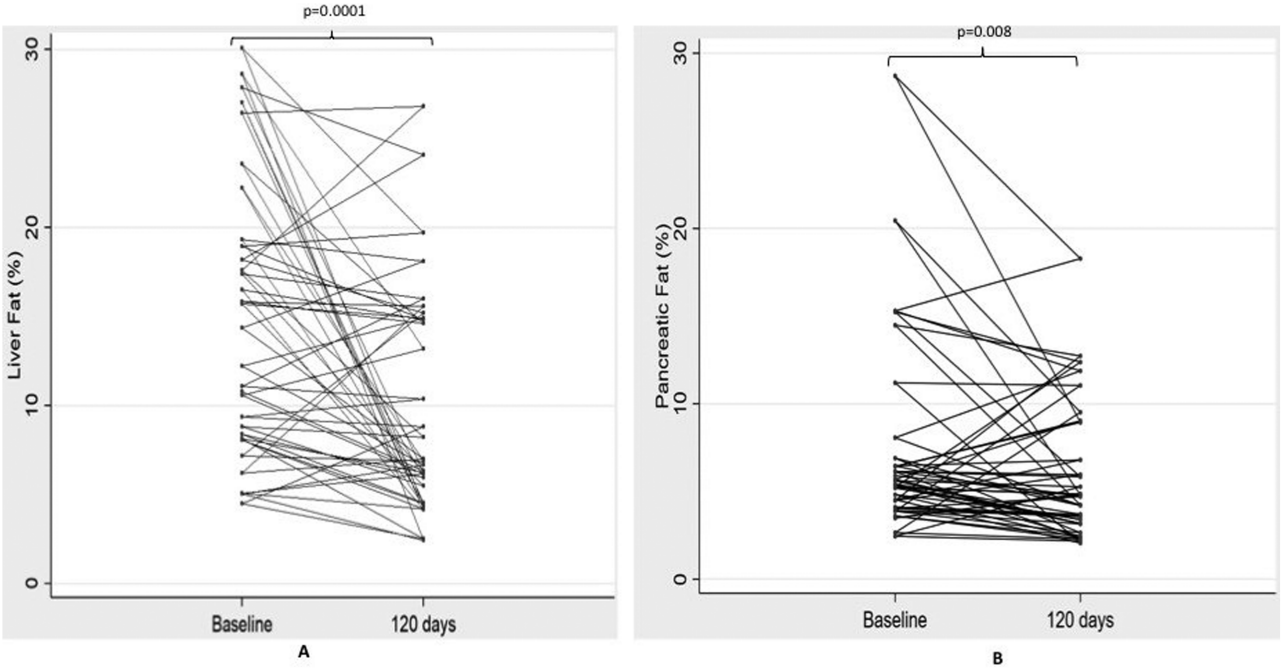

Figure 2. Changes in A, liver fat fraction and B, pancreatic fat fraction at baseline and at 120 days of treatment.

were given ipragliflozin, dapagliflozin, and luseogliflozin for at least 4 weeks; that led to a statistically significant increase in hand grip strength both in men and women (37). These findings indicate that the use of dapagliflozin has the potential to increase muscle function while muscle mass remains intact.

A few previous studies have shown a decrease in insulin resistance with the use of SGLT2is. In our study we clearly showed decreased fasting and postprandial C-peptide levels in addition to HOMA-IR. Decrease in HOMA-IR, similar to our data, were also shown previously in a study in which

Table 5. Multivariate linear regression coefficients for liver and pancreatic fat

Variables	Unadjusted (95% CI)	*P*	Adjusted (95% CI)	*P*
Liver fat fraction change	0.109 (0.186 to 0.633)	.001	0.385 (0.15 to 0.61)	.002
Pancreatic fat fraction change	0.430 (–0.114 to 0.976)	.11	0.22 (–0.188 to 0.751)	.23

P value less than .05 is statistically significant.

T2DM patients with obstructive sleep apnea were given dapagliflozin and metformin vs metformin and glimepiride for 24 weeks (38). Further, increased fasting adiponectin levels after dapagliflozin treatment were seen in our study, and were also found by others. In a single-arm, nonrandomized, open-label study (n = 16) patients with percutaneous liver biopsy-confirmed nonalcoholic steatohepatitis and T2DM were prescribed dapagliflozin 5 mg/d for 24 weeks that led to an increase in adiponectin levels ($P < .01$) (39). Overall, our data regarding improvement in surrogate markers of insulin resistance and insulin secretion are clinically important. However, it is well known that the HOMA-IR, as used in our study, may not be reliable when used in patients of T2DM. Further, the results of HOMA-IR could differ by ethnicity. Finally, results obtained from the hyperinsulinemic euglycemic clamp may be more reliable than those obtained by HOMA-IR. All these may explain differences in our results as compared to those of Latva-Rascu et al (25).

Limitations

The first and most important limitation, which we acknowledged earlier, is the lack of a control group. Further, a longer duration of study would have yielded more robust data. Finally, it is well known that HOMA-IR, as used in our study, may not be reliable when used as a surrogate marker of insulin resistance in patients with T2DM (40).

Conclusions

After 120 days of treatment with dapagliflozin, a statistically significant decrease in mean liver FF and mean pancreatic FF was seen after dapagliflozin therapy. Compared to baseline, reduction in liver fat after treatment was statistically significant after adjustment for changes in weight. In addition to weight loss, reductions in subcutaneous and abdominal adiposity, glycemia, and insulin resistance were seen.

Acknowledgments

We would like to thank all our patients who participated in this study.

Financial Support

This work was supported by an investigator-initiated study grant funded by Astra Zeneca Pharma India Ltd (No. ESR-18-13506). The funding agency did not play a role in the design and conduct of the study; collection, management, analysis, or interpretation of the data; or preparation, review, or approval of the manuscript.

Author Contributions

A.M. contributed to the study concept and design, reviewed and edited the manuscript, and approved final submission; A.G. conducted the study, collected data, wrote the manuscript, and provided critical revision; K.D., K.T., and I.A. contributed in conducting study and data collection; R.G. analyzed and contributed to discussion. V.K.V. and H.M. conducted MRI and MRI analysis, interpretation, and contributed to discussion; S.P. contributed to the study concept and design, conducted the study, collected data, conducted biochemical analysis, and contributed to writing the manuscript and critical revision; R.P. and S.P. statistically analyzed and interpreted the data, and contributed to discussion; A.M. is the guarantor for this manuscript.

Disclosures

A.M. discloses financial or business/organizational interests in AstraZeneca Pharma India Ltd, Janssen Pharmaceuticals, Boehringer Ingelheim, Sun Pharmaceuticals Industries Ltd, and Lupin India; R.G. discloses financial or business/organizational interests in AstraZeneca Pharma India Ltd, Janssen Pharmaceuticals, Boehringer Ingelheim, Sun Pharmaceuticals Industries Ltd, and Lupin India; A.G. discloses financial or business/organizational interests in Janssen Pharmaceuticals, Boehringer Ingelheim, Sun Pharmaceuticals Industries Ltd, and Lupin India; the other authors have nothing to disclose.

Data Availability

Complete data have been incorporate into this manuscript.

Clinical Trial Information

Clinical trial registration number: CTRI/2019/08/020909 (registered 26 August 2019).

References

1. Hills AP, Arena R, Khunti K, *et al*. Epidemiology and determinants of type 2 diabetes in south Asia. *Lancet Diabetes Endocrinol*. 2018;6(12):966-978.
2. Misra A, Sattar N, Tandon N, *et al*. Clinical management of type 2 diabetes in south Asia. *Lancet Diabetes Endocrinol*. 2018;6(12):979-991.
3. Bhatt SP, Misra A, Nigam P, Guleria R, Pasha MA. Phenotype, body composition, and prediction equations (Indian fatty liver index) for non-alcoholic fatty liver disease in non-diabetic Asian Indians: a case-control study. *PLoS One*. 2015;10(11):e0142260.
4. Stefan N, Staiger H, Wagner R, *et al*. A high-risk phenotype associates with reduced improvement in glycaemia during a lifestyle intervention in prediabetes. *Diabetologia*. 2015;58(12):2877-2884.
5. Lazo M, Solga SF, Horska A, *et al;* Fatty Liver Subgroup of the Look AHEAD Research Group. Effect of a 12-month intensive lifestyle intervention on hepatic steatosis in adults with type 2 diabetes. *Diabetes Care*. 2010;33(10):2156-2163.
6. Perdomo CM, Frühbeck G, Escalada J. Impact of nutritional changes on nonalcoholic fatty liver disease. *Nutrients*. 2019;11(3):677.
7. Pinnick KE, Collins SC, Londos C, Gauguier D, Clark A, Fielding BA. Pancreatic ectopic fat is characterized by adipocyte infiltration and altered lipid composition. *Obesity (Silver Spring)*. 2008;16(3):522-530.
8. Misra A, Anoop S, Gulati S, Mani K, Bhatt SP, Pandey RM. Body fat patterning, hepatic fat and pancreatic volume of non-obese

Asian Indians with type 2 diabetes in North India: a case-control study. *PLoS One*. 2015;10(10):e0140447.
9. Lim EL, Hollingsworth KG, Aribisala BS, Chen MJ, Mathers JC, Taylor R. Reversal of type 2 diabetes: normalisation of beta cell function in association with decreased pancreas and liver triacylglycerol. *Diabetologia*. 2011;54(10):2506-2514.
10. Jiang Y, Spurny M, Schübel R, *et al*. Changes in pancreatic fat content following diet-induced weight loss. *Nutrients*. 2019;11(4):912:3518-3525.
11. Al-Mrabeh A, Hollingsworth KG, Shaw JAM, *et al*. 2-year remission of type 2 diabetes and pancreas morphology: a post-hoc analysis of the DiRECT open-label, cluster-randomised trial. *Lancet Diabetes Endocrinol*. 2020;8(12):939-948.
12. Budd J, Cusi K. Role of agents for the treatment of diabetes in the management of nonalcoholic fatty liver disease. *Curr Diab Rep*. 2020;20(11):59.
13. Nigam P, Bhatt SP, Misra A, Vaidya M, Dasgupta J, Chadha DS. Non-alcoholic fatty liver disease is closely associated with subclinical inflammation: a case-control study on Asian Indians in North India. *PLoS One*. 2013;8(1):e49286.
14. Dudeja V, Misra A, Pandey RM, Devina G, Kumar G, Vikram NK. BMI does not accurately predict overweight in Asian Indians in northern India. *Br J Nutr*. 2001;86(1):105-112.
15. Misra A, Chowbey P, Makkar BM, *et al;* Consensus Group. Consensus statement for diagnosis of obesity, abdominal obesity and the metabolic syndrome for Asian Indians and recommendations for physical activity, medical and surgical management. *J Assoc Physicians India*. 2009;57:163-170.
16. Saadeh S, Younossi ZM, Remer EM, *et al*. The utility of radiological imaging in nonalcoholic fatty liver disease. *Gastroenterology*. 2002;123(3):745-750.
17. Belfiore F, Iannello S, Volpicelli G. Insulin sensitivity indices calculated from basal and OGTT-induced insulin, glucose, and FFA levels. *Mol Genet Metab*. 1998;63(2):134-141.
18. Neumann S, Kwisda S, Krettek C, Gaulke R. Comparison of the grip strength using the Martin-vigorimeter and the JAMAR-dynamometer: establishment of normal values. *In Vivo*. 2017;31(5):917-924.
19. Tam KM, Wu JS. Ultrasonographic diagnosis of fatty liver [article in Chinese]. *Taiwan Yi Xue Hui Za Zhi*. 1986;85(1):45-53.
20. Misra A, Sharma R, Gulati S, *et al;* National Dietary Guidelines Consensus Group. Consensus dietary guidelines for healthy living and prevention of obesity, the metabolic syndrome, diabetes, and related disorders in Asian Indians. *Diabetes Technol Ther*. 2011;13(6):683-694.
21. Misra A, Nigam P, Hills AP, *et al;* Physical Activity Consensus Group. Consensus physical activity guidelines for Asian Indians. *Diabetes Technol Ther*. 2012;14(1):83-98.
22. Dwinata M, Putera DD, Hasan I, Raharjo M. SGLT2 inhibitors for improving hepatic fibrosis and steatosis in non-alcoholic fatty liver disease complicated with type 2 diabetes mellitus: a systematic review. *Clin Exp Hepatol*. 2020;6(4):339-346.
23. Bolinder J, Ljunggren Ö, Kullberg J, *et al*. Effects of dapagliflozin on body weight, total fat mass, and regional adipose tissue distribution in patients with type 2 diabetes mellitus with inadequate glycemic control on metformin. *J Clin Endocrinol Metab*. 2012;97(3):1020-1031.
24. Johansson L, Hockings PD, Johnsson E, *et al*. Dapagliflozin plus saxagliptin add-on to metformin reduces liver fat and adipose tissue volume in patients with type 2 diabetes. *Diabetes Obes Metab*. 2020;22(7):1094-1101.
25. Latva-Rasku A, Honka MJ, Kullberg J, *et al*. The SGLT2 inhibitor dapagliflozin reduces liver fat but does not affect tissue insulin sensitivity: a randomized, double-blind, placebo-controlled study with 8-week treatment in type 2 diabetes patients. *Diabetes Care*. 2019;42(5):931-937.
26. Shimizu M, Suzuki K, Kato K, *et al*. Evaluation of the effects of dapagliflozin, a sodium-glucose co-transporter-2 inhibitor, on hepatic steatosis and fibrosis using transient elastography in patients with type 2 diabetes and non-alcoholic fatty liver disease. *Diabetes Obes Metab*. 2019;21(2):285-292.
27. Kinoshita T, Shimoda M, Nakashima K, *et al*. Comparison of the effects of three kinds of glucose-lowering drugs on non-alcoholic fatty liver disease in patients with type 2 diabetes: a randomized, open-label, three-arm, active control study. *J Diabetes Investig*. 2020;11(6):1612-1622.
28. Eriksson JW, Lundkvist P, Jansson PA, *et al*. Effects of dapagliflozin and n-3 carboxylic acids on non-alcoholic fatty liver disease in people with type 2 diabetes: a double-blind randomised placebo-controlled study. *Diabetologia*. 2018;61(9):1923-1934.
29. Kurinami N, Sugiyama S, Yoshida A, *et al*. Dapagliflozin significantly reduced liver fat accumulation associated with a decrease in abdominal subcutaneous fat in patients with inadequately controlled type 2 diabetes mellitus. *Diabetes Res Clin Pract*. 2018;142(8):254-263.
30. Wagner R, Eckstein SS, Yamazaki H, *et al*. Metabolic implications of pancreatic fat accumulation. *Nat Rev Endocrinol*. 2022;18(1):43-54.
31. Wagner R, Jaghutriz BA, Gerst F, *et al*. Pancreatic steatosis associates with impaired insulin secretion in genetically predisposed individuals. *J Clin Endocrinol Metab*. 2020;105(11):3518-3525.
32. Begovatz P, Koliaki C, Weber K, *et al*. Pancreatic adipose tissue infiltration, parenchymal steatosis and beta cell function in humans. *Diabetologia*. 2015;58(7):1646-1655.
33. Gaborit B, Ancel P, Abdullah AE, *et al*. Effect of empagliflozin on ectopic fat stores and myocardial energetics in type 2 diabetes: the EMPACEF study. *Cardiovasc Diabetol*. 2021;20(1):57.
34. Wei R, Cui X, Feng J, *et al*. Dapagliflozin promotes beta cell regeneration by inducing pancreatic endocrine cell phenotype conversion in type 2 diabetic mice. *Metabolism*. 2020;111(10):154324.
35. Misra A, Soares M, Mohan V, *et al*. Body fat, metabolic syndrome and hyperglycemia in South Asians. *J Diabetes Complications*. 2018;32(11):1068-1075.
36. Sugiyama S, Jinnouchi H, Kurinami N, *et al*. Dapagliflozin reduces fat mass without affecting muscle mass in type 2 diabetes. *J Atheroscler Thromb*. 2018;25(6):467-476.
37. Sano M, Meguro S, Kawai T, Suzuki Y. Increased grip strength with sodium-glucose cotransporter 2. *J Diabetes*. 2016;8(5):736-737.
38. Tang Y, Sun Q, Bai XY, Zhou YF, Zhou QL, Zhang M. Effect of dapagliflozin on obstructive sleep apnea in patients with type 2 diabetes: a preliminary study. *Nutr Diabetes*. 2019;9(1):32.
39. Tobita H, Sato S, Miyake T, Ishihara S, Kinoshita Y. Effects of dapagliflozin on body composition and liver tests in patients with nonalcoholic steatohepatitis associated with type 2 diabetes mellitus: a prospective, open-label, uncontrolled study. *Curr Ther Res Clin Exp*. 2017;87(7):13-19.
40. Wallace TM, Levy JC, Matthews DR. Use and abuse of HOMA modeling. *Diabetes Care*. 2004;27(6):1487-1495.