

Additional Appendix

Comparison of Tofogliflozin and Glimepiride Effects on Nonalcoholic Fatty Liver

Disease in Participants with Type 2 Diabetes: A randomized, 48 -Weeks, Open-

Label, Active-controlled Trial

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Table S1. Trial schedule of data collection

	Screening		Treatment (TD, treatment day)				Follow-up
	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7
	(Max -12 weeks to TD1)	(1-2 weeks prior to TD1)	(Week 12)	(Week 24)	(Week 36)	(1-7 days + Week 48 /End of Treatment)	(12 weeks after EOT)
Informed consent	X						
Clinical assessment	X	X	X	X	X	X	X
Vital signs	X	X	X	X	X	X	X
Screening blood test	X		X	X	X	X	X
Liver biopsy	X					X	
Genes of the liver	X					X	
Transient Elastography	X		X			X	
Study medication	X	X	X	X	X	X	X
Adverse/clinical events			X	X	X	X	X
bioelectrical impedance		X	X	X	X	X	X
Standard blood and urine test		X	X	X	X	X	X
Oxidative stress markers, cytokine		X				X	

Clinical assessment (complete history/examination, physical and mental conditions);
Vital signs (blood pressure, heart rate, weight, height, waist: hip circumferences);
Screening blood test (fasting plasma glucose, HbA1c); Study medication (If the study patient meets the eligibility criteria, he/she will be randomized at TD1 to receive tofogliflozin or sulfonylurea.); Standard blood and urine test (full blood count, renal function, electrolytes, lipid profile).

Table S2. The compliance of study medication

Variable	ALL	Tofogliflozin	Glimepiride
	(N=40)	(N=20)	(N=20)
	<i>number of patients (percent)</i>		
100% - no. (%)	31 (78)	15 (75)	16 (80)
more than 80% less than 100% - no. (%)	9 (23)	5 (25)	4 (20)
less than 80% - no. (%)	0 (0)	0 (0)	0 (0)

Table S3. Baseline concomitant medication of the study subjects

Variable	Total	Tofogliflozin	Glimepiride	P value* (Tofogliflozin vs. Glimepiride)
	(N=40)	(N=20)	(N=20)	
	<i>number of patients (percent)</i>			
Diabetes	40 (100)	20 (100)	20 (100)	NA
Medications	31 (78)	14 (70)	17 (85)	0.225
Metformin	22 (55)	8 (40)	14 (70)	0.057
Dipeptidyl peptidase-4 inhibitor	17 (43)	8 (40)	9 (45)	0.749
alpha-glucosidase inhibitors	2 (5)	1 (5)	1 (5)	0.756
Pioglitazone	1 (3)	1 (5)	0 (0)	0.500
GLP1 receptor agonist	7 (18)	3 (15)	4 (20)	0.500
Long-acting insulin	4 (10)	1 (5)	3 (15)	0.302
Rapid-acting insulin	3 (8)	1 (5)	2 (10)	0.500
Hypertension	24 (60)	12 (60)	12 (60)	1.000
Medications	19 (48)	9 (45)	11 (55)	0.527
Calcium channel blocker	15 (38)	7 (35)	8 (40)	0.744
Angiotensin II receptor antagonist	12 (30)	4 (20)	8 (40)	0.168
Angiotensin-converting enzyme inhibitors	1 (3)	1 (5)	0 (0)	0.500
Mineralocorticoid receptor antagonists	1 (3)	0 (0)	1 (5)	0.500
Dyslipidemia	32 (80)	16 (80)	16 (80)	0.653
Medications	22 (55)	12 (60)	10 (50)	0.525
Statin	18 (45)	10 (50)	8 (40)	0.525
Fibrate	2 (5)	1 (5)	2 (10)	0.500
Ezetimib	2 (5)	2 (10)	0 (0)	0.244

* Parameters were analyzed using the χ^2 test (or Fisher exact test) in the intergroup comparison. NA; not analyzed

Table S4. Changes in liver related parameters compared between baseline and week 48 by treatment group

	Tofogliflozin (N=20)	Glimepiride (N=20)	P value†
Total activity score for non alcoholic fatty liver disease			
Baseline	4.40 (1.76)	4.50 (1.19)	0.904
Week 52	2.35 (1.57)*	3.90 (1.51)*	0.003
Change from baseline	-2.05 (1.47)	-0.60 (1.10)	0.002
Aspartate transaminase (IU/L)			
Baseline	28.0 (24.3 - 54.5)	30.0 (21.3 - 49.0)	0.602
At week 48	21.0 (16.3 - 26.0)*	28.0 (18.5 - 49.0)	0.142
Change from baseline at week 48	-8.5 (-31.0 - -3.3)	-4.0 (-14.8 - 16.3)	0.060
Alanine aminotransferase (IU/L)			
Baseline	36.0 (28.0 - 77.5)	48.0 (35.5 - 60.0)	0.398
Week 48	24.5 (17.3 - 41.8)*	38.5 (19.0 - 85.0)	0.096
Change from baseline at week 48	-12.0 (-51.8 - -9.0)	-13.5 (-24.5 - 8.0)	0.157
Gamma-glutamyl transferase (IU/L)			
Baseline	50.0 (36.5 - 77.8)	42.5 (30.0 - 59.8)	0.221
Week 48	27.5 (21.3 - 39.3)*	38.5 (24.8 - 65.0)	0.121
Change from baseline at week 48	-18.0 (-34.8 - -9.3)	-0.5 (-12.8 - 8.3)	<0.001
Alkaline phosphatase (U/L)			
Baseline	238.0 (173.5 - 286.0)	218.5 (191.8 - 258.0)	0.947
Week 48	217.5 (171.5 - 236.0)*	195.0 (181.3 - 240.8)	0.799
Change from baseline at week 48	-24.5 (-49.0 - 3.8)	-21.0 (-44.8 - 5.8)	0.666
Total bilirubin (mg/dl)			
Baseline	0.70 (0.63 - 0.90)	0.80 (0.60 - 1.00)	0.602
Week 48	0.80 (0.63 - 1.00)	0.80 (0.60 - 0.90)	0.377
Change from baseline at week 48	0.10 (-0.10 - 0.10)	-0.10 (-0.20 - 0.08)	0.604
FIB-4 index			
Baseline	1.10 (0.83 - 1.48)	0.95 (0.50 - 1.49)	0.277
Week 48	1.00 (0.69 - 1.26)*	1.02 (0.64 - 1.51)	0.779
Change from baseline at week 48	-0.14 (-0.31 - 0.05)	0.09 (-0.10 - 0.31)	0.015
The percentage of steatosis (%)			
Baseline	39.8 (24.2)	40.5 (18.9)	0.919
Week 48	18.9 (18.6)*	36.1 (21.9)	0.007
Change from baseline at week 48	-20.9 (19.4)	-4.4 (21.2)	0.014
Liver steatosis, as assessed by Fibroscan-dB/m			
Baseline	288.6 (37.9)	300.4 (28.9)	0.223
Week 48	261.8 (58.1)	282.7 (38.7)	0.161
Change from baseline at week 48	-26.8 (16.8)	-17.7 (8.0)	0.612
Liver stiffness, as assessed by Fibroscan-kPa			
Baseline	5.7 (4.3 - 7.3)	6.4 (4.7 - 11.3)	0.581
Week 48	5.2 (3.7 - 6.3)*	6.9 (34.5 - 13.4)	0.176
Change from baseline at week 48	-1.3 (0.5)	-0.1 (0.9)	0.236

Data at baseline and week 48 are mean (SD) or median (inter-quartile range), change

from baseline at week 48 are presented as mean (SE) or median (inter-quartile range). The intergroup comparison[†] was performed with Mann-Whitney's U test in nonparametric parameters or the two-sample t-test in normal distribution. The internal group comparison* between baseline and 48 weeks was performed with the Wilcoxon signed-rank test.

Table S5. Changes in metabolic parameters compared between baseline and week 48 by treatment group

	Tofogliflozin (N=20)	Glimepiride (N=20)	P value †
Fasting plasma glucose (mg/dl)			
Baseline	144.0 (120.0 - 157.8)	141.0 (128.3 - 158.0)	0.947
Week 48	111.0 (100.8 - 124.0)*	125.0 (108.3 - 134.5)*	0.092
Change from baseline at week 48	-34.5 (-45.0 - -9.5)	-20.5 (-28.5 - -2.5)	0.114
Glycated hemoglobin (%)			
Baseline	7.9 (7.4 - 8.4)	8.2 (7.3 - 9.2)	0.565
Week 48	7.0 (6.1 - 7.3)*	7.4 (6.7 - 7.8)*	0.040
Change from baseline at week 48	-1.0 (-2.0 - -0.2)	-1.0 (-1.9 - -0.1)	0.445
Glycated hemoglobin (mmol/mol)			
Baseline	63.0 (57.0 - 67.8)	65.5 (55.3 - 76.8)	0.565
Week 48	53.0 (43.3 - 55.8)*	57.0 (50.3 - 62.0)*	0.040
Change from baseline at week 48	-11.0 (-22.0 - -2.5)	-5.0 (-21.0 - -0.5)	0.429
C-peptide immunoreactivity (ng/mL)			
Baseline	2.81 (0.92)	2.86 (0.92)	0.852
Week 48	2.81 (1.22)	3.12 (0.87)	0.289
Change from baseline at week 48	0.00 (0.23)	0.26 (0.15)	0.063
3-hydroxybutyric acid (mmol/L)			
Baseline	75.0 (50.3 - 121.0)	62.0 (40.0 - 111.5)	0.622
Week 48	81.0 (50.5 - 185.8)	60.0 (43.8 - 103.0)	0.189
Change from baseline at week 48	15.5 (-20.3 - 41.8)	5.0 (-63.8 - 28.5)	0.482
Weight (kg)			
Baseline	79.3 (18.2)	84.7 (25.4)	0.449
Week 48	75.2 (17.6)*	85.5 (26.1)	0.154
Change from baseline at week 48	-4.2 (0.6)	0.8 (1.0)	<0.001
Body-mass index			
Baseline	31.0 (6.7)	32.0 (8.8)	0.705
Week 48	29.0 (6.2)*	32.3 (9.1)	0.383
Change from baseline at week 48	-2.0 (0.5)	0.3 (0.4)	<0.001
Waist circumference (cm)			
Baseline	97.0 (90.3 - 105.8)	103.8 (90.0 - 114.4)	0.383
Week 48	94.8 (88.0 - 103.8)	99.5 (87.3 - 114.8)	0.565
Change from baseline at week 48	-0.3 (-8.6 - 3.6)	0.8 (-4.5 - 4.8)	0.620
Body fat mass (kg)			
Baseline	25.1 (22.6 - 31.8)	27.4 (17.4 - 40.3)	0.841
Week 48	21.9 (19.7 - 28.3)*	25.7 (17.2 - 44.1)	0.602
Change from baseline at week 48	-2.3 (-5.7 - -0.8)	0.2 (-1.6 - 1.6)	0.020
Body fat (%)			
Baseline	38.0 (9.2)	35.5 (9.4)	0.404
Week 48	33.6 (9.0)*	35.3 (10.5)	0.589
Change from baseline at week 48	-4.5 (1.9)	-0.3 (0.5)	0.020
Skeletal muscle mass (kg)			
Baseline	25.9 (5.5)	28.7 (7.2)	0.167
Week 48	26.0 (6.1)	29.0 (7.4)	0.172
Change from baseline at week 48	0.1 (0.6)	0.2 (0.1)	0.007
Systolic blood pressure (mmHg)			
Baseline	129.3 (12.7)	130.0 (14.8)	0.864
Week 48	124.7 (13.5)	130.7 (14.5)	0.184
Change from baseline at week 48	-4.6 (2.4)	0.7 (3.3)	0.201
Heart rate (beat/min)			
Baseline	81.2 (13.1)	84.2 (12.6)	0.471
Week 48	81.3 (16.6)	81.6 (9.9)	0.954
Change from baseline at week 48	0.1 (3.6)	-2.6 (2.1)	0.520
Total cholesterol (mg/dL)			
Baseline	170.1 (28.1)	176.5 (40.7)	0.567
Week 48	174.4 (26.5)	179.0 (30.8)	0.616
Change from baseline at week 48	4.4 (5.7)	2.5 (8.2)	0.858
Triglycerides (mg/dL)			
Baseline	140.0 (115.0 - 204.0)	140.5 (123.0 - 228.0)	0.602
Week 48	152.5 (82.3 - 190.3)	158.5 (125.5 - 188.0)	0.398
Change from baseline at week 48	-18.0 (-56.8 - 51.3)	-16.0 (-45.3 - 40.8)	0.862
High-density lipoprotein cholesterol (mg/dL)			
Baseline	44.8 (11.6)	40.7 (8.1)	0.204
Week 48	46.9 (12.5)	41.0 (9.0)	0.096
Change from baseline at week 48	2.2 (2.1)	0.4 (1.4)	0.470
Remnant lipoprotein cholesterol (mg/dL)			
Baseline	5.8 (4.2 - 9.3)	5.9 (3.6 - 10.3)	0.947
Week 48	6.5 (4.1 - 9.1)	6.3 (5.3 - 9.3)	0.758
Change from baseline at week 48	0.7 (-1.4 - 2.9)	0.6 (-1.9 - 2.8)	0.640
Small dense low-density lipoprotein cholesterol (mg/dL)			
Baseline	34.0 (17.3)	37.4 (16.8)	0.541
Week 48	32.7 (15.6)	39.4 (19.2)	0.233
Change from baseline at week 48	-1.3 (2.2)	2.1 (3.5)	0.422

Data at baseline and week 48 are mean (SD) or median (inter-quartile range), change from baseline at week 48 are presented as mean (SE) or median (inter-quartile range). The intergroup comparison[†] was performed with Mann-Whitney's U test in nonparametric parameters or the two-sample t-test in normal distribution. The internal group comparison* between baseline and 48 weeks was performed with the Wilcoxon signed-rank test.

Table S6. Changes in oxidative stress markers, and cytokines compared between baseline and week 48 by treatment group

	Tofogliflozin (N=20)	Glimepiride (N=20)	P Value †
Ferittin (ng/mL)			
Baseline	231.5 (111.5 - 548.8)	188.0 (83.5 - 5372.0)	0.602
Week 48	76.5 (40.5 - 192.3)*	124.0 (46.0 - 1243.5)*	0.355
Change from baseline at week 48	-134.0 (-267.3 - -57.5)	-42.0 (-134.0 - -9.0)	0.096
Urinary 8-hydroxy-2'-Deoxyguanosine (ng/mg Cre)			
Baseline	12.1 (8.6 - 17.0)	9.0 (8.2 - 11.3)	0.425
Week 48	12.7 (8.0 - 23.2)	8.5 (6.7 - 12.3)*	0.099
Change from baseline at week 48	0.1 (-5.6 - 8.3)	-0.7 (-2.6 - 0.4)	0.232
Urinary 8-Isoprostane/Cre (pg/mg Cre)			
Baseline	275.5 (187.3 - 366.3)	265.0 (232.5 - 331.5)	0.525
Week 48	255.5 (202.0 - 342.8)	272.0 (219.5 - 407.0)	0.710
Change from baseline at week 48	-35.0 (-72.5 - 108.0)	-9.0 (-36.5 - 63.5)	0.493
Tumor necrosis factor-alpha (pg/mL)			
Baseline	1.23 (0.93 - 1.54)	1.23 (1.13 - 1.64)	0.939
Week 48	1.24 (0.83 - 1.71)	1.18 (1.06 - 1.91)	0.841
Change from baseline at week 48	-0.03 (-0.21 - 0.16)	-0.03 (-0.40 - 0.37)	0.620
Leptin (ng/mL)			
Baseline	29.0 (13.6 - 63.7)	12.7 (10.6 - 43.6)	0.231
Week 48	28.9 (14.1 - 71.8)	18.8 (12.1 - 41.0)	0.602
Change from baseline at week 48	1.7 (-5.8 - 12.1)	3.3 (-1.2 - 7.6)	0.341
Adiponectine (µg/mL)			
Baseline	1.78 (0.85 - 1.92)	0.93 (0.75 - 1.88)	0.947
Week 48	1.70 (0.95 - 2.70)	1.01 (0.80 - 1.51)	0.398
Change from baseline at week 48	0.15 (-0.15 - 0.38)	-0.01 (-0.23 - 0.19)	0.192

Data at baseline and week 48 are median (inter-quartile range), change from baseline at week 48 are presented as median (inter-quartile range). The intergroup comparison† was performed with Mann-Whitney's U test in nonparametric parameters. The internal group comparison* between baseline and 48 weeks was performed with the Wilcoxon signed-rank test.

Table S7. The association between the baseline characteristics, the change of the laboratory data, and the change in histology in both groups

	Tofogliflozin								Glimepiride							
	delta steatosis score		delta hepatocellular ballooning score		delta lobular inflammation score		delta fibrosis score		delta steatosis score		delta hepatocellular ballooning score		delta lobular inflammation score		delta fibrosis score	
	ρ	P	ρ	P	ρ	P	ρ	P	ρ	P	ρ	P	ρ	P	ρ	P
Age (years)	0.317	0.173	-0.006	0.979	-0.335	0.149	0.113	0.636	0.276	0.240	0.392	0.088	-0.132	0.578	0.179	0.449
Sex	0.070	0.770	0.060	0.801	-0.161	0.497	0.182	0.444	-0.135	0.572	-0.378	0.100	0.287	0.220	-0.308	0.186
Fibrosis score at baseline	0.433	0.057	0.163	0.493	0.066	0.781	-0.252	0.284	0.423	0.076	0.055	0.818	0.054	0.820	-0.168	0.479
HbA1c at baseline (%)	-0.274	0.242	-0.258	0.273	0.339	0.144	-0.582	0.007	0.014	0.952	-0.030	0.900	0.354	0.125	0.297	0.204
Weight at baseline (kg)	0.016	0.945	0.061	0.797	0.139	0.560	-0.095	0.690	0.216	0.361	-0.210	0.373	-0.016	0.947	0.051	0.832
BMI at baseline	0.115	0.628	0.065	0.786	0.075	0.753	-0.115	0.629	0.162	0.494	-0.250	0.287	0.098	0.681	0.003	0.992
Body fat mass at baseline (kg)	0.012	0.961	-0.109	0.648	-0.080	0.737	-0.080	0.737	0.226	0.337	-0.230	0.329	0.168	0.480	0.016	0.946
Body fat mass at baseline (%)	0.009	0.970	-0.106	0.658	-0.175	0.460	0.040	0.867	0.182	0.443	-0.290	0.214	0.255	0.278	-0.053	0.824
AST at baseline (IU/L)	-0.017	0.945	0.001	0.997	-0.227	0.335	0.040	0.867	0.241	0.306	0.160	0.500	-0.464	0.039	0.005	0.982
ALT at baseline (IU/L)	-0.029	0.904	-0.135	0.569	0.008	0.975	-0.120	0.613	0.181	0.445	-0.010	0.967	-0.501	0.024	-0.061	0.799
GTP at baseline (IU/L)	0.164	0.489	-0.237	0.314	-0.159	0.502	0.178	0.453	0.498	0.026	0.151	0.526	-0.438	0.053	0.053	0.823
FIB-4 index at baseline	0.168	0.478	-0.021	0.931	-0.631	0.003	0.165	0.486	0.467	0.038	0.551	0.012	-0.289	0.216	0.354	0.126
delta HbA1c	0.559	0.010	0.240	0.307	-0.178	0.453	0.524	0.018	0.570	0.009	0.361	0.118	-0.046	0.847	0.122	0.609
delta weight	0.665	0.001	0.130	0.584	0.108	0.649	-0.290	0.214	0.144	0.543	0.080	0.737	0.101	0.671	-0.092	0.699
delta BMI	0.443	0.050	-0.013	0.956	0.222	0.347	-0.411	0.052	0.107	0.653	0.050	0.834	0.136	0.568	-0.104	0.663
delta body fat mass (kg)	0.217	0.357	-0.030	0.900	0.242	0.304	-0.121	0.146	0.246	0.295	0.290	0.214	0.149	0.531	0.102	0.669
delta body fat mass (%)	0.253	0.282	0.045	0.851	0.281	0.230	-0.291	0.214	0.245	0.297	0.190	0.421	0.045	0.852	-0.060	0.800
delta AST	0.372	0.106	0.106	0.658	0.094	0.695	0.048	0.842	0.045	0.852	0.271	0.249	0.248	0.292	0.102	0.668
delta ALT	0.279	0.233	0.098	0.682	-0.003	0.989	0.088	0.713	0.083	0.728	0.391	0.089	0.380	0.098	0.206	0.384
delta GTP	0.253	0.282	0.434	0.056	0.235	0.319	-0.070	0.769	0.160	0.500	0.221	0.349	0.338	0.144	0.290	0.215
delta FIB-4 index	0.203	0.391	-0.180	0.447	-0.215	0.362	-0.050	0.834	0.066	0.782	0.090	0.706	-0.006	0.980	-0.313	0.178

The association was performed by the Spearman analysis. BMI, body mass index; AST, aspartate transaminase; ALT, Alanine aminotransferase; GTP, Gamma-glutamyl transferase

Table S8. Differential gene ontology (biological process) altered by treatment with tofogliflozin or glimepiride

No.	GO category	GO term	Number of genes	LS permutation p-value	KS permutation p-value	Up or down	Representative genes
Tofogliflozin							
Metabolism							
1	GO:0001676	Long-chain fatty acid metabolic process	73	0.00001	0.00001	Up	SLC27A5, ACSL5, EPHX2
2	GO:0006730	One-carbon metabolic process	25	0.00001	0.00024	Up	GNMT, AHCY, MTHFD1
3	GO:0009063	Cellular amino acid catabolic process	95	0.00001	0.00001	Up	CBS, HAAO, GCDH
4	GO:0009072	Aromatic amino acid family metabolic process	18	0.00001	0.00001	Up	QDPR, GSTZ1, KYNU
5	GO:0009404	Toxin metabolic process	19	0.00001	0.0013	Up	CYP1A1, MPST, ACAA1
6	GO:0042737	Drug catabolic process	100	0.00001	0.00071	Up	PCK2, SULT1A2, QDPR
7	GO:0043648	Dicarboxylic acid metabolic process	90	0.00001	0.00004	Up	HAAO, L2HGDH, GLS2
8	GO:0098754	Detoxification	83	0.00001	0.00043	Up	MT1X, PON3, MT1E
9	GO:1901606	Alpha-amino acid catabolic process	81	0.00001	0.00001	Up	QDPR, GCAT, AGXT
10	GO:0051262	Protein tetramerization	99	0.00006	0.00039	Up	ST13, AASS, CDA
11	GO:0006805	Xenobiotic metabolic process	97	0.00006	0.00153	Up	SULT1A2, CYP2A6, CYP2A7
12	GO:0046653	Tetrahydrofolate metabolic process	18	0.00009	0.00167	Up	MTHFD1, ALDH1L1, GCH1
13	GO:0019400	Alditol metabolic process	18	0.00015	0.00008	Up	PCK1, GALK1, COQ3
14	GO:0009064	Glutamine family amino acid metabolic process	57	0.00017	0.00017	Up	GLS2, ASS1, AMDHD1
15	GO:0055069	Zinc ion homeostasis	27	0.00023	0.00637	Up	MT1E, MT1M, MT2A
16	GO:0033559	Unsaturated fatty acid metabolic process	76	0.00052	0.00017	Up	EPHX2, CYP1A1, SIRT1
17	GO:1903825	Organic acid transmembrane transport	79	0.00084	0.00171	Up	SLC16A10, SLC38A4, SLC7A2
18	GO:0019842	Vitamin binding	96	0.00091	0.09142	Up	GNMT, KYNU, GPT
19	GO:0009062	Fatty acid catabolic process	90	0.00163	0.00001	Up	MLYCD, ACOX2, CYP4A11
20	GO:0006637	Acyl-CoA metabolic process	86	0.00314	0.00246	Up	ACSM3, DGAT2, HMGCS2
21	GO:0019395	Fatty acid oxidation	81	0.00323	0.00001	Up	PHYH, ETFB, PPARGC1A
22	GO:0006699	Bile acid biosynthetic process	29	0.00331	0.00064	Up	AKR1C4, AKR1D1, ABCB11
23	GO:0006641	Triglyceride metabolic process	73	0.00353	0.00362	Up	APOA5, APOC3, CETP
Cell cycle							
1	GO:2000134	Negative regulation of G1/S transition of mitotic ce	79	0.00001	0.00018	Down	BTG2, CDKN1A, CCNB1
2	GO:0044774	Mitotic DNA integrity checkpoint	82	0.00002	0.00356	Down	TOP2A, CLSPN, RAD9A
3	GO:0006270	DNA replication initiation	33	0.00003	0.00364	Down	MCM2, MCM6, PRIM2
4	GO:0044783	G1 DNA damage checkpoint	53	0.00022	0.00195	Down	TFDP1, BAX, SOX4
Cell death							
1	GO:0097300	Programmed necrotic cell death	37	0.00196	0.00579	Down	BIRC3, FAS, TRAF2
2	GO:0008630	Intrinsic apoptotic signaling pathway in response to	85	0.0033	0.00097	Down	BRCA2, RAD9A, PHLDA3
Stress response							
1	GO:0055093	Response to hyperoxia	18	0.00001	0.00005	Down	TP53, CAT, ATG7
2	GO:0036498	IRE1-mediated unfolded protein response	64	0.00095	0.00067	Down	ARFGAP1, KDELR3, WFS1
Inflammation							
1	GO:1905517	Macrophage migration	26	0.00023	0.01731	Down	LGALS3, CCL2, CCL5
2	GO:0002687	Positive regulation of leukocyte migration	76	0.00025	0.00529	Down	PLA2G7, MOSPD2, ICAM1
3	GO:0072606	Interleukin-8 secretion	24	0.00213	0.00362	Down	FCN1, TMSB4X, CD2
T cell response							
1	GO:0042129	Regulation of T cell proliferation	98	0.00095	0.01283	Down	GPNMB, RASAL3, CD3E
2	GO:0046645	Positive regulation of gamma-delta T cell activation	5	0.0023	0.00003	Down	NOD2, SYK, NCKAP1L
Fibrosis							
1	GO:0030199	Collagen fibril organization	34	0.00001	0.00064	Down	COL5A1, COL1A1, ANXA2
2	GO:0032963	Collagen metabolic process	77	0.00001	0.00024	Down	PDGFRB, COL4A1, ADAMTS2
3	GO:0032964	Collagen biosynthetic process	27	0.00007	0.00008	Down	CBX8, ENG, F2R
Glimepiride							
Metabolism							
1	GO:0006635	Fatty acid beta-oxidation	60	0.00001	0.00001	Up	PEX7, ABCD3
2	GO:0009308	Amine metabolic process	99	0.00001	0.00001	Up	GDE1, PSMD4, PSMA7
3	GO:0032543	Mitochondrial translation	92	0.00001	0.00001	Up	MRPL51, MTRF1, MRPL32
4	GO:0007031	Peroxisome organization	29	0.00057	0.00002	Up	PEX7, ABCD3
5	GO:0006637	Acyl-CoA metabolic process	86	0.00074	0.00001	Up	DGAT1, ACOT1, TDO2
6	GO:0006063	Uronic acid metabolic process	19	0.0008	0.0001	Up	UGT2B15, UGT1A1, UGT2B4
7	GO:0006720	Isoprenoid metabolic process	92	0.00135	0.00324	Up	BCO2, ALDH3A2, AKR1C1
8	GO:0045939	Negative regulation of steroid metabolic process	18	0.00244	0.0026	Up	INSIG2, UGT1A1

SLC27A5, Solute Carrier Family 27 Member 5; ACSL5, Acyl-CoA Synthetase Long Chain Family Member 5; EPHX2, Epoxide Hydrolase 2; AHCY, Adenosylhomocysteinase; MTHFD1, Methylenetetrahydrofolate Dehydrogenase, Cyclohydrolase And Formyltetrahydrofolate Synthetase 1; CBS, Cystathionine Beta-Synthase; HAAO, 3-Hydroxyanthranilate 3,4-Dioxygenase; GCDH, Glutaryl-CoA

Dehydrogenase; QDPR, GSTZ1 Quinoid Dihydropteridine Reductase; GSTZ1, Glutathione S-Transferase Zeta 1; KYNU, Kynureninase; CYP1A1, Cytochrome P450 Family 1 Subfamily A Member 1; ACAA1, Acetyl-CoA Acyltransferase 1; MPST, Mercaptopyruvate Sulfurtransferase; PCK2, Phosphoenolpyruvate Carboxykinase 2; SULT1A2, Sulfotransferase Family 1A Member 2; L2HGDH, L-2-Hydroxyglutarate Dehydrogenase; GLS2, Glutaminase 2; MT1X, Metallothionein 1X; PON3, Paraoxonase 3; MT1E, Metallothionein 1E; GCAT, Glycine C-Acetyltransferase; AGXT, Alanine--Glyoxylate And Serine--Pyruvate Aminotransferase; ST13, ST13 Hsp70 Interacting Protein; AASS, Amino adipate-Semialdehyde Synthase; CDA, Cytidine Deaminase; CYP2A6, Cytochrome P450 Family 2 Subfamily A Member 6; CYP2A7, Cytochrome P450 Family 2 Subfamily A Member 7; ALDH1L1, Aldehyde Dehydrogenase 1 Family Member L1; GCH1, GTP Cyclohydrolase 1; PCK1, Phosphoenolpyruvate Carboxykinase 1; GALK1, Galactokinase 1; COQ3, Coenzyme SYKQ3, Methyltransferase; ASS1, Argininosuccinate Synthase 1; AMDHD1, Amidohydrolase Domain Containing 1; MT1M, Metallothionein 1M; MT2A, Metallothionein 2A; SIRT1, Sirtuin 1; SLC16A10, Solute Carrier Family 16 Member 10; SLC38A4, Solute Carrier Family 38 Member 4; SLC7A2, Solute Carrier Family 7 Member 2; GNMT, Glycine N-Methyltransferase; GPT, Glutamic--Pyruvic Transaminase; MLYCD, Malonyl-CoA Decarboxylase; ACOX2, Acyl-CoA Oxidase 2; CYP4A11, Cytochrome P450 Family 4 Subfamily A Member 11; ACSM3, Acyl-CoA Synthetase Medium Chain Family Member 3; DGAT2, Diacylglycerol O-Acyltransferase 2; HMGCS2, 3-Hydroxy-3-Methylglutaryl-CoA Synthase 2; PHYH, Phytanoyl-CoA 2-Hydroxylase; ETFB, Electron Transfer Flavoprotein Subunit Beta; PPARGC1A, PPARG Coactivator 1 Alpha; AKR1C4, Aldo-Keto Reductase Family 1 Member C4; AKR1D1, Aldo-Keto Reductase Family 1 Member D1; ABCB11, ATP Binding Cassette Subfamily B Member 11; APOA5, Apolipoprotein A5; APOC3, Apolipoprotein C3; CETP, Cholesteryl Ester Transfer Protein; BTG2, BTG Anti-Proliferation Factor 2; CDKN1A, Cyclin Dependent Kinase Inhibitor 1A; CCNB1, Cyclin B1; TOP2A, DNA Topoisomerase II Alpha; CLSPN, Claspin; RAD9A, RAD9 Checkpoint Clamp Component A; MCM2, Minichromosome Maintenance Complex Component 2; MCM6, Minichromosome Maintenance Complex Component 6; PRIM2, DNA Primase Subunit 2; TFDP1, Transcription Factor Dp-1; BAX, BCL2 Associated X, Apoptosis Regulator; SOX4, SRY-Box Transcription Factor 4; BIRC3, Baculoviral IAP Repeat Containing 3; FAS, Fas Cell Surface Death Receptor; TRAF2, TNF Receptor Associated Factor 2; BRCA2, BRCA2 DNA Repair Associated; PHLDA3, Pleckstrin Homology Like Domain Family A Member 3; TP53, Tumor Protein P53;

CAT, Catalase; ATG7, Autophagy Related 7; ARFGAP1, ADP Ribosylation Factor GTPase Activating Protein 1; KDELR3, KDEL Endoplasmic Reticulum Protein Retention Receptor 3; WFS1, Wolframin ER Transmembrane Glycoprotein; LGALS3, Galectin 3; CCL2, C-C Motif Chemokine Ligand 2; CCL5, C-C Motif Chemokine Ligand 5; PLA2G7, Phospholipase A2 Group VII; MOSPD2, Motile Sperm Domain Containing 2; ICAM1, Intercellular Adhesion Molecule 1; FCN1, Ficolin 1; TMSB4X, Thymosin Beta 4 X-Linked; CD2, CD2 Molecule; GPNMB, Glycoprotein Nmb; RASAL3, RAS Protein Activator Like 3; CD3E, CD3e Molecule; NOD2, Nucleotide Binding Oligomerization Domain Containing 2; SYK, Spleen Associated Tyrosine Kinase; NCKAP1L, NCK Associated Protein 1 Like; COL5A1, Collagen Type V Alpha 1 Chain; COL1A1, Collagen Type I Alpha 1 Chain; ANXA2, Annexin A2; PDGFRB, Platelet Derived Growth Factor Receptor Beta; COL4A1, Collagen Type IV Alpha 1 Chain; ADAMTS2, ADAM Metallopeptidase With Thrombospondin Type 1 Motif 2; CBX8, Chromobox 8; ENG, Endoglin; F2R, Coagulation Factor II Thrombin Receptor; PEX7, Peroxisomal Biogenesis Factor 7; ABCD3, ATP Binding Cassette Subfamily D Member 3; GDE1, Glycerophosphodiester Phosphodiesterase 1; PSMD4, Proteasome 26S Subunit Ubiquitin Receptor, Non-ATPase 4; PSMA7, Proteasome 20S Subunit Alpha 7; MRPL51, Mitochondrial Ribosomal Protein L51; MTRF1, Mitochondrial Translation Release Factor 1; MRPL32, Mitochondrial Ribosomal Protein L32; DGAT1, Diacylglycerol O-Acyltransferase 1; ACOT1, Acyl-CoA Thioesterase 1; TDO2, Tryptophan 2,3-Dioxygenase; UGT2B15, UDP Glucuronosyltransferase Family 2 Member B15; UGT1A1, UDP Glucuronosyltransferase Family 1 Member A1; UGT2B4, UDP Glucuronosyltransferase Family 2 Member B4; BCO2, Beta-Carotene Oxygenase 2; ALDH3A2, Aldehyde Dehydrogenase 3 Family Member A2; AKR1C1, Aldo-Keto Reductase Family 1 Member C1; INSIG2, Insulin Induced Gene 2

Table S9. Gene set enrichment analysis using resident cells gene sets in liver defined by single cell RNA-seq analyses*

No.	Cell components	Number of genes	Tofogliflozin			Glimepiride		
			LS permutation p-value	KS permutation p-value	Up or down by Tofogliflozin	LS permutation p-value	KS permutation p-value	Up or down by Glimepiride
1	$\gamma\delta$ T cells-2	17	< 0.00001	< 0.00001	Down	0.00382	0.00079	Up
2	Hepatocytes (zone3)	539	< 0.00001	< 0.00001	Up	< 0.00001	< 0.00001	Up
3	Hepatocytes (zone2)	140	< 0.00001	0.00001	Up	0.00008	< 0.00001	Up
4	Inflammatory Macs	217	< 0.00001	< 0.00001	Down	N.S.	N.S.	-
5	Stellate cells	62	< 0.00001	0.00022	Down	N.S.	N.S.	-
6	Plasma cell	70	0.00011	0.00188	Down	N.S.	N.S.	-
7	Central LSEC	259	0.00053	0.00255	Up	N.S.	N.S.	-

* Resident cells gene sets in liver were retributed from Nat Commun. 2018; 9:4383.

Gene sets were retributed from twenty clusters of genes consisting of hepatocytes (1-6), cholangiocytes, central liver sinusoidal endothelial cell (LSEC), periportal LSEC, portal endothelial cells, stellate cells, inflammatory macrophages (Macs), non-inflammatory Macs, $\alpha\beta$ T cells, $\gamma\delta$ T cells-1, $\gamma\delta$ T cells-2, NK cells, mature B cells, plasmacells and erythoroid cells. N.S.; not significant

Table S10. Adverse events*

Event	Tofogliflozin (N=20) <i>number of patients (percent)</i>	Glimepiride (N=20)
Itching in the genital area	7(35)	0
Hypoglycemia	0	2 (10)
Urinating pain	1 (5)	0
Cystitis	1 (5)	0
Nocturia	1 (5)	0
Vaginal candida	1 (5)	0
Rash	1 (5)	0
Dry mouth	1 (5)	0
Lower abdominal pain	1 (5)	0
Diarrhea	1 (5)	0
Arthritis	1 (5)	0
Thirst	0	1 (5)
Right abdominal dent	0	1 (5)
Get annoyed	0	1 (5)
COVID19	0	1 (5)
Pancreatic cancer	0	1 (5)†

* All adverse events occurred during the on-treatment observation period unless otherwise specified. Data are reported for all the patients. † One patient in the glimepiride group dropout at the 48weeks during the trial (confirmed by the internal committee as pancreas cancer). The patient had had type 2 diabetes and intraductal papillary mucinous neoplasms at the baseline, and the event was considered unlikely to be related to glimepiride by both the investigator and the internal committee.

Table S11. Comparison of hepatic histologic scores improvement -% in previously reported RCT with liver biopsy

		Steatosis	Hepatocellular ballooning	Lobular inflammation	Fibrosis
Belfort et al. 2006					
Placebo	24 weeks	38	24	29	33
Pioglitazone	24 weeks	65	54	65	46
Sanyal et al. 2010					
Placebo	96 weeks	31	29	35	31
Vitamin E	96 weeks	54	50	54	41
Pioglitazone	96 weeks	69	44	60	44
Neuschwander et al. 2015					
Placebo	72 weeks	38	31	35	19
Obeticholic acid	72 weeks	61	46	53	35
Matthew et al. 2016					
Placebo	48 weeks	45	32	55	16
Liraglutide	48 weeks	83	61	48	26
Newsome et al. 2020					
Placebo	72 weeks	26	39	26	31
Semaglutide0.1mg	72 weeks	53	53	41	46
Semaglutide0.2mg	72 weeks	60	71	47	32
Semaglutide0.4mg	72 weeks	63	74	38	43
This study					
Tofogliflozin	48 weeks	65	55	50	60
Glimepiride	48 weeks	30	25	15	35

Table S12. Hepatic histologic scores in each gender

Histologic Features	Male						Female					
	Tofogliflozin (N=7)			Glimepiride (N=14)			Tofogliflozin (N=13)			Glimepiride (N=6)		
	Before	After	P Value†	Before	After	P Value†	Before	After	P Value†	Before	After	P Value†
Steatosis												
Score-no. of subjects												
0(<5%)	0	2		0	0		0	3		0	0	
1(5-33%)	4	5		5	8		4	6		1	3	
2(33-66%)	2	0		5	2		6	3		4	3	
3(>66%)	1	0		4	4		3	1		1	0	
Improvement-%		71.4	0.034		28.6	0.180		61.5	0.008		33.3	0.180
Hepatocellular ballooning												
Score-no. of subjects												
0(None)	2	5		1	3		1	5		0	2	
1(Few balloon cells)	3	2		10	8		7	7		4	3	
2(Many balloon cells)	2	0		3	3		5	1		2	1	
Improvement-%		57.1	0.059		14.3	0.157		53.8	0.011		50	0.083
Lobular inflammation												
Score-no. of subjects												
0(0 focus)	1	2		0	0		0	2		0	0	
1(<2 foci per 200*field)	4	5		9	11		7	11		4	3	
2(2-4 foci per 200*field)	2	0		5	3		5	0		2	3	
3(>4 foci per 200*field)	0	0		0	0		1	0		0	0	
Improvement-%		42.9	0.083		21.4	0.317		53.8	0.014		0	0.317
Fibrosis												
Score-no. of subjects												
0(None)	1	4		2	4		2	6		0	2	
1(Perisinusoidal or periportal)	2	2		8	6		5	5		3	1	
2(Perisinusoidal and portal or periportal)	3	0		2	1		5	1		1	2	
3(Bridging fibrosis)	1	1		1	3		1	1		2	1	
4(Cirrhosis)	0	0		1	0		0	0		0	0	
Improvement-%		71.4	0.034		21.4	0.317		53.8	0.011		66.7	0.180

†The P values were calculated with the Wilcoxon signed-rank test. ‡ The between-group comparison for the effect of treatment (change from baseline) was performed with the chi-square test

Table S13. Patients with changes in score -no./total no. (%) in each group

	Tofogliflozin				Glimepiride			
	Reductuin 2P	Reduction 1P	No change	Worsing 1P	Reductuin 2P	Reduction 1P	No change	Worsing 1P
	number of patients (percent)				number of patients (percent)			
(a) Total patients with Changes in Score -no./Total no. (%) in Each Group, Tofogliflozin (N=20) and Glimepiride (N=20)								
Steatosis	3 (15)	10 (50)	7 (35)	0 (0)	1 (5)	5 (25)	13 (65)	1 (5)
Hepatocellular ballooning	2 (10)	9 (45)	9 (45)	0 (0)	0 (0)	5 (25)	15 (75)	0 (0)
Lobular inflammation	2 (10)	8 (40)	10 (50)	0 (0)	0 (0)	3 (15)	15 (75)	2 (10)
Fibrosis	2 (10)	10 (50)	8 (40)	0 (0)	0 (0)	7 (35)	11 (55)	2 (10)
(b) Male Patients with Changes in Score -no./male patients no. (%) in Each Group, Tofogliflozin (N=7) and Glimepiride (N=14)								
Steatosis	1 (14.3)	4 (57.1)	2 (28.6)	0 (0)	0 (0)	4 (28.6)	9 (64.3)	1 (7.1)
Hepatocellular ballooning	1 (14.3)	3 (42.9)	3 (42.9)	0 (0)	0 (0)	2 (14.3)	12 (85.7)	0 (0)
Lobular inflammation	0 (0)	3 (42.9)	4 (57.1)	0 (0)	0 (0)	3 (21.4)	10 (71.4)	1 (7.1)
Fibrosis	1 (14.3)	4 (57.1)	2 (28.5)	0 (0)	0 (0)	3 (21.4)	10 (71.4)	1 (7.1)
(c) Female Patients with Changes in Score -no./female patients no. (%) in Each Group, Tofogliflozin (N=13) and Glimepiride (N=6)								
Steatosis	2 (15.3)	6 (46.2)	5 (38.5)	0 (0)	1 (16.7)	1 (16.7)	4 (66.7)	0 (0)
Hepatocellular ballooning	1 (7.7)	6 (46.2)	6 (46.2)	0 (0)	0 (0)	3 (50)	3 (50)	0 (0)
Lobular inflammation	2 (15.3)	5 (38.5)	6 (46.2)	0 (0)	0 (0)	0 (0)	5 (83.3)	1 (16.7)
Fibrosis	1 (7.7)	6 (46.2)	6 (46.2)	0 (0)	0 (0)	4 (66.7)	1 (16.7)	1 (16.7)

Figure S1 Patient flow

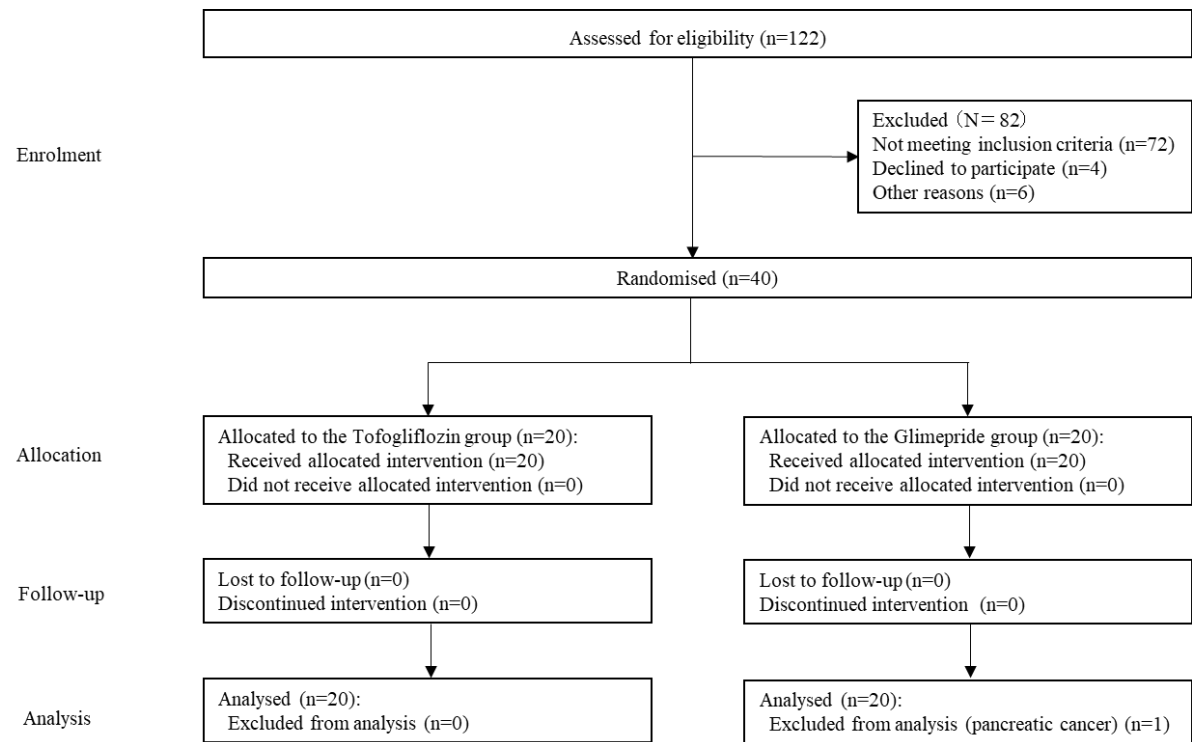


Figure S2. Flow chart of the study schedule

