Supplementary Table 1-Antibodies used in FACS analysis.

Antibody	
PerCP-Cyanine5.5-conjugated NK1.1	eBioscience
PerCP-Cyanine5.5-conjugated CD3	eBioscience
PerCP-Cyanine5.5-conjugated CD19	eBioscience
PerCP-Cyanine5.5-conjugated TER-119	eBioscience
allophycocyanin (APC)-eFluor 780-conjugated	eBioscience
phycoerythrin (PE)-conjugated CD11c	eBioscience
eFluor 450-conjugated Ly-6G (Gr-1)	eBioscience
APC-conjugated CD8	eBioscience
eFluor 450-conjugated CD3	eBioscience
PE-conjugated NK1.1	eBioscience
fluorescein isothiocyanate (FITC)-conjugated	eBioscience
PE/Cy7-conjugated F4/80	Biolegend
Alexa Fluor 647-conjugated CD206	Biolegend
APC-conjugated Ly-6C	Biolegend
PE Texas Red-conjugated CD4	Abcam
APC-Cy7-conjugated CD11b	BD
PE-Texas Red-conjugated CD11b	Invitrogen

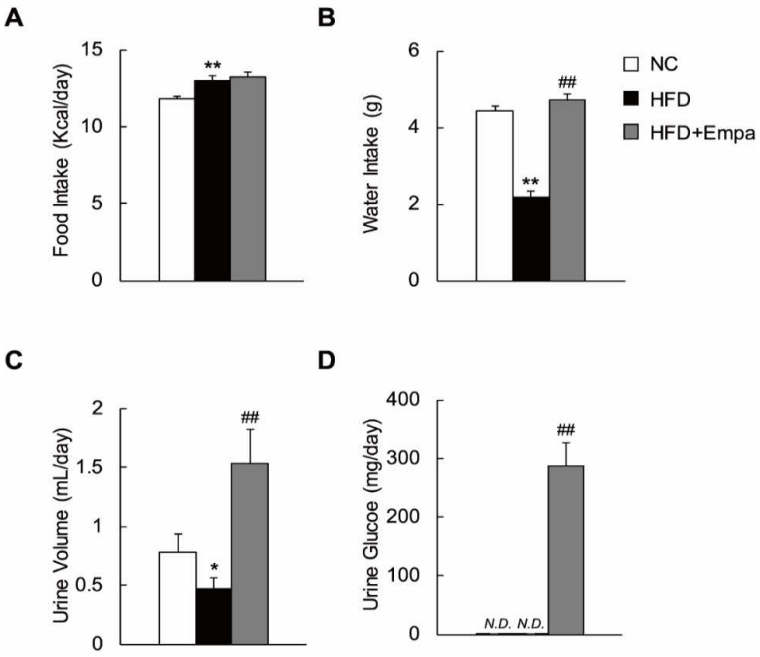
Supplementary Table 2-Primer sequences.

Gene	5’ Primer	3’ Primer
Adiponectin	AGCCGCTTATATGTATCGCTC	TGCCGTCATAATGATTCTGTT
Arg1	CTCCAAGCCAAAGTCCTTAGA	AGGAGCTGTCATTAGGGACAT
Cat	CCAGCGACCAGATGAAGCAG	CCACTCTCTCAGGAATCCGC
Ccr2	ATTCTCCACACCCTGTTTCG	GATTCCTGGAAGGTGGTCAA
Cd11c	AAAATCTCCAACCCATGCTG	CACCACCAGGGTCTTCAAGT
Cd206	CAAGGAAGGTTGGCATTTGT	CCTTTCAGTCCTTTGCAAGC
Cidea	ATCACAACTGGCCTGGTTACG	TACTACCCGGTGTCCATTTCT
Cpt1α	AAACCCACCAGGCTACAGTG	TCCTTGTAATGTGCGAGCTG
Dio2	CAGTGTGGTGCACGTCTCCAA	TGAACCAAAGTTGACCACCA
F4/80	CTTTGGCTATGGGCTTCCAGT	GCAAGGAGGACAGAGTTTAT
Gp91phox	TTG GGT CAG CAC TGG CTC	TGG CGG TGT GCA GTG CTA
Gpx1	TTCGGACACCAGGAGAATGG	TAAAGAGCGGGTGAGCCTTC
Il-1β	CTGAACTCAACTGTGAAATGC	AAAGGTTTGGAAGCAGCCCT
Il-6	GTTCTCTGGGAAATCGTGGA	GGAAATTGGGGTAGGAAGGA
Il-10	GCTCTTACTGACTGGCATGAG	CGCAGCTCTAGGAGCATGTG
Mcp1	AGGTCCCTGTCATGCTTCTGG	CTGCTGCTGGTGATCCTCTTG
P22phox	GTCCACCATGGAGCGATGTG	CAATGGCCAAGCAGACGGTC
P40phox	GCCGCTATCGCCAGTTCTAC	GCAGGCTCAGGAGGTTCTTC
P47phox	GATGTTCCCCATTGAGGCCG	GTTTCAGGTCATCAGGCCGC
P67phox	CTGGCTGAGGCCATCAGACT	AGGCCACTGCAGAGTGCTTG
Pgc-1α	ATGTGTCGCCTTCTTGCTCT	ATCTACTGCCTGGGGACCTT
Pparα	GAGGGTTGAGCTCAGTCA GG	GGTCACCTACGAGTGGCATT
Prdm16	GGCGAGGAAGCTAGCCAAA	GGTCTCCTCCTCGGCACTCT
Scd1	CATCATTCTCATGGTCCTGCT	CCCAGTCGTACACGTCATTTT
Sod	CAGCATGGGTTCCACGTCCA	CACATTGGCCACACCGTCCT
Srebp-1c	GGAGCCATGGATTGCACATT	GGCCCGGGAAGTCACTGT
Ucp1	ACTGCCACACCTCCAGTCATT	CTTTGCCTCACTCAGGATTGG
β-actin	AGG CCC AGA GCA AGA GAG	GGG GTG TTG AAG GTC TCA

Supplementary Table 3-Antibodies used in immunoblotting.

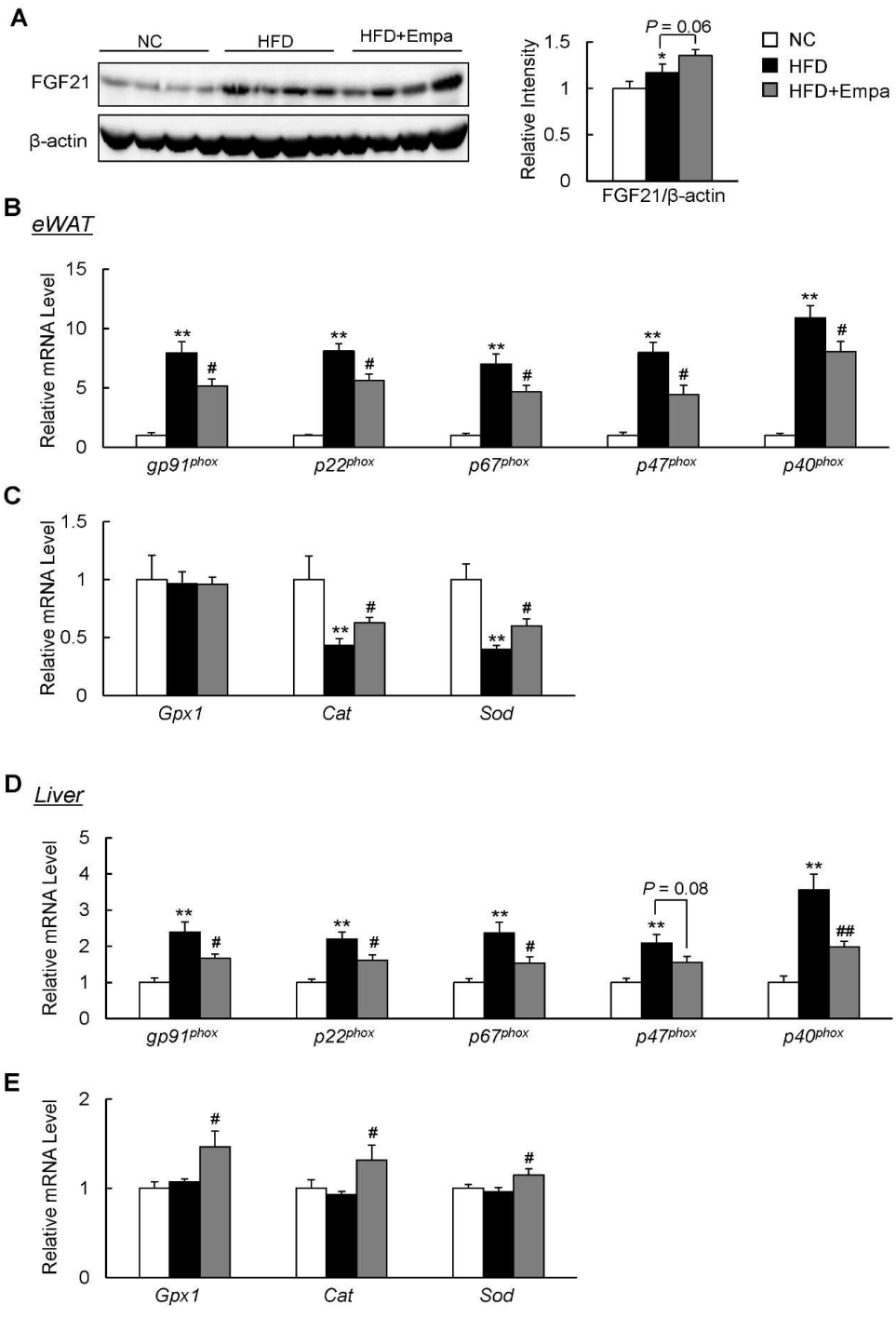
Antibody	
anti-phospho-p38 MAPK	Cell signaling (#9211)
anti-p38 MAPK	Cell signaling (#9212)
anti-phospho-NF-κB p65	Cell signaling (#3033)
anti -NF-κB p65	Cell signaling (#3034)
anti-phospho-IR β	Cell signaling (#3021)
anti-IR β	Cell signaling (#3025)
anti-phospho-Akt	Cell signaling (#9271)
anti-Akt	Cell signaling (#9272)
anti-phospho-Erk 1/2	Cell signaling (#9101)
anti-Erk 1/2	Cell signaling (#9102)
Anti-Fgf21	Abcam (ab64857)
anti-Ucp1	Abcam (ab10983)
Monoclonal anti-β-actin	Sigma-Aldrich (A5441)

Supplementary Figure S1. Empagliflozin increased urine glucose excretion in HFD-fed mice. (A) Daily food and (B) water intake of mice in the study. (C) Urine volume and (D) urine glucose excretion rates of mice in the study. N.D., no data. Data are presented as means ± SEM, n = 7–8. * and ** indicate P <0.05 and 0.01, respectively, for comparisons with NC-fed mice; # and ## indicate P <0.05 and 0.01, respectively, for comparisons with HFD-fed mice.

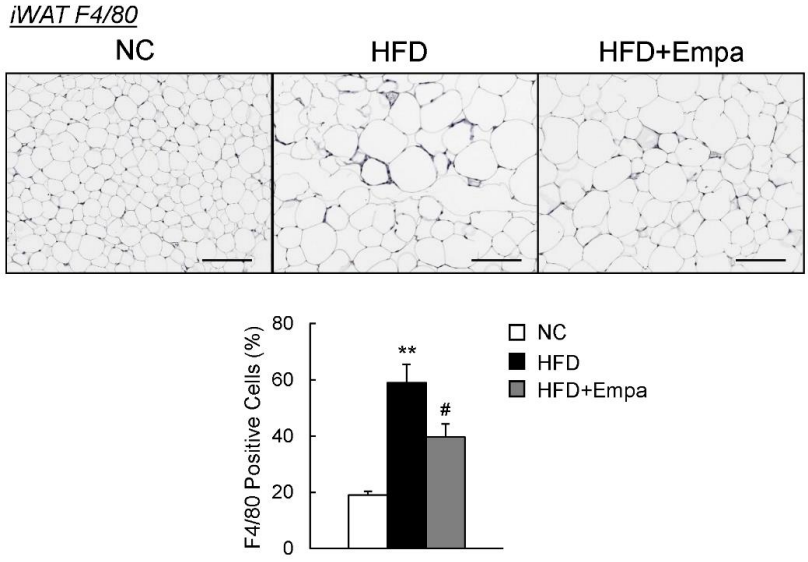


Supplementary Figure S2. Empagliflozin increased hepatic FGF21 expression and attenuated HFD-induced oxidative stress in mice. (A) Immunoblots of FGF21 in the liver. (B) Levels of NADPH oxidase complex mRNAs in the eWAT. (C) Levels of antioxidative stress-related gene mRNAs in the eWAT. (D) Levels of NADPH oxidase complex mRNAs in the liver. (E) Levels of antioxidative stress-related gene mRNAs in the liver. Data are presented as means ± SEM, n = 7–8. * and ** indicate P <0.05 and

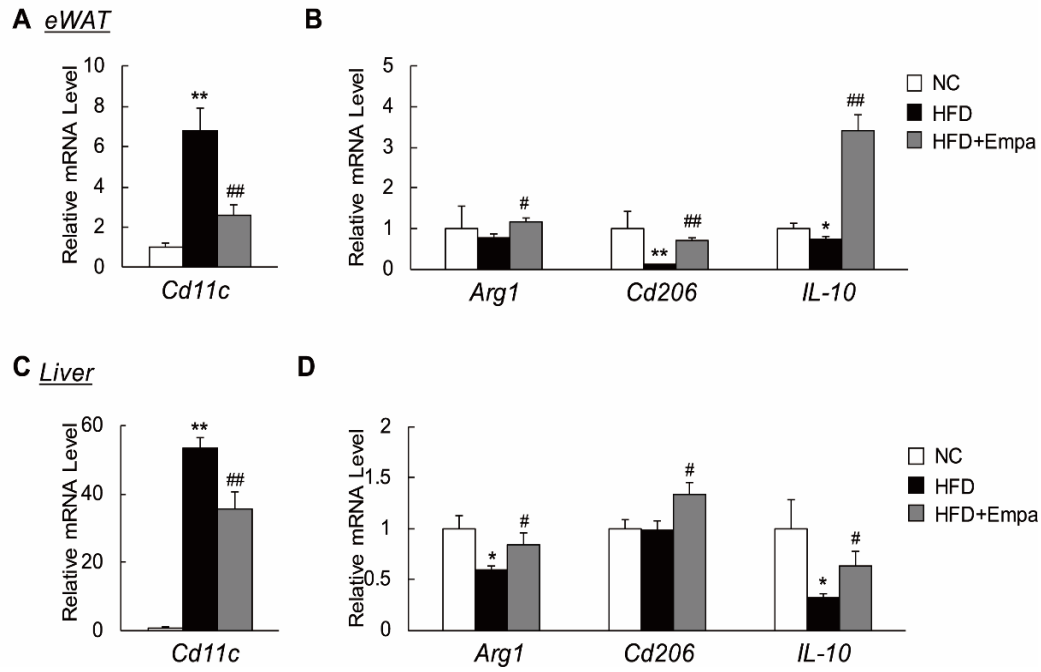
0.01, respectively, for comparisons with NC-fed mice; # and ## indicate *P* <0.05 and 0.01, respectively, for comparisons with HFD-fed mice.



Supplementary Figure S3. Empagliflozin decreased F4/80^{+} cell abundance in the iWAT of DIO mice. F4/80 immunostaining in the iWAT. Scale bars = 100 μm. ** indicate P <0.01 for comparisons with NC-fed mice; # indicate P <0.05 for comparisons with HFD-fed mice.



Supplementary Figure S4. Empagliflozin decreased M1 marker expression and increased M2 marker expression in the eWAT and liver. (A) Expression of M1 marker (*Cd11c*) mRNA in the eWAT. (B) Expression of M2 marker (*Arg1*, *Cd206*, and *IL-10*) mRNAs in the eWAT. (C) Expression *Cd11c* mRNA in the liver. (D) Expression of *Arg1*, *Cd206*, and *IL-10* mRNAs in the liver. Data are presented as means ± SEM, n= 7–8. * and ** indicate P <0.05 and 0.01, respectively, for comparisons with NC-fed mice; # and ## indicate P <0.05 and 0.01, respectively, for comparisons with HFD-fed mice.



Supplementary Figure S5. Empagliflozin decreased CD3⁺, CD4⁺, and CD8⁺ T cell abundance in the eWAT and liver. (A) Representative plots of $CD3^+$ T cells in the eWAT. (B) $CD3^+$, $CD8^+$, and $CD4^+$ T cell abundance in the eWAT. (C) Representative plots of $CD3^+$ T cells in the liver. (D) $CD3^+$, $CD8^+$, and $CD4^+$ T cell abundance in the liver. Data are presented as means ± SEM, n=7–8. * and ** indicate P <0.05 and 0.01, respectively, for comparisons with NC-fed mice; # and ## indicate P <0.05 and 0.01,

respectively, for comparisons with HFD-fed mice.