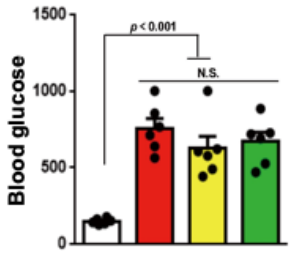
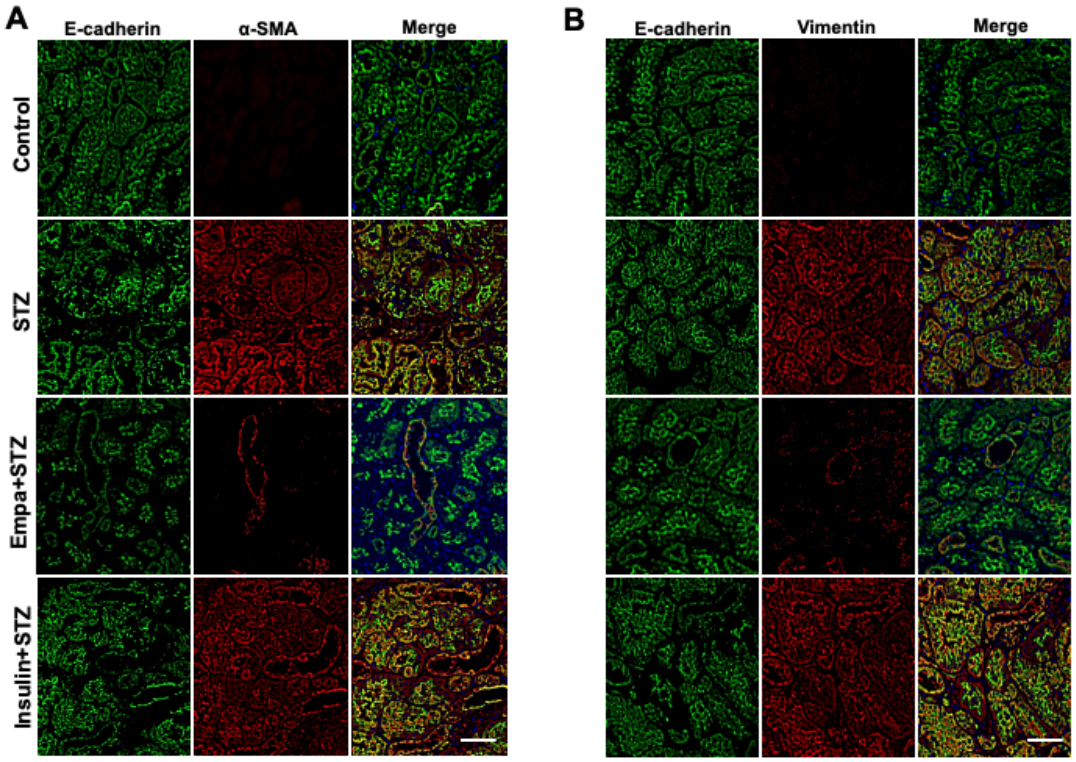
Fig. S 1



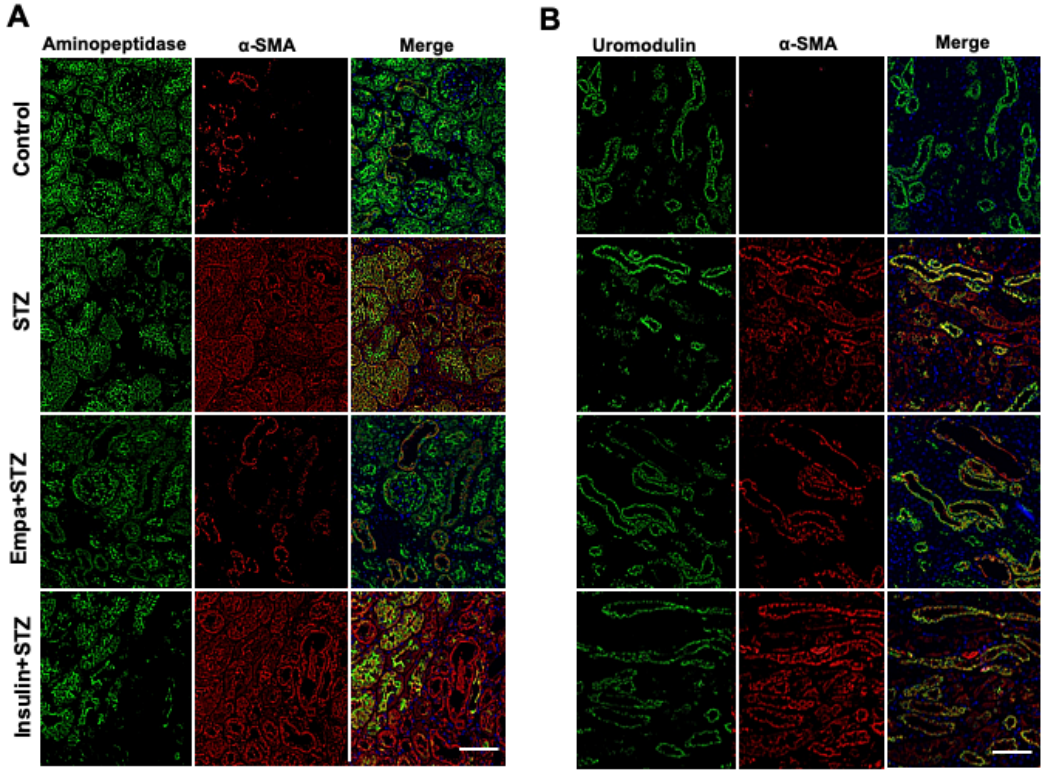
Supplementary Fig 1. Short-term intervention of empagliflozin failed to alter the blood glucose. For each group **N=6**.

Fig. S 2

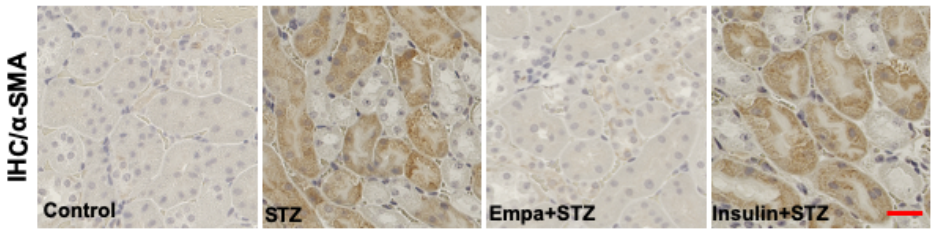


Supplementary Fig 2 Each color images of Figure 2.

Fig. S 3

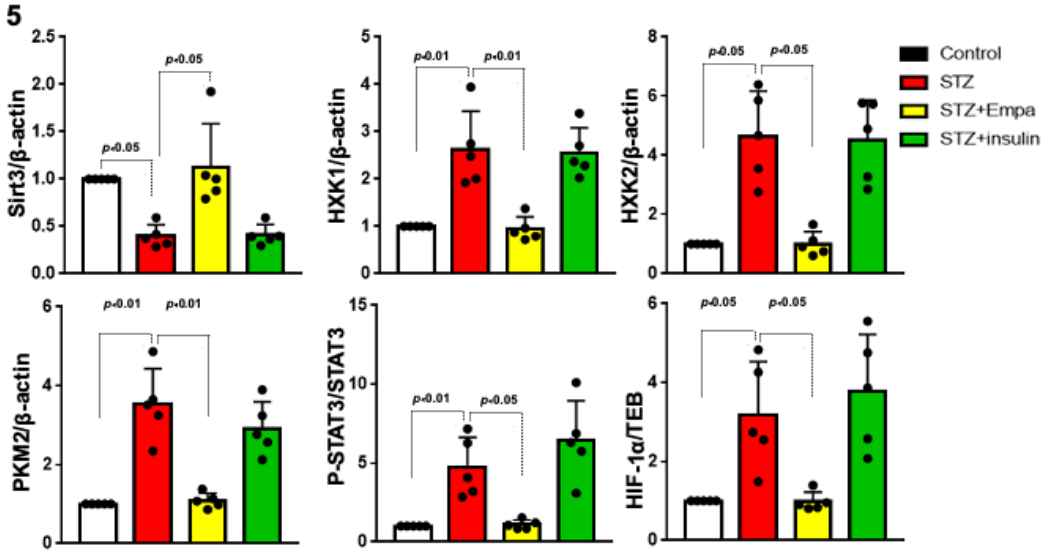


Supplementary Fig 3. Each color images of Figure 2.

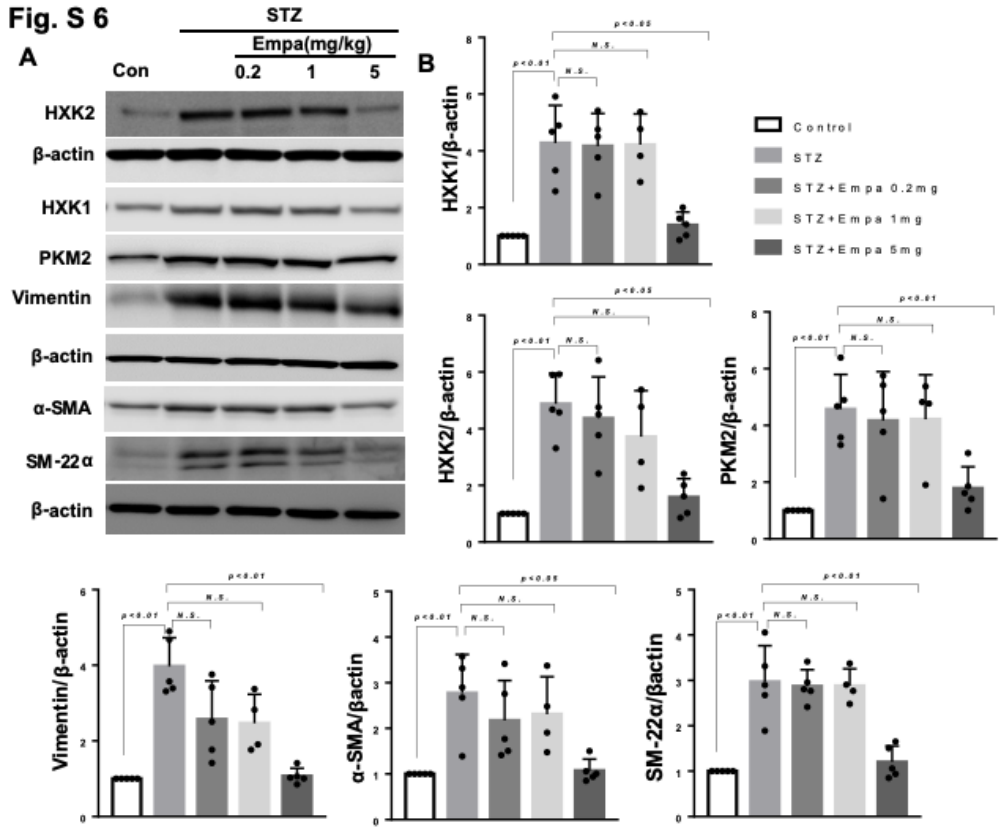


Supplementary Fig 4. Immunohistochemical analysis for α-SMA. Deparaffinized sections were analyzed from each group of mice. N=5. Scale bar: 60 μm.

Fig. S 5

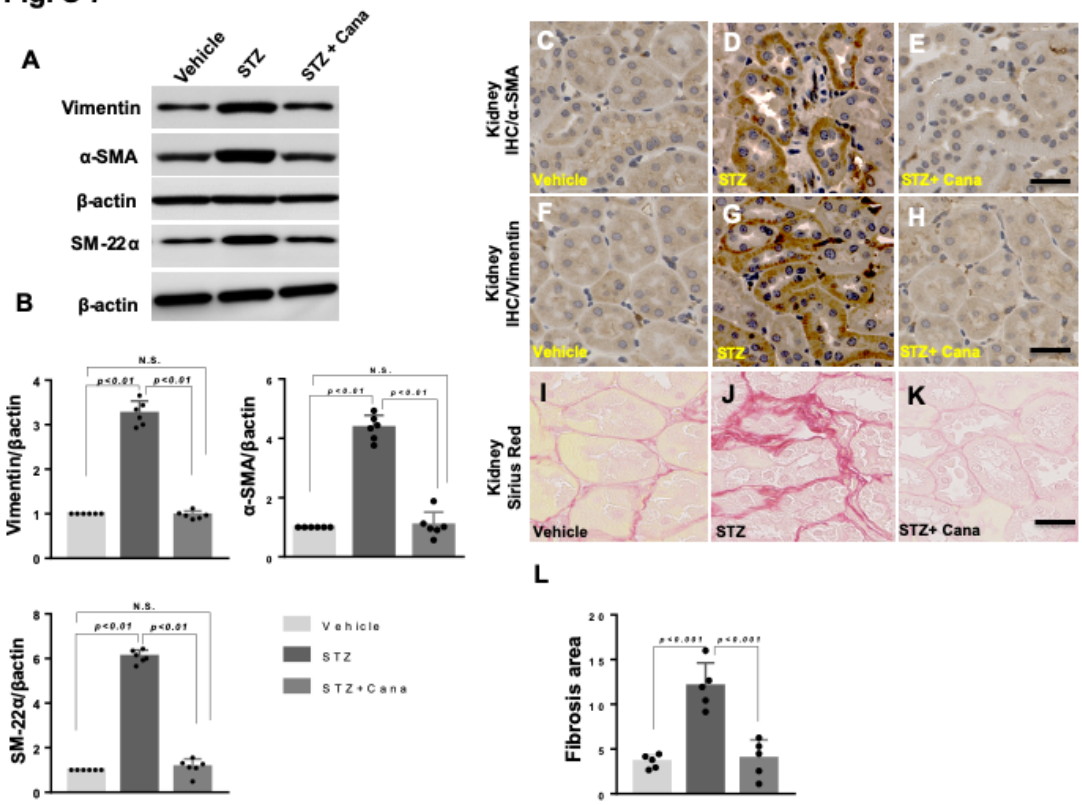


Supplementary Fig 5. Quantification of the western blotting images from Fig 4. Representative western blots analysis data for Sirt3, P-STAT3 and aberrant glycolysis-associated molecules from five independent experiments. Densitometric analysis of the indicated molecules. The data are expressed as the mean ± s.e.m in the graph. One-way analysis of variance followed by Tukey's multiple comparison test was used to determine significance, which was defined as $P<0.05$. Empagliflozin was designated as Empa in the figure.

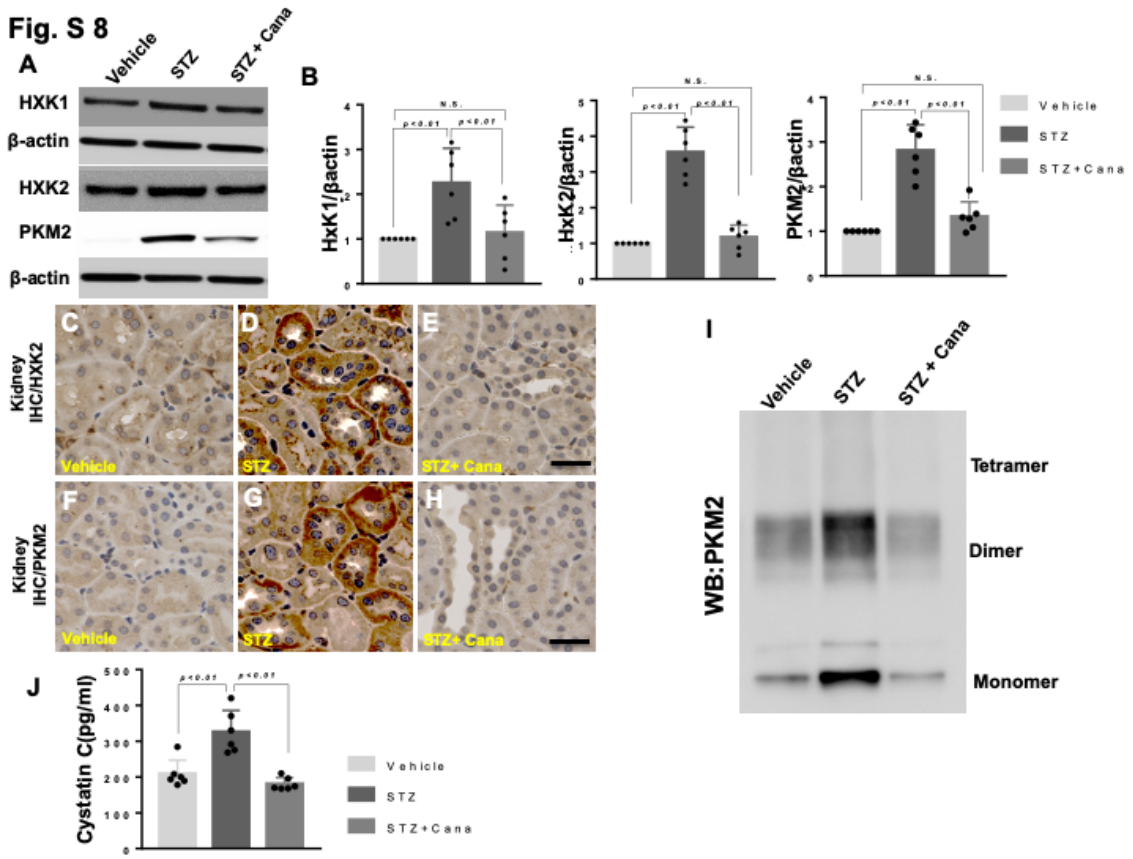


Supplementary Fig 6: Empagliflozin suppressed the kidney fibrosis on dose-dependent in diabetic CD-1 mice. (A, B) Western blotting analysis of the mesenchymal and glycolysis markers in the kidney tissues**.** Densitometric analysis of the indicated molecules. N=5. The data are expressed as the mean ± s.e.m. β-actin from same gel are shown under the corresponding blots as loading control. One-way analysis of variance followed by Tukey's multiple comparison test was used to determine significance, which was defined as $P<0.05$. Empagliflozin was designated as Empa in the Figure.

Fig. S 7

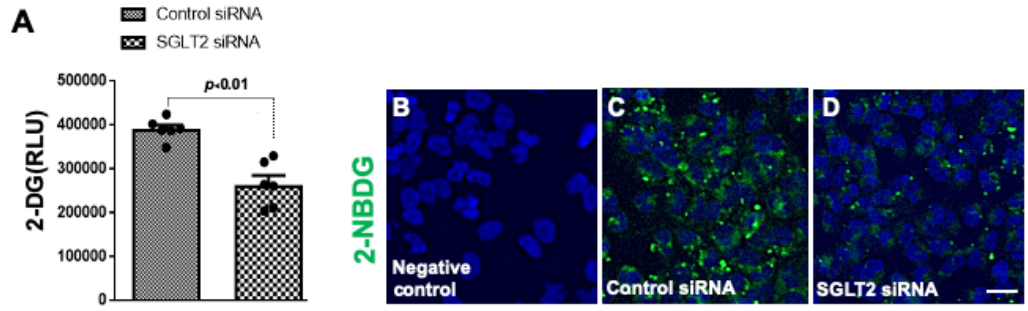


Supplementary Fig 7: Canagliflozin suppressed the kidney fibrosis associated with inhibition of the EMT program in diabetic kidney. **(A, B)** western blotting analysis of the mesenchymal markers in kidney samples**.** β-actin from same gel are shown under the corresponding blots as loading control. Densitometric analysis of the indicated molecules. N=5. **(C-H)** Immunohistochemical analysis for α-SMA and vimentin. Deparaffinized sections were analyzed from each group of mice. N=5. Scale bar: 50 µm. Representative data are shown. Higher magnification (x300) **(I-K)** images of Sirius Red staining for fibrosis, scale bar 60 µm. **(L)** Relative fibrosis areas were calculated using the ImageJ software. Five independent high magnification images of the staining were analyzed. N=5. The data are expressed as the mean ± s.e.m. One-way analysis of variance followed by Tukey's multiple comparison test was used to determine significance, which was defined as $P<0.05$. Empagliflozin was designated as Empa in the Figure.

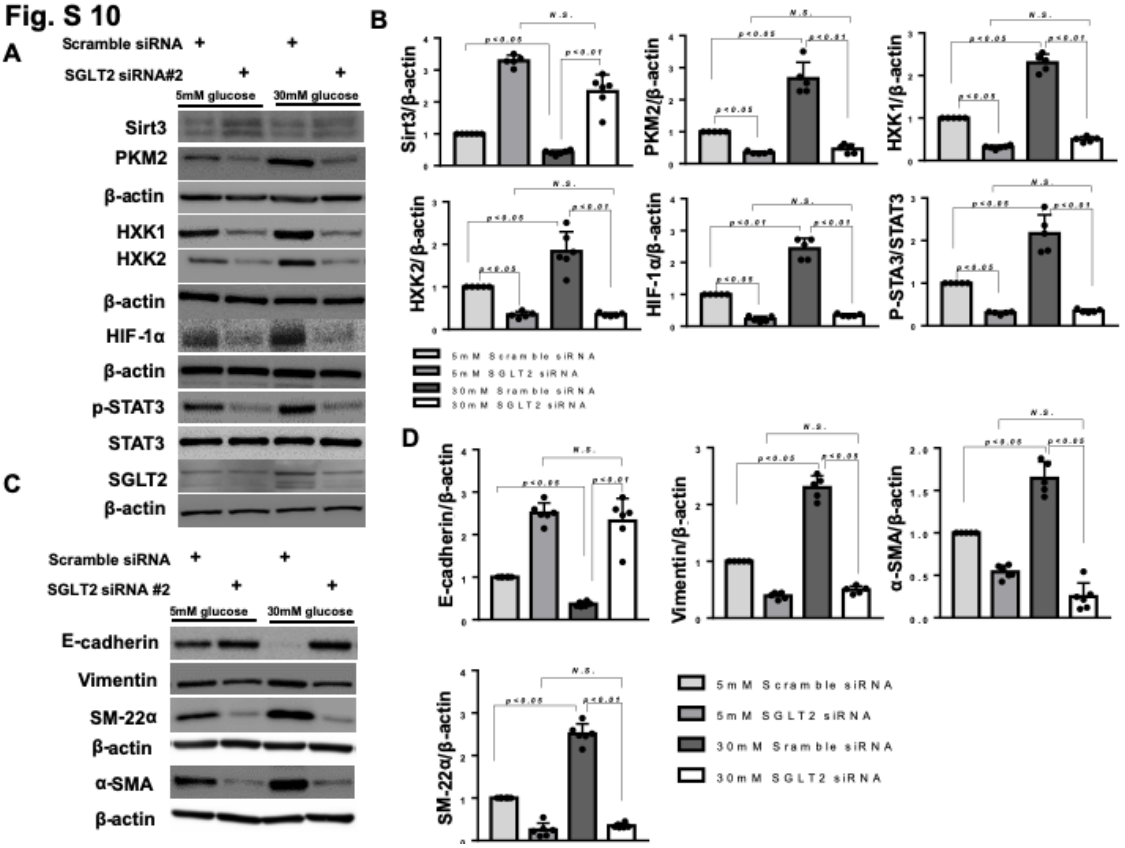


Supplementary Fig 8: Canagliflozin inhibited aberrant glycolysis in the diabetic kidney. (A, B) western blotting analysis of the glycolysis markers in the kidney samples**.** Densitometric analysis of the indicated molecules. β-actin from same gel are shown under the corresponding blots as loading control. N=5. **(C-H)** Immunohistochemical analysis for HXK2 and PKM2. Deparaffinized sections were analyzed from each group of mice. N=5. Scale bar: 40 μm. **(I)** Chemical crosslinking analysis of PKM2. Kidney lysates were treated with glutaraldehyde and separated in gels. Representative analysis from five independent experiments is shown. **(J)** plasma cystatin C was shown, N=6. The data are expressed as the mean ± s.e.m in the graph. One-way analysis of variance followed by Tukey's multiple comparison test was used to determine significance, which was defined as $P<0.05$. Empagliflozin was designated as Empa in the Figure.

Fig. S 9

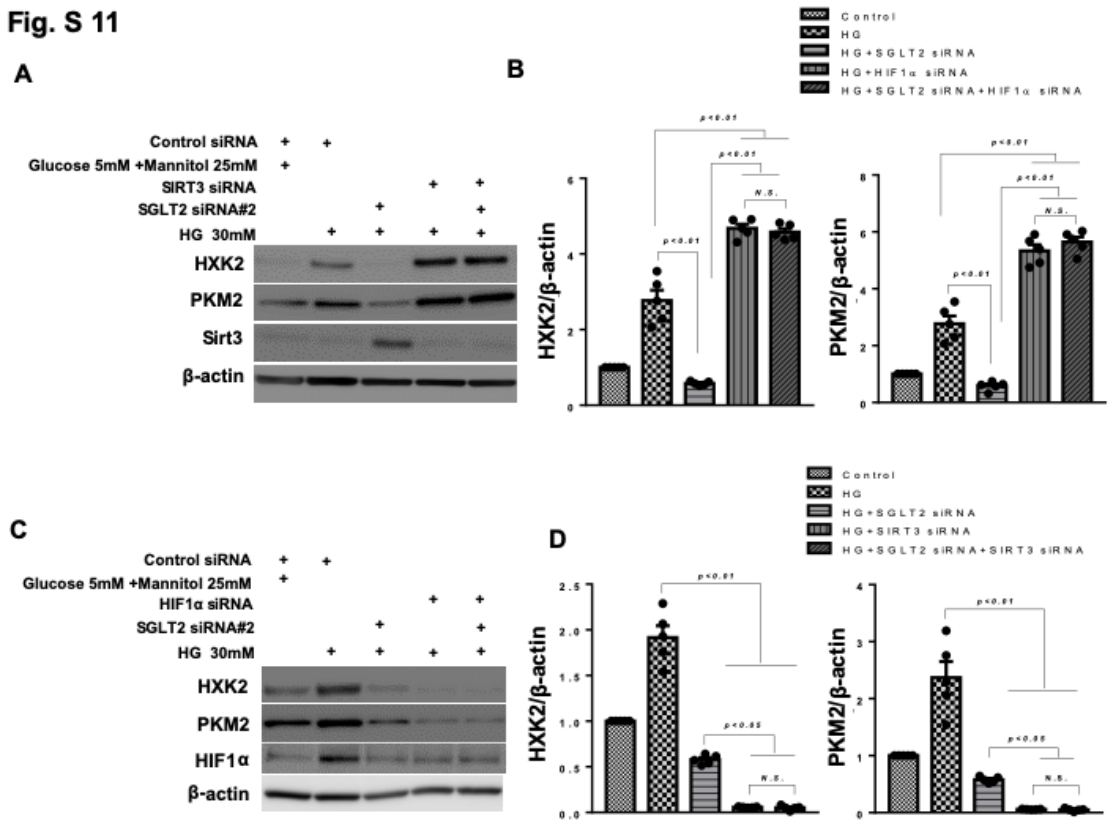


Supplementary Fig 9. SGLT2 knockdown decreased the glucose uptake in HK2 cells.
The HK2 cells were transfected by SGLT2 or scramble siRNA for 48 hour. **(A)** Elisa assay analysis of 2-DG in cultured HK2 cells. N=6. **(B-D)** Immunofluoresence analysis of 2-NBDG. For each slide, images of six different fields of view were evaluated. The scale bar is 50 μm in each panel.

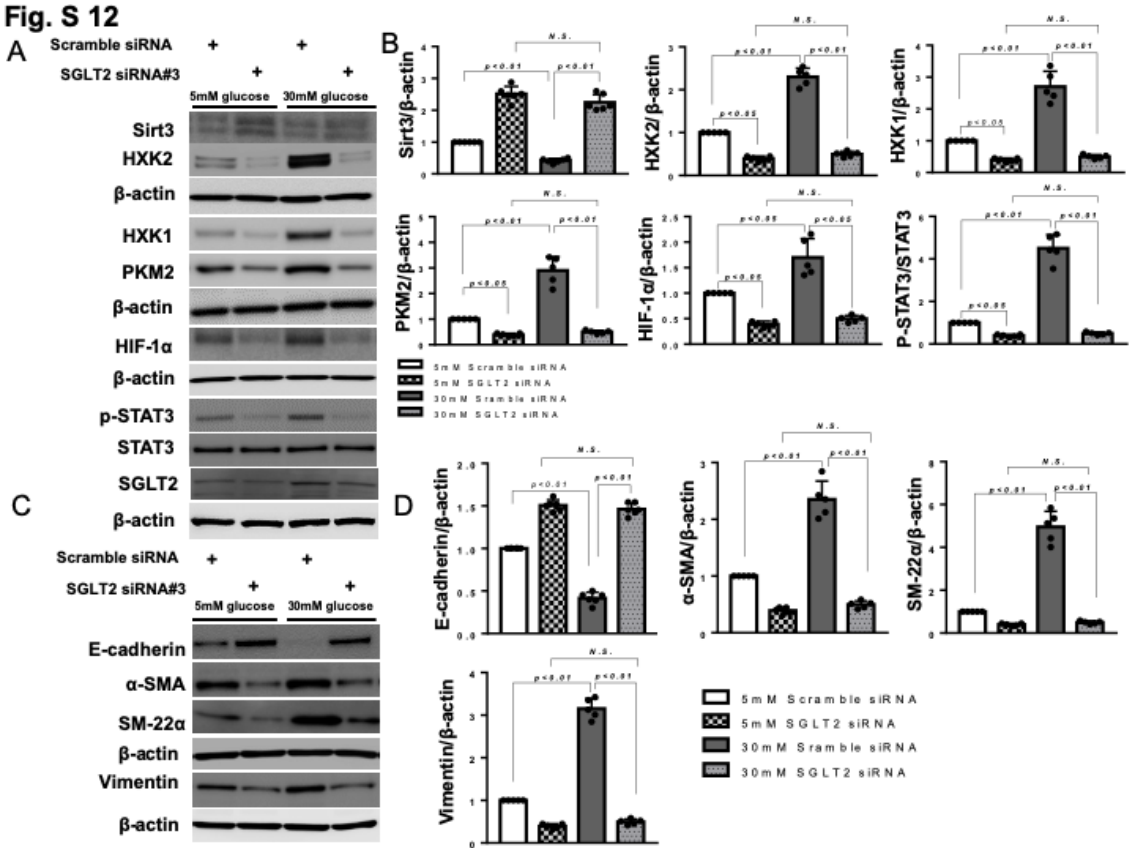


Supplementary Fig 10: SGLT2 siRNA#2 protected HK2 cells against high glucose-induced EMT associated with suppression of aberrant glycolysis. (A) Representative western blotting analysis data for Sirt3, P-STAT3 and the molecules relevant for aberrant glycolysis from five independent experiments. β-actin from same gel are shown under the corresponding blots as loading control. T-STAT3 was analyzed in different gels using same samples as P-STAT3. **(B)** Densitometric analysis of the indicated molecules. N=5. **(C)** Representative western blot analysis data for the EMT from five independent experiments. β-actin from same gel are shown under the corresponding blots as loading control except for E-cadherin for which β-actin was run in different gel using same samples.. **(D)** Densitometric analyses of the indicated molecules. N=5. The data are expressed as the mean ± s.e.m in the graph. One-way analysis of variance followed by Tukey's multiple comparison test was used to determine significance, which was defined as $P<0.05$.

Fig. S 11

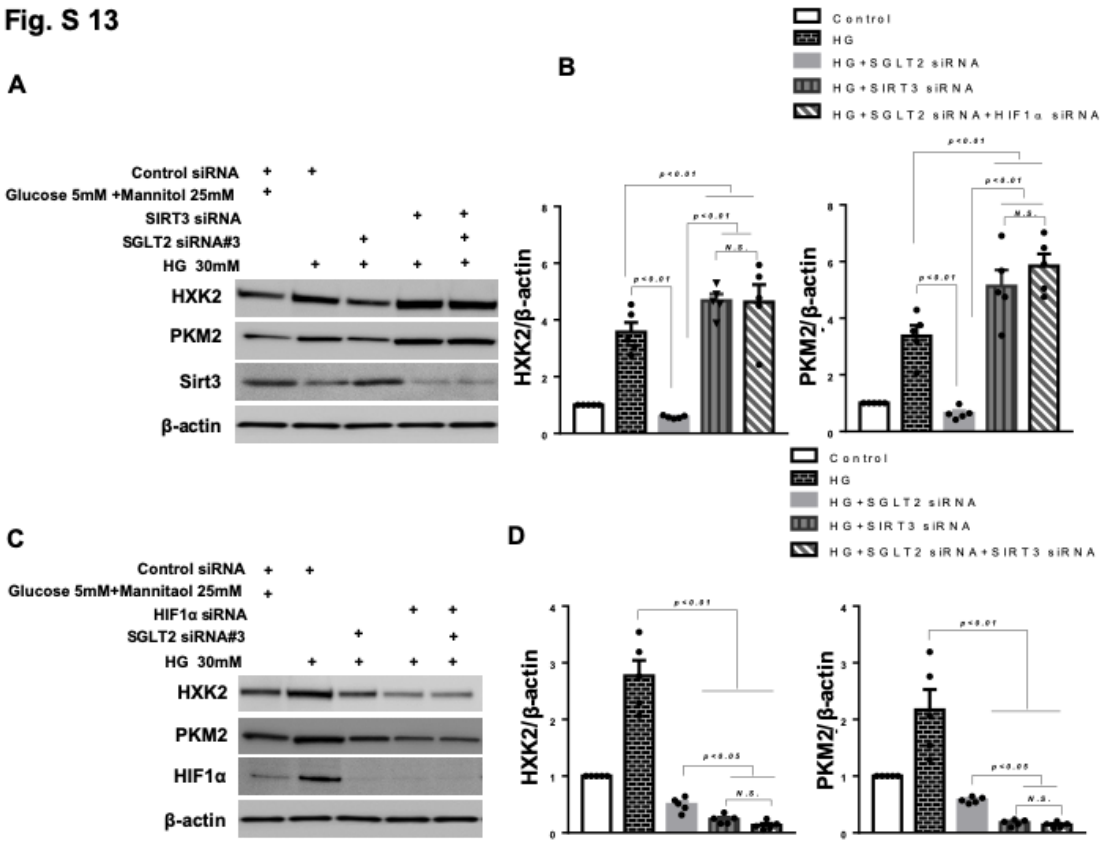


Supplementary Fig 11. SGLT2 siRNA#2 suppressed the aberrant glycolysis depended on SIRT3 pathway. The SGLT2 siRNA**#2** with or without Sirt3 or HIF1α siRNA were transfected into HK2 cells, after 6 hours, changed the fresh medium with high glucose incubation for 48 hours. (**A-D)** Western blotting analysis of glycolysis markers. Representative analysis from five independent experiments is shown. β-actin from same gel are shown under the corresponding blots as loading control. The data were normalized to β-actin and are shown as the mean ± s.e.m. One-way analysis of variance followed by Tukey's multiple comparison test was used to determine significance, which was defined as $P<0.05$.



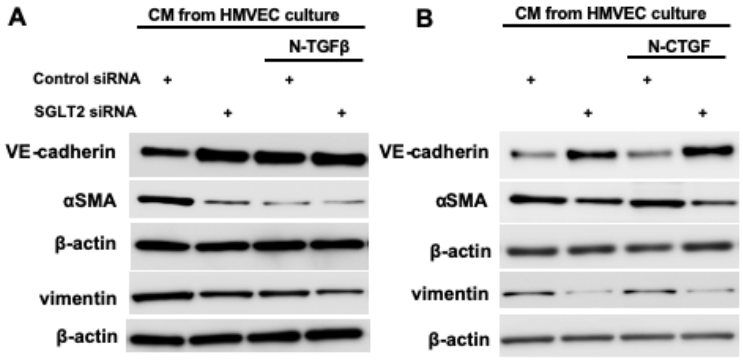
Supplementary Fig 12: SGLT2 siRNA#3 protected HK2 cells against high glucose-induced EMT associated with suppression of aberrant glycolysis. (A) Representative western blotting analysis data for Sirt3, P-STAT3 and the molecules relevant for aberrant glycolysis from five independent experiments. β-actin from same gel are shown under the corresponding blots as loading control. **(B)** Densitometric analysis of the indicated molecules. N=5. **(C)** Representative western blot analysis data for the EMT from five independent experiments. β-actin from same gel are shown under the corresponding blots as loading control. (**D)** Densitometric analyses of the indicated molecules. N=5. The data are expressed as the mean ± s.e.m in the graph. One-way analysis of variance followed by Tukey's multiple comparison test was used to determine significance, which was defined as $P<0.05$.

Fig. S 13



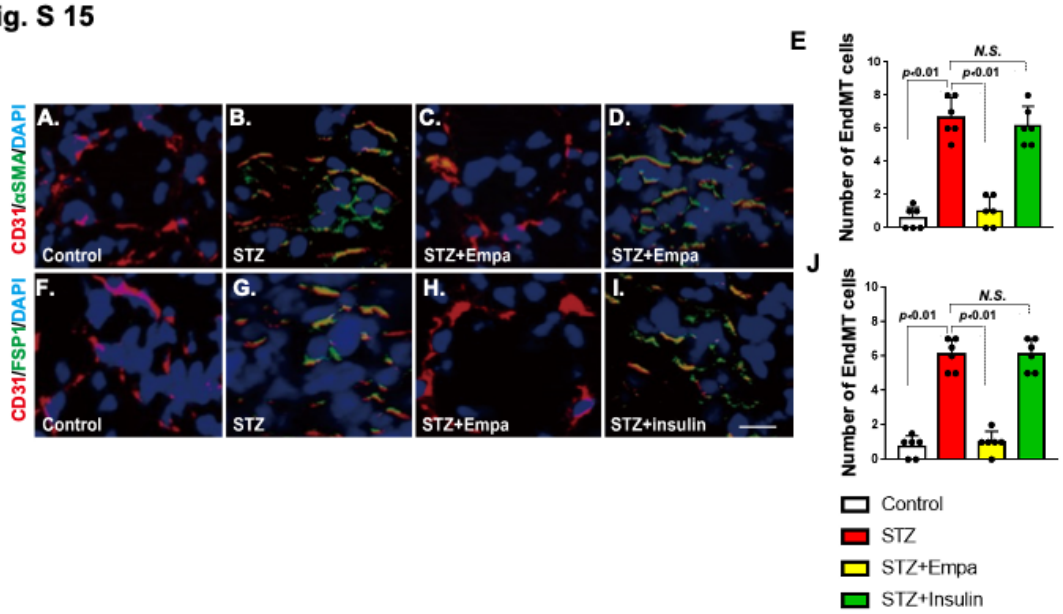
Supplementary Fig 13. SGLT2 siRNA#3 suppressed the aberrant glycolysis depended on SIRT3 pathway. The SGLT2 siRNA**#3** with or without Sirt3 or HIF1α siRNA were transfected into HK2 cells, after 6 hours, changed the fresh medium with high glucose incubation for 48 hours. **(A-D)** Western blotting analysis of glycolysis markers. Representative analysis from five independent experiments is shown. β-actin from same gel are shown under the corresponding blots as loading control. The data were normalized to β-actin and are shown as the mean ± s.e.m. One-way analysis of variance followed by Tukey's multiple comparison test was used to determine significance, which was defined as $P<0.05$.

Fig. S 14



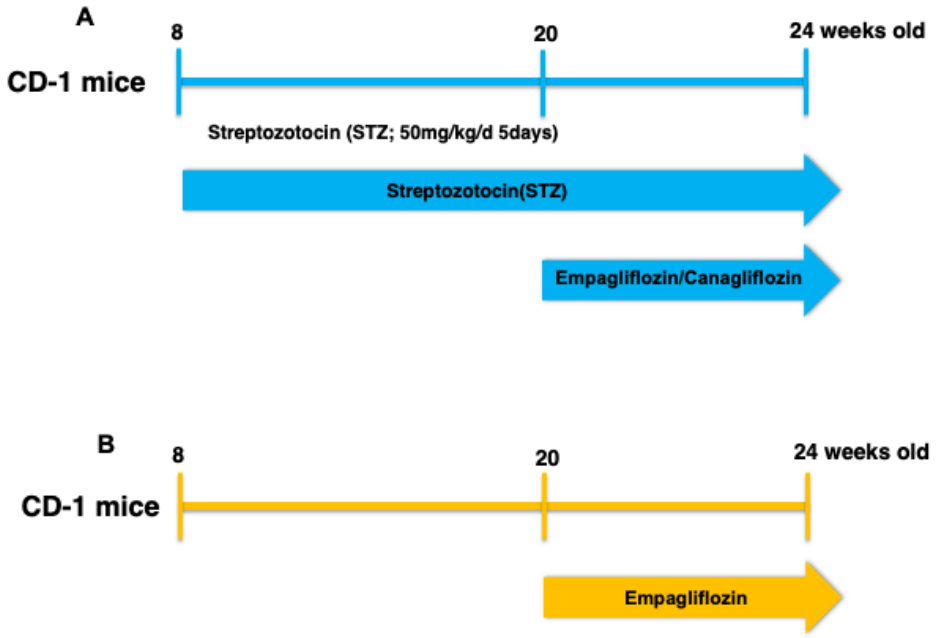
Supplementary Fig 14. The conditioned medium from EMT induction led to EndMT depended on TGFβ pathway. Design of the conditioned media (CM) experiment. The HK2 cells were transfected by SGLT2 or scramble siRNA. After 48 hours, HMVECs was incubated into CM with or without neutralizing TGFβ or CTGF antibody treatment. (**A, B)** Western blot analysis of VE-cadherin, αSMA and vimentin. β-actin from same gel are shown under the corresponding blots as loading control.

Fig. S 15



Supplementary Fig 15. Empagliflozin suppressed the EndMT induction in diabetic kidney. **(A-J)** EndMT analysis. CD31 and αSMA double-positive (**A-D**) and CD31 and FSP1 double-positive (**F-I**) cells were recognized as the cells undergoing the EndMT. (**E, J**) The cells undergoing the EndMT were counted and quantified in 6 different fields in each sample for 5 mice from each group. Scale bar: 50um. Empagliflozin was designated as Empa in the figure

Fig. S 16



Supplementary Fig 16. Scheme of animal experiments. A. CD-1 Diabetic mice were respective treated with (empagliflozin [0.2, 1, 5 mg/kg BW/day], canagliflozin [30 mg/kg BW/day], placebo [methylcellulose], or insulin pellets) for one month. B. CD-1 control mice were treated with empagliflozin (5 mg/kg BW/day) for one month.