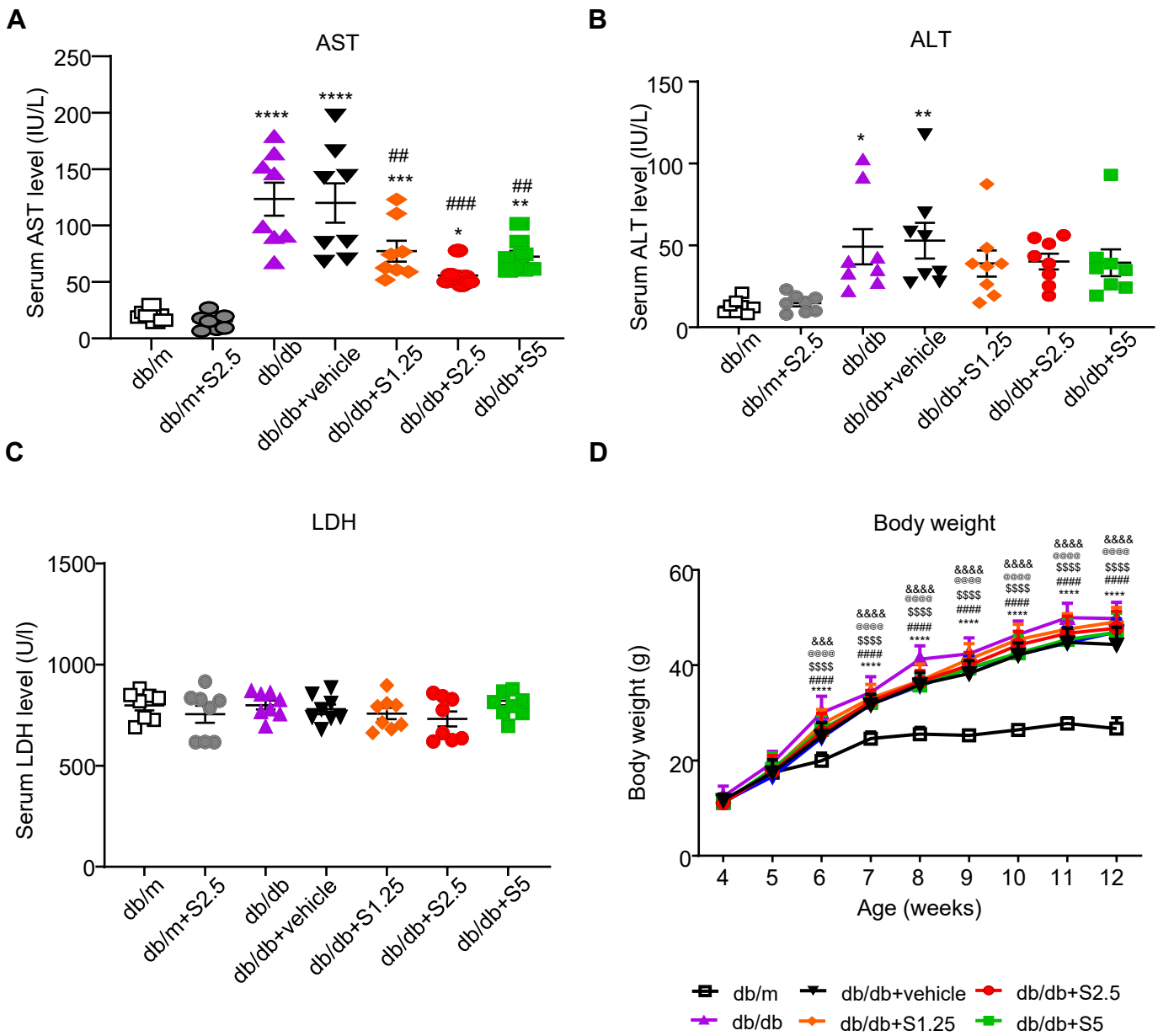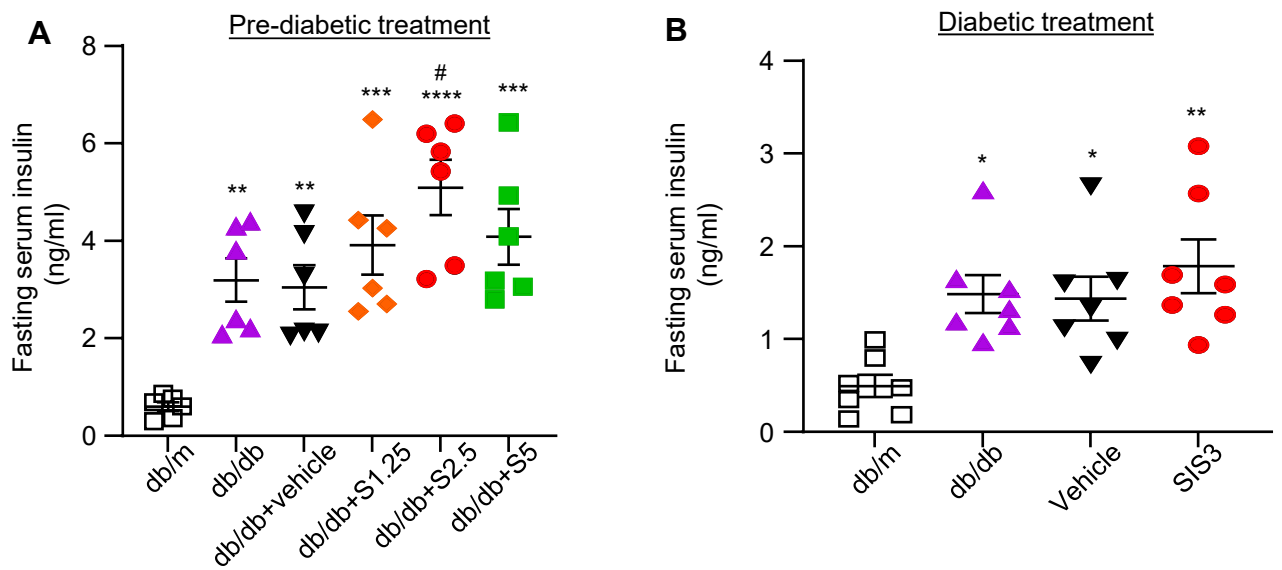Supplementary Figure S1. Prediabetic treatment of db/db mice with SIS3 from the age of 4 weeks to 12 weeks in a dose-dependent manner shows no systemic toxicity in db/db mice. (A-C) The serum levels of AST, ALT, and LDH in db/m and db/db mice received 8 weeks of SIS3 treatment (weeks 4-12); *$P<0.05$, **$P<0.01$, ***$P<0.001$, ****$P<0.0001$ versus normal db/m mice; ##$P<0.01$, ###$P<0.001$ compared with the control-treated db/db mice (vehicle). (D) Effect of SIS3 treatment on body weight. ####$P<0.0001$: S1.25-treated db/db mice versus normal db/m mice; ****$P<0.0001$: S2.5-treated db/db mice versus normal db/m mice; @@@@$P<0.0001$ S5-treated db/db mice versus normal db/m mice; &&&$P<0.001$, &&&&$P<0.0001$: vehicle-treated db/db mice versus normal db/m mice; $$$$$P<0.0001$ untreated db/db mice versus normal db/m mice. Data represents the mean ± SEM for at least 6 mice per group. SIS3 dosages used: S1.25=SIS3 1.25 mg/kg.bw, S2.5=SIS3 2.5 mg/kg.bw, S5=SIS3 5 mg/kg.bw.
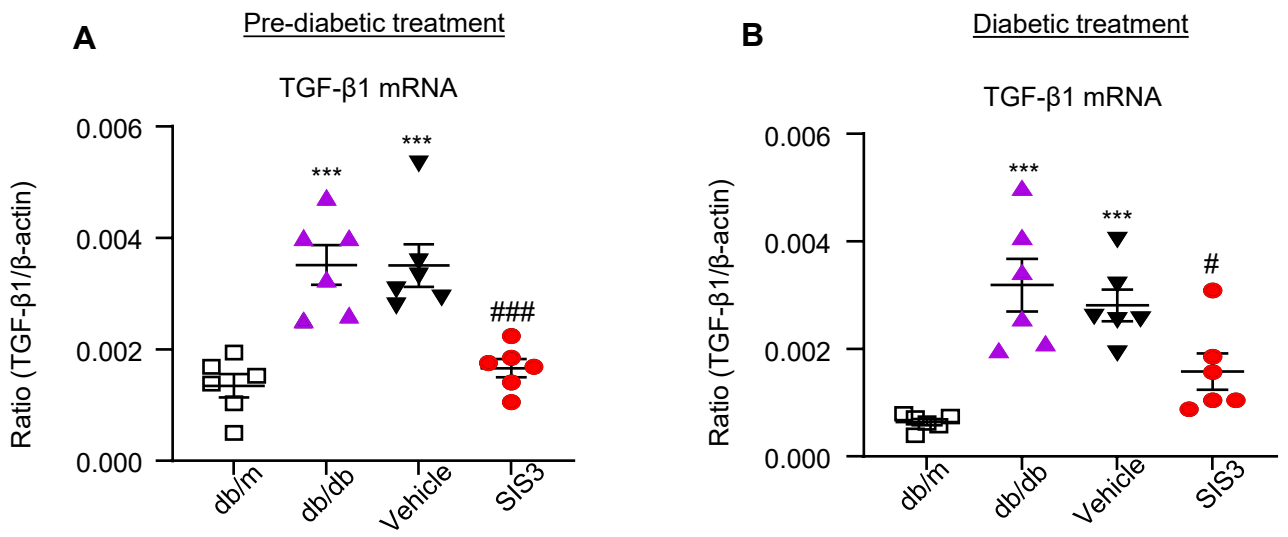
Diabetic treatment

A AST

B ALT

C LDH
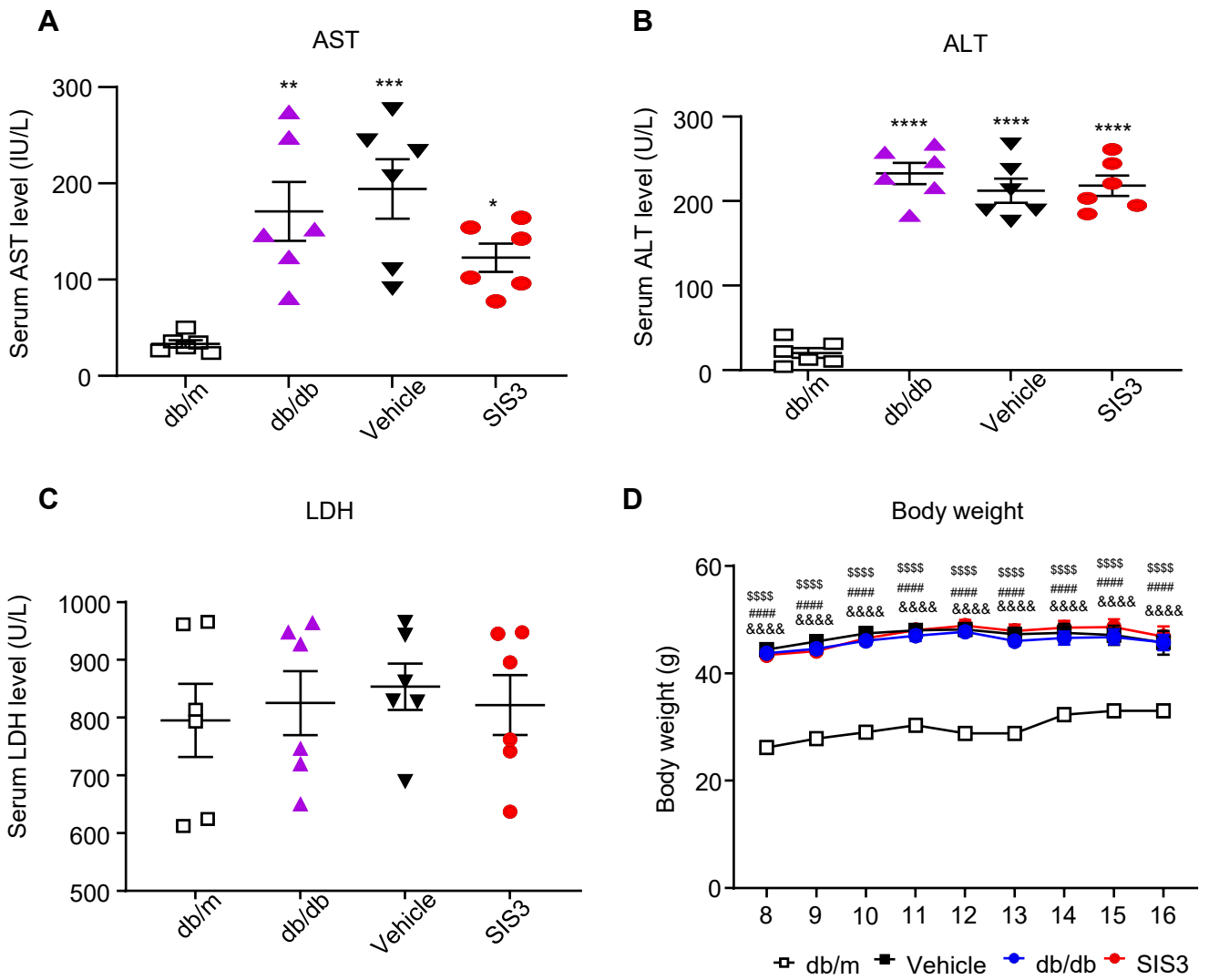
D Body weight

Supplementary Figure S2. Treatment of db/db mice aged 8 to 16 weeks with an optimal dose of 2.5 mg/kg SIS3 shows no systemic toxicity in db/db mice. (A-C) Serum ALT, AST and LDH levels at 16 weeks. $^{*}P<0.05$, $^{**}P<0.01$, $^{***}P<0.001$, $^{****}P<0.0001$ versus normal db/m mice. (D) Body weight at 16 weeks after SIS3 treatment (weeks 8-16). $^{\&\&\&\&}P<0.0001$: SIS3-treated db/db mice versus normal db/m mice. $^{####}P<0.0001$: vehicle-treated db/db mice versus normal db/m mice. $^{\$\$\$\$}P<0.0001$: untreated db/db mice versus normal db/m mice. Data represents the mean ± SEM for at least 6 mice per group. SIS3 dosages used: SIS3=SIS3 2.5 mg/kg.bw.

Supplementary Figure S3. Effect of SIS3 treatment on fasting serum insulin levels in prediabetic and diabetic db/db mice. (A) Fasting serum insulin at 12 weeks after SIS3 treatment (weeks 4-12). (B) Fasting serum insulin at 16 weeks after SIS3 treatment (weeks 8-16). Data represents the mean ± SEM for at least 6 mice per group. $^{*}P<0.05$, $^{**}P<0.01$, $^{***}P<0.001$, $^{****}P<0.0001$ versus normal db/m mice. $^{\#}P<0.05$ compared with the control-treated db/db mice (vehicle). SIS3 dosages used: S1.25=SIS3 1.25 mg/kg.bw, SIS3 or S2.5=SIS3 2.5 mg/kg.bw, S5=SIS3 5 mg/kg.bw.

A Pre-diabetic treatment

TGF-β1 mRNA

B Diabetic treatment

TGF-β1 mRNA

Supplementary Figure S4. Effect of SIS3 treatment on expression of TGF-β1 in renal tissues in prediabetic and diabetic db/db mice. (A) Real-time PCR analysis of TGF-β1 in renal tissues in db/db mice at 12 weeks after SIS3 treatment (weeks 4-12). (B) Real-time PCR analysis of TGF-β1 in renal tissues in db/db mice at 16 weeks after SIS3 treatment (weeks 8-16). Data represents the mean ± SEM for at least 6 mice per group. [***]$P<0.001$ versus normal db/m mice. [#]$P<0.05$, [###]$P<0.001$ compared with the control-treated db/db mice (vehicle). SIS3 dosages used: SIS3 =SIS3 2.5 mg/kg.bw.
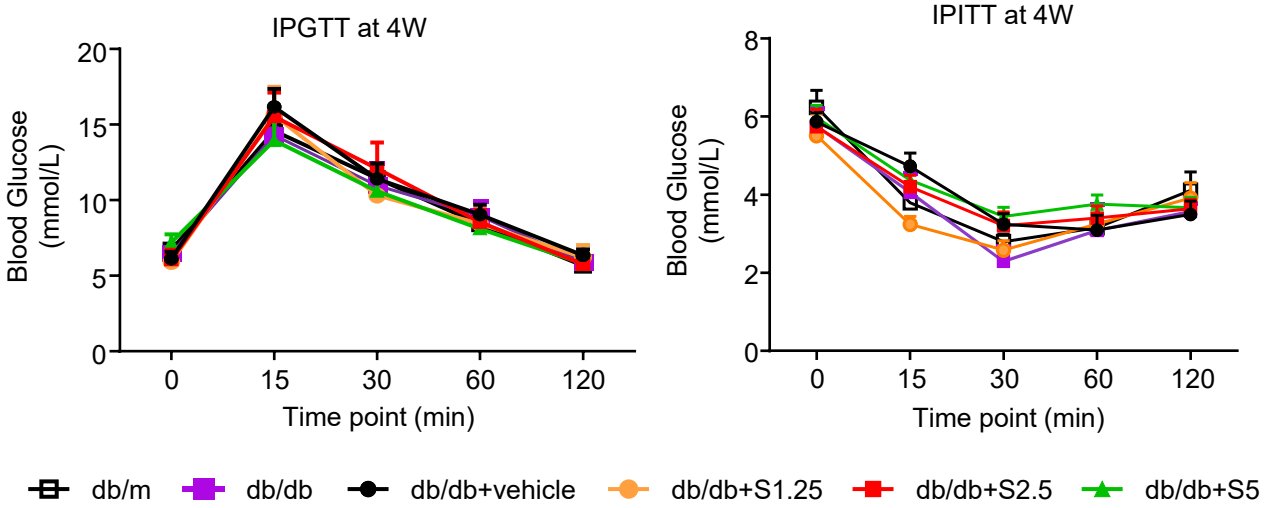
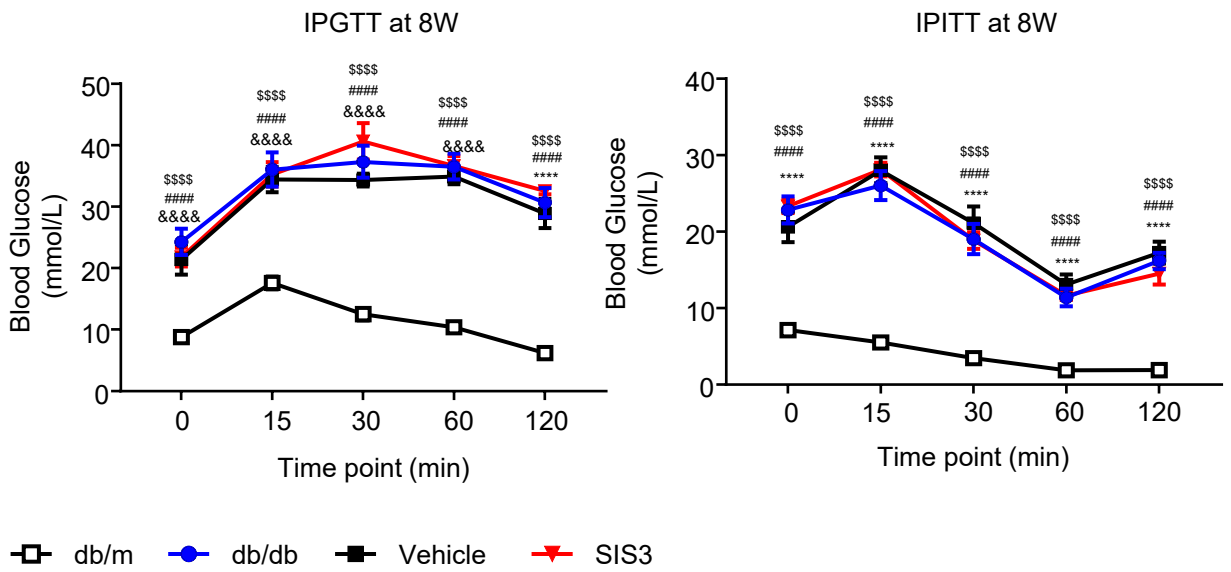**Supplementary Figure S5. Blood glucose levels during intraperitoneal glucose tolerance test (IPGTT) and intraperitoneal insulin tolerance test (IPITT) at 4 weeks or 8 weeks db/db mice.** (A) IPGTT and IPITT in db/db mice at 4 weeks. $^{****}P<0.0001$ versus normal db/m mice. (B) IPGTT and IPITT in db/db mice at 8 weeks. $^{****}P<0.0001$: SIS3-treated db/db mice versus normal db/m mice; $^{####}P<0.0001$: vehicle-treated db/db mice versus normal db/m mice; $^{\$\$\$\$}P<0.0001$: control-treated db/db mice versus normal db/m mice. Data represents the mean ± SEM for at least 6 mice per group. SIS3 dosages used: S1.25=SIS3 1.25 mg/kg.bw, SIS3 or S2.5=SIS3 2.5 mg/kg.bw, S5=SIS3 5 mg/kg.bw.
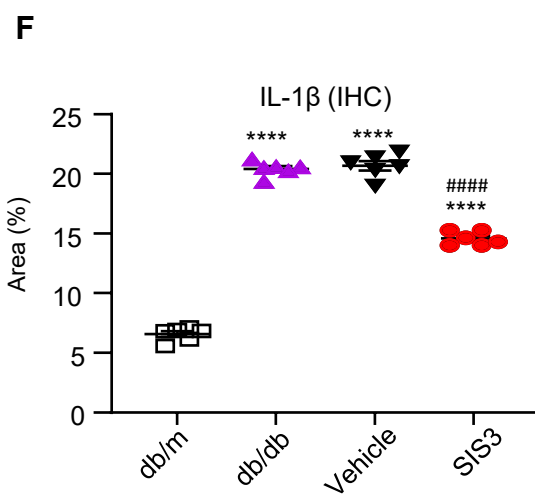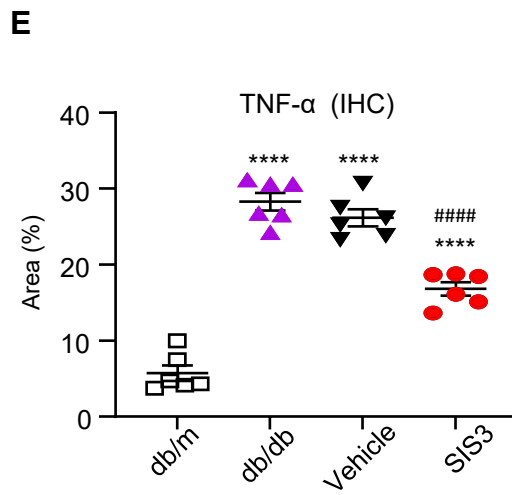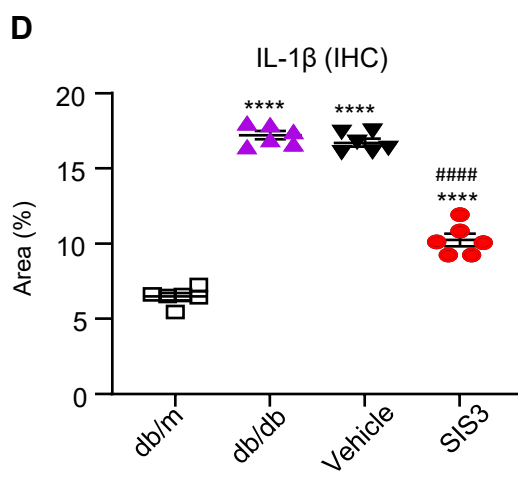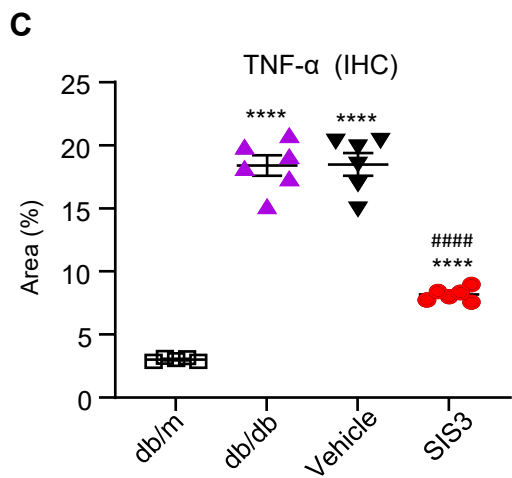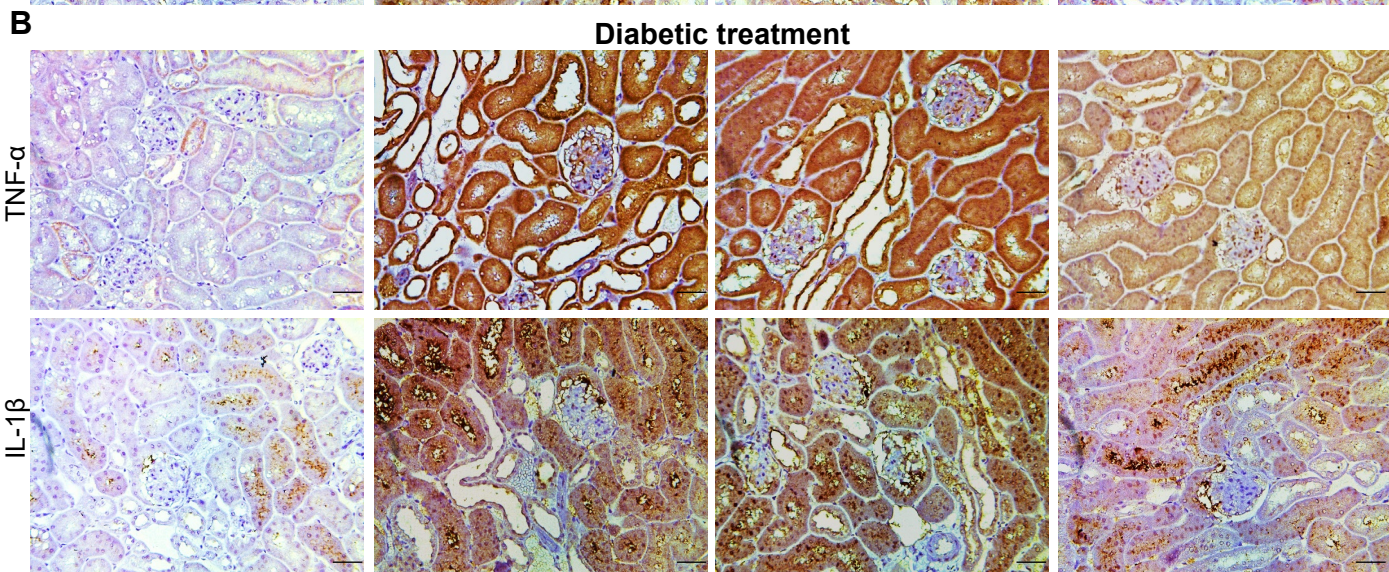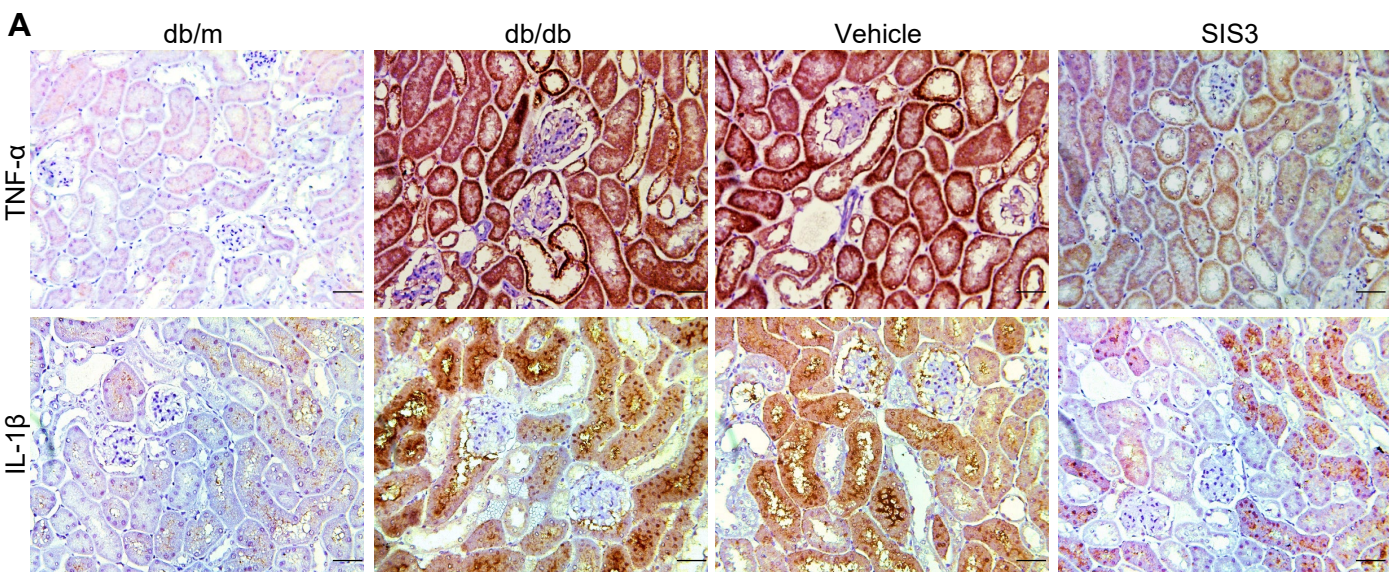
Supplementary Figure S6. Effect of prediabetic versus late diabetic treatment with SIS3 on kidney IL-1β and TNF-α expression in db/db mice. (A, C-D) Immunostaining and semi-quantitative analysis for IL-1β and TNF-α in the kidney of db/m and db/db mice at 12 weeks. (B, E-F) Immunostaining and semi-quantitative analysis for IL-1β and TNF-α in the kidney of db/m and db/db mice at 16 weeks. ****P<0.0001 versus normal db/m mice. ####P<0.0001 compared with the control-treated db/db mice (vehicle). SIS3 dosages used: SIS3 =SIS3 2.5 mg/kg.bw. Data represents the mean ± SEM for at least 5 mice per group. Scale bar, 50μm.