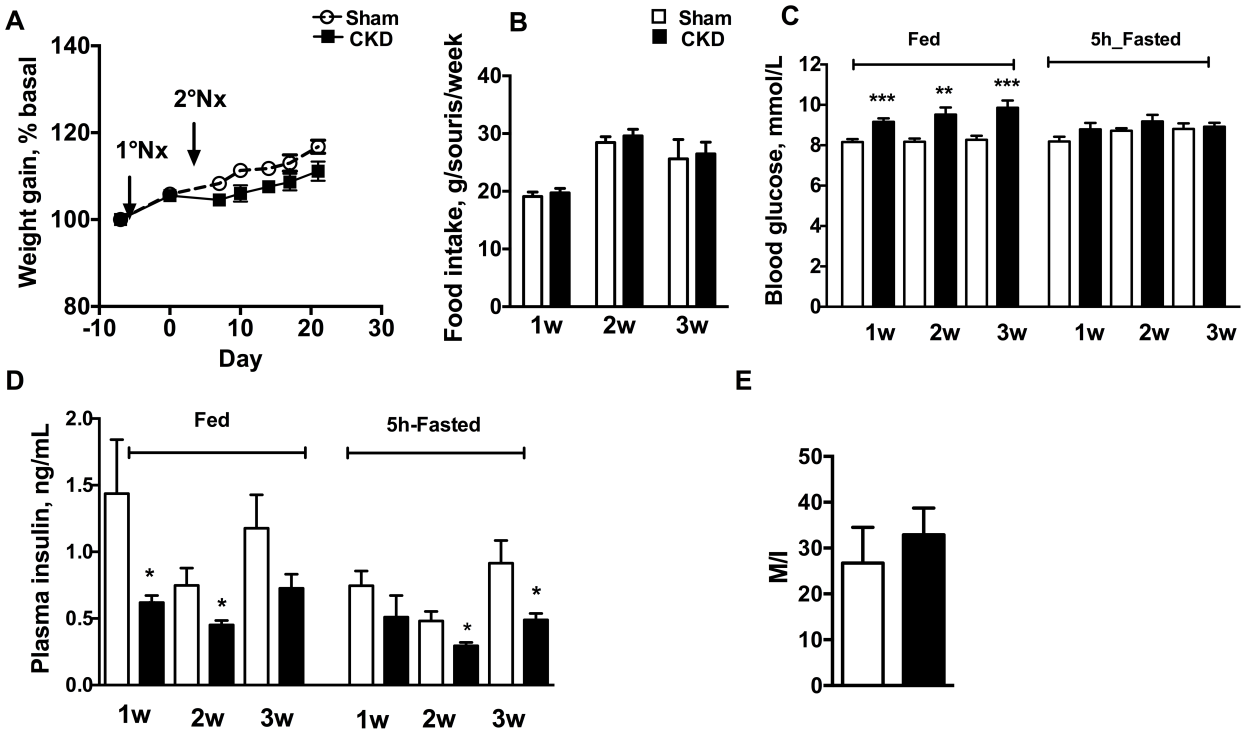

Figure S1: Body weight, food intake and metabolic parameters in sham and CKD mice (**A**) Weight gain (n=32-36). (**B**) Food intake (n=22-35). (**C**) Fed and 5h-fasting blood glucose (n=10-20) and (**D**) plasma insulin (n=5-11). (**E**) M/I index during hyperglycemic clamp (n=7). Data are mean ± S.E.M., *p<0.05, **p<0.01, ***p<0.001 vs. sham; two-way ANOVA Bonferroni post hoc test for A, B, C and D and unpaired two-tailed Student's *t* test for E.

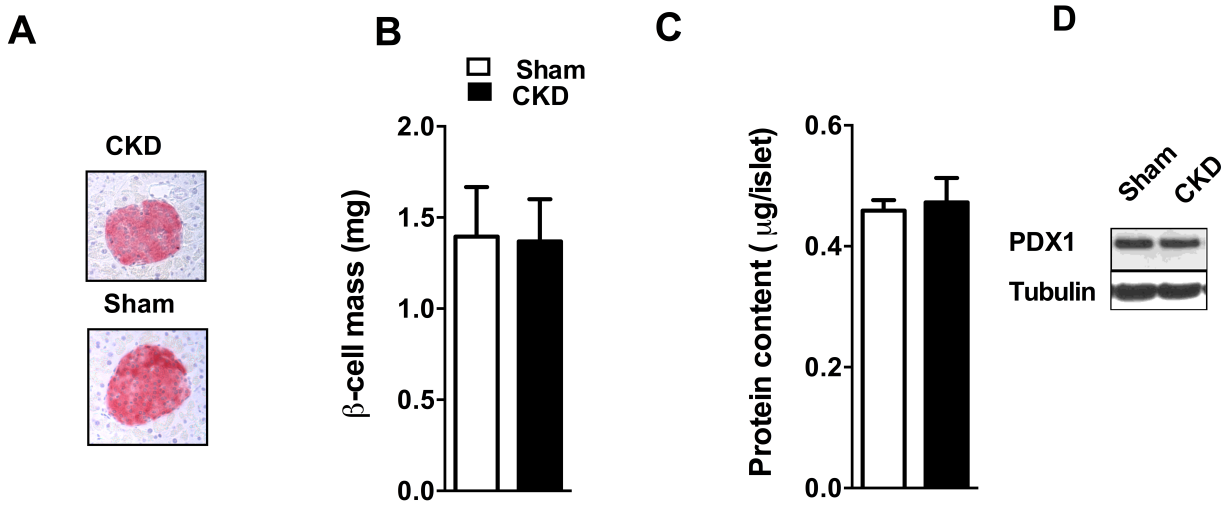

Figure S2: β-cell mass and protein content in islets from sham and CKD mice at 3 weeks post-surgery. (**A**) Representative pancreatic sections stained for insulin (**B**) β-cell mass measured in pancreatic sections by insulin immunostaining and morphometric analysis (n=3-4). (**C**) Protein content in sham and CKD islets (n=4). (**D**) Representative Western Blot for PDX-1 CKD islets (n=2). Data are mean ± S.E.M., unpaired two-tailed Student's *t* test.

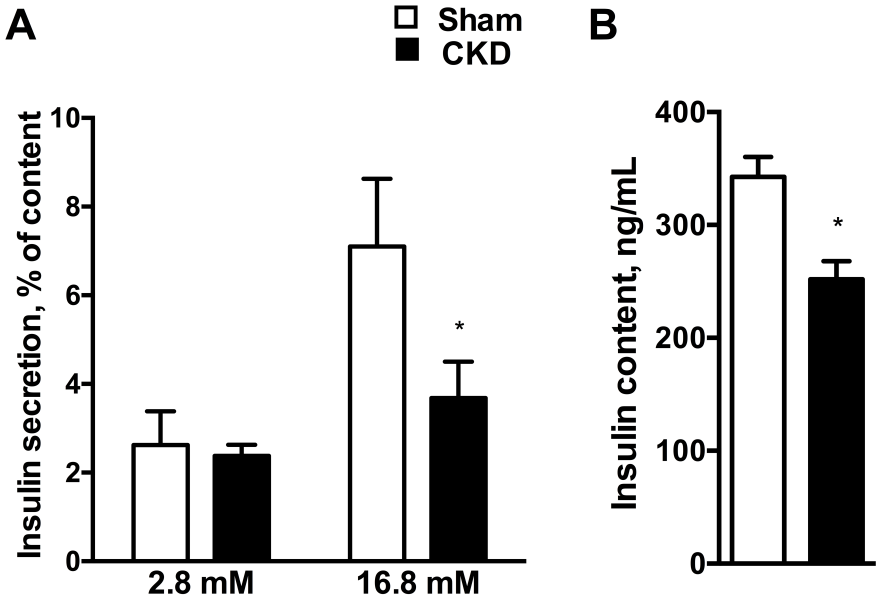

Figure S3: Insulin secretion in isolated islets from CKD and sham mice at 6 weeks post-surgery. (**A**) Insulin secretion, shown as % insulin content, was assessed in 1-h static incubations in islets isolated from CKD and sham-operated mice in response to 2.8 or 16.8 mmol/L (mM) glucose 6 weeks after surgery. (**B**) Total islet insulin content. Data are mean ± S.E.M from 4-5 mice in each group. *p<0.05 vs. control for the same incubation condition by one-way ANOVA Bonferroni post hoc test for A and Student's *t* test for B.

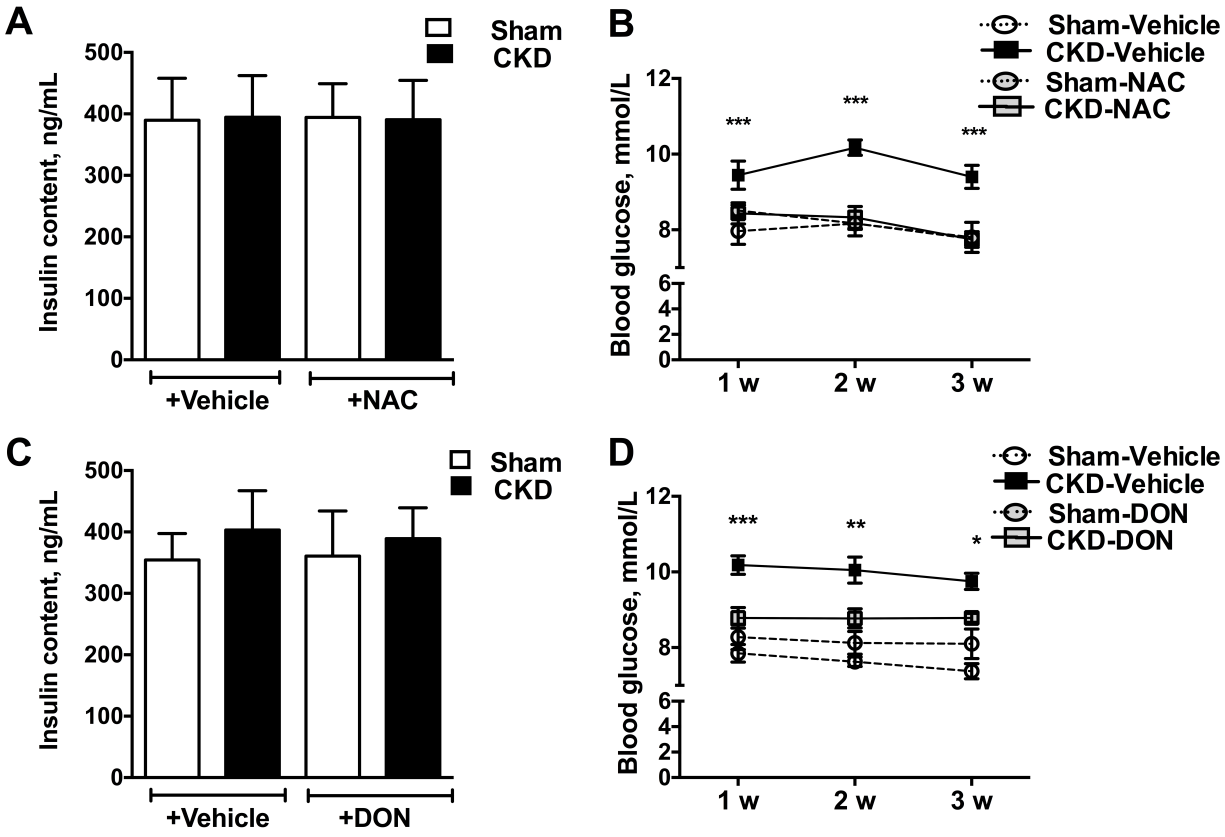

Figure S4: Islet insulin content and fed blood glucose levels in CKD and sham mice ± NAC or DON treatment. (A) Islet insulin content and (**B**) fed blood glucose in CKD mice ± NAC treatment (n=6-8). (**C**) Islet insulin content and (**D**) fed blood glucose and in CKD mice ± DON treatment (n=5-8). Data are mean ± S.E.M., *p<0.05, **p<0.01, ***p<0.001 vs. vehicle; one way-ANOVA Bonferroni post hoc test.

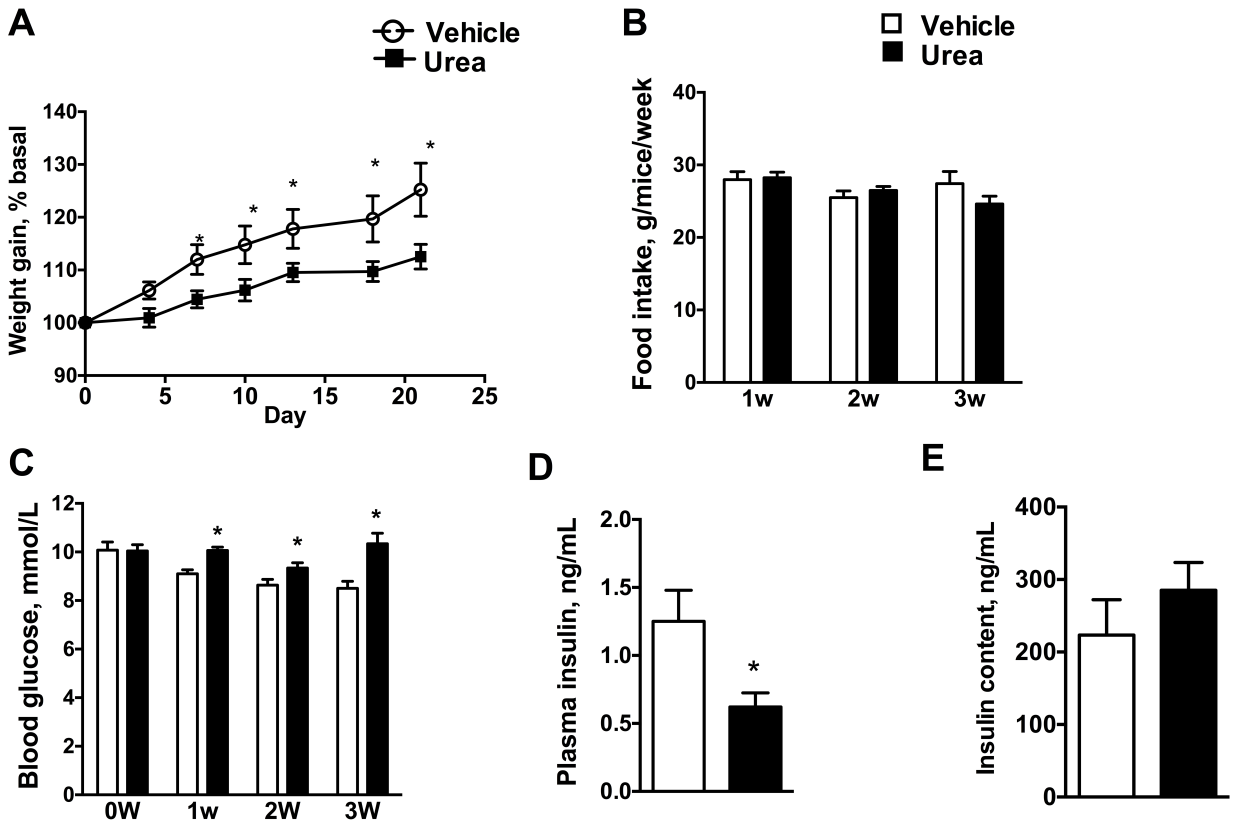

Figure S5: Body weight, food intake, metabolic parameters, and islet insulin content from normal mice ± urea administration. (**A**) Percentage of weight gain and (**B**) total food intake in normal mice ± urea administration (n=8-10) (**C**) Fed blood glucose (8-10) and (**D**) Fed plasma insulin in normal mice ± urea (n=3-4). (**E**) Islet insulin content after 3 weeks in mice ± urea (n=6). Data are mean ± S.E.M., *p<0.05, vs. vehicle; two-way ANOVA Bonferroni post hoc test for A, B and C and Student's *t* test for D and E.

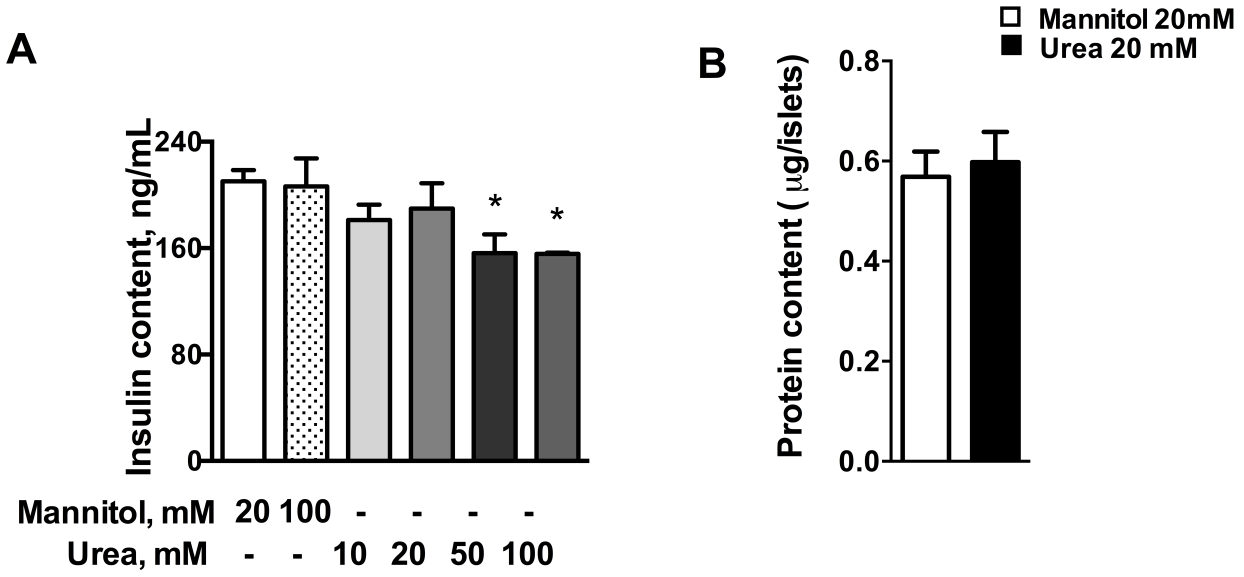

Figure S6: Insulin and protein content in urea-treated islets. (**A**) Islet insulin content from normal mice cultured for 24 h with increasing urea concentrations (n=3-5). (**B**) Protein content in mannitol- and urea-treated islets (n=4). Data are mean ± S.E.M., *p<0.05; two-way ANOVA, Bonferroni post hoc test for A and Student's *t* test for B.

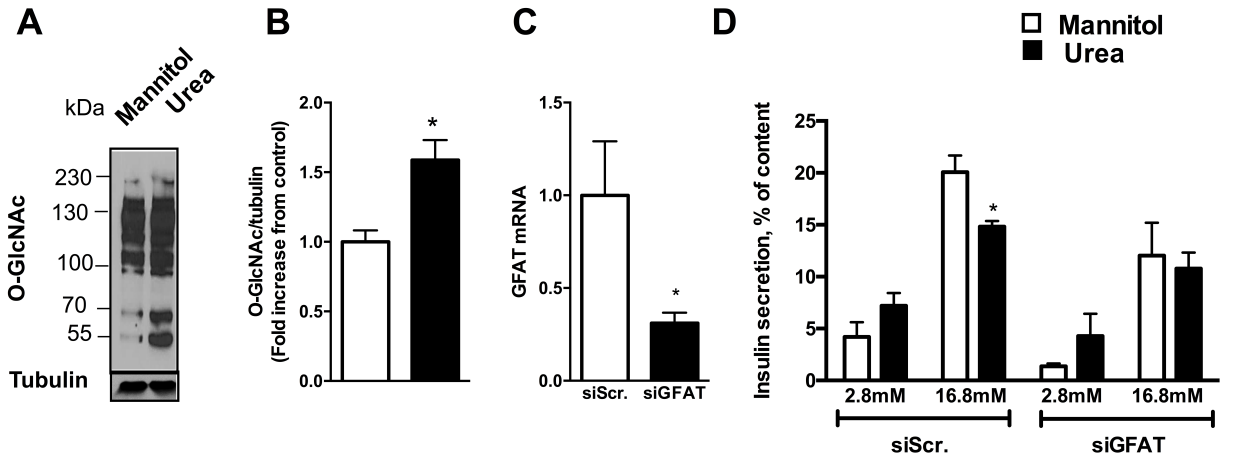

Figure S7: Islet protein O-GlcNAcylation after urea treatment and insulin secretion after transfection with siGFAT in MIN6 cells. (**A**) Representative Western Blot and (**B**) quantification of total protein O-GlcNAcylation in MIN6 cells ± 24-h urea (20mmol/L) treatment (n=3). (**C**) GFAT mRNA levels of MIN6 cells transfected with either scrambled (siScr) or GFAT-1 (siGFAT) siRNAs (n=3). (**D**) 1-h static insulin incubations of MIN6 cultured for 24 h with urea (20mmol/L) or mannitol (20mmol/L) transfected with either siScr (left) or siGFAT (right) (n=3). Data are expressed as mean ± S.E.M., *p<0.05 vs. mannitol for the same incubation condition; two-way ANOVA for D and Student's t test for B and C.

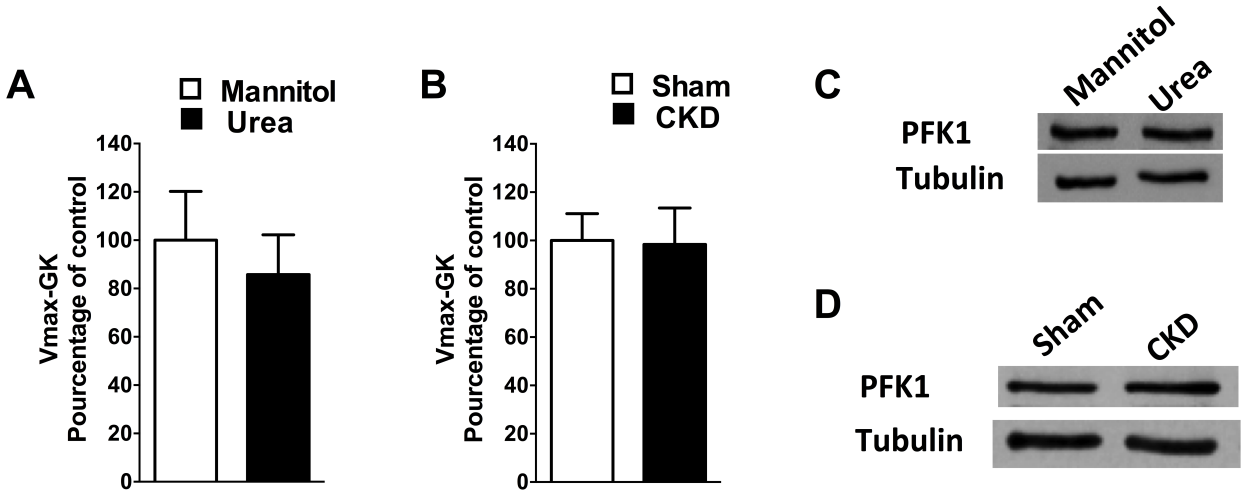

Figure S8: Glucokinase activity and phosphofructokinase-1 expression in urea-treated and CKD islets. Glucokinase enzymatic activity in (**A**) urea-treated and (**B**) CKD islets (n=3). Immunoblotting for PFK1 protein expression levels in (**C**) urea-treated islets and (**D**) CKD islets (representative Western blots of 3 replicate experiments). Data are mean ± S.E.M., Student's *t* test.

Table S1.

Biometry and metabolic parameters in sham and CKD mice ± NAC treatment for 3 weeks

	Sham-Vehicle	CKD-Vehicle	Sham-NAC	CKD-NAC
Mice (n)	6	7	10	10
Biometry				
Body weight, g	23.0 ± 0.6	22.0 ± 0,4	24.5 ± 0.5*	22.8 ± 0.4
Metabolic parameters				
Urea, mmol/L	11.3 ± 1.8	30.5 ± 5.1*	12.3 ± 1.4	30.0 ± 3.4*
Fed glycemia, mmol/L	8.2 ± 1.0	9.4 ± 0.5*	7.7 ± 0.2	7.8 ± 0.2
Fed insulinemia, ng/mL	1.5 ± 0.2	0.6 ± 0.1*	1.1 ± 0.2	1.3 ± 0.3

Data are mean ± S.E.M.

*p<0.05 by one-way ANOVA vs. control, Bonferroni post hoc test

Table S2

Characteristics of human pancreatic tissue donors

	Urea (mmol/L)	Creatinemia (µmol/L)	DFG (mL/min/1.73m2)	Sexe	Age	Cause of death
CKD	13	209	26	H	77	Sepsis
	11	231	16	F	88	Lung cancer
	15	160	27	F	73	Sepsis
Controls	2,9	32	115	F	63	Sepsis
	6,9	43	98	F	72	Inflammatory disease
	5	50	103	H	72	Lung cancer

Table S3.

Biometry and metabolic parameters in sham and CKD mice ± DON treatment for 3 weeks

	Sham-Vehicle	CKD-Vehicle	Sham-DON	CKD-DON
Mice (n)	4	6	4	7
Biometry				
Body weight, g	24.5 ± 0.6*	22.5 ± 0.6	24.1 ± 0,8	22.7 ± 0.3
Metabolic parameters				
Urea, mmol/L	11.0 ± 0.8	32.0 ± 2.2*	7.9 ± 1.1	26.6 ± 1.1*
Fed glycemia, mmol/L	7.4 ± 0.2	9.7 ± 0,2*	8.1 ± 0.4	8.8 ± 0.1

Data are mean ± SEM

*p<0.05 by one-way ANOVA vs. control, Bonferroni post hoc test

Table S4.
Biometry and metabolic parameters in urea- (25 g/L in drinking water) or vehicle-treated mice

	Vehicle			Urea			p value
Mice (n)	6			7			
Biometry							
Body weight, g	25.6	±	0.9	25.1	±	1.4	0.68
Metabolic parameters							
Fed glycemia, mmol/L	8.5	±	0.29	10.34	±	0.43	0.01
Fasted glycemia, mmol/L	9.30	±	0.5	10.3	±	0.6	0.16
Fed insulinemia, ng/mL	0.89	±	0.15	0.47	±	0.02	0.03
Fasted insulinemia, ng/mL	0.90	±	0.13	0.91	±	0.19	0.99

Data are mean ± SEM

Table S5.

Islet donor characteristics		
Sex	Age	BMI
4F/6M	48.3±4.2	28.3±2.3

Table S6.
Antibodies

	Provider	Reference	Dilution
Insulin	Dako	A0564	1/500
Tubulin	Abcam	Ab4074	1/2000
O-GlucNac	Abcam	Ab2739	1/400 (IHC)
			1/1000 (WB)
8-OHDG	Abcam	Ab62623	1/150
PDX-1	R&D systems	AF2517	1/1000
PFK-1	Santa-Cruz	sc-67028	1/250 (WB)
PFK-1M	R&D systems	MAB7687	1/250 (O-GlcNac)