Supplemental Table1: Body weight, blood glucose in the groups of mice at end of study.

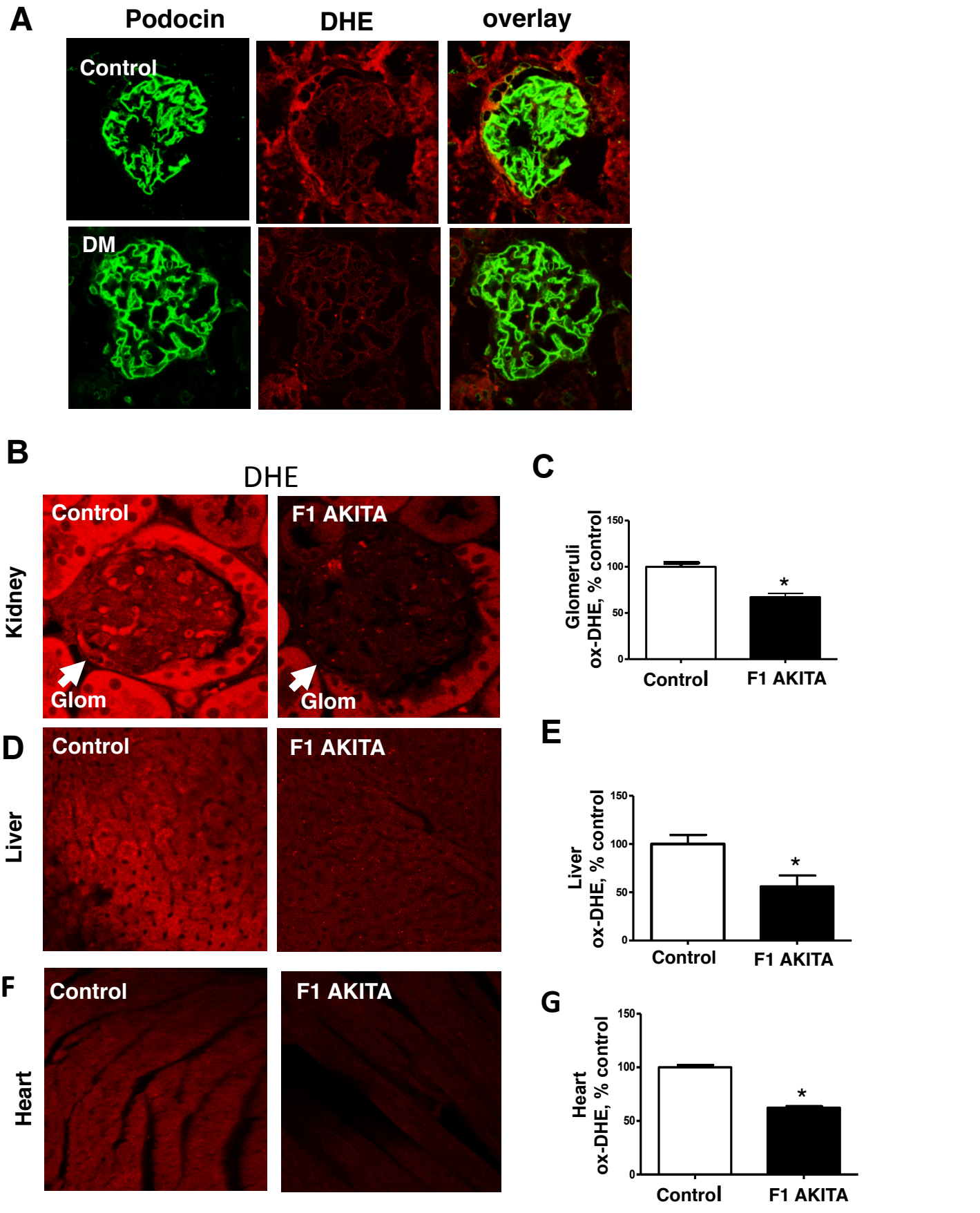
	AICAR or Metformin for 2weeks	n	Age (weeks)	Body weight After treatment (g)	Blood glucose after treatment (mg/dl)
Observational					
Control	-	10	16	25.45 ± 3.44	145 ± 29.24
STZ-DM	-	12	16	25.26 ± 1.97	429±110.72*
Interventional					
Control	-	21	16	27.38 ± 2.64	177 ± 41.68
STZ-DM	-	20	16	24.26 ± 2.01*	551 ± 51.65*
STZ-DM	+ AICAR	16	16	25.64 ± 1.53*	564 ± 35.51*
AKITA	-	10	16	22.67 ± 2.31*	565 ± 60.62
AKITA	+ AICAR	10	16	24.67 ± 1.15*	571 ± 50.22
F1 Control	-	10	12	27.80±1.19	271 ± 23.28
F1 Control	+ AICAR	6	12	28.63±1.47	245 ± 20.41
F1 AKITA	-	10	12	26.63±1.76*	< 600
F1 AKITA	+AICAR	6	12	25.17±1.22*	< 600
F1 AKITA	+metformin	6	12	25.84±1.96*	< 600

* $p < 0.05$ corresponding control. Values are mean ± SEM.

Supplemental Table 2. Body weight and blood glucose in STZ treated $SOD2^{+/+}$ or $SOD2^{+/-}$ C57BL6 mice.

	n	Duration of DM (Week)	Body weight After treatment (g)	Blood Glucose 24 weeks (mg/dL)
$SOD2^{+/+}$ Control (C)	10	24	32.7 ± 1.2	114.3 ± 3.6
$SOD2^{+/+}$ Diabetic (DM)	8	24	25.7 ± 1.3 *	366.8 ± 73.4 *
$SOD2^{+/-}$ Control (C)	10	24	35 ± 1.3	114.2 ± 6.7
$SOD2^{+/-}$ Diebetic (DM)	9	24	27.1 ± 0.9 *	370.7 ± 36.4 *

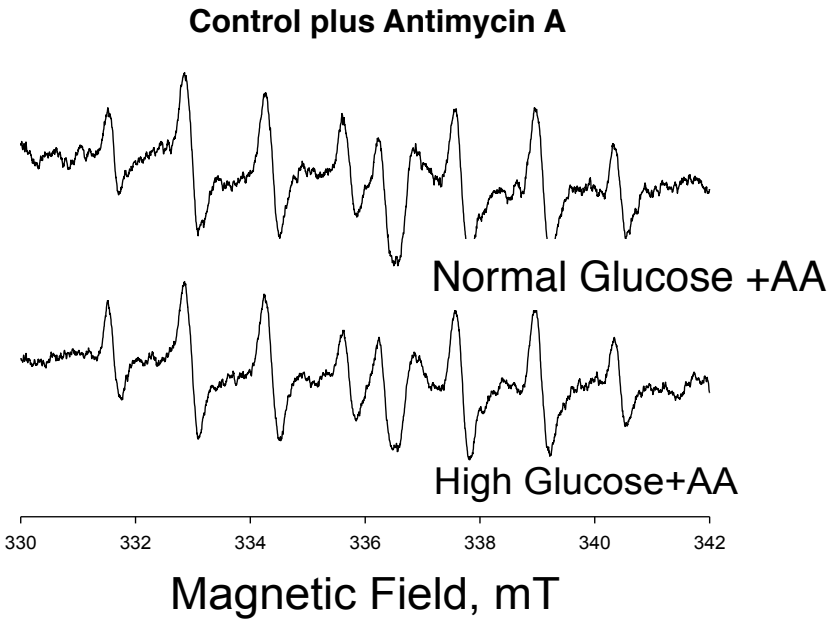
* $p < 0.05$ corresponding control. Values are mean ± SEM.


A
Podocin
DHE
overlay
Control
DM
B
DHE
Kidney
Control
F1 AKITA
Glom
Glom
C
Glomeruli ox-DHE, % control
150
100
50
0
*
Control
F1 AKITA
D
Liver
Control
F1 AKITA
E
Liver ox-DHE, % control
150
100
50
0
*
Control
F1 AKITA
F
Heart
Control
F1 AKITA
G
Heart ox-DHE, % control
150
100
50
0
*
Control
F1 AKITA

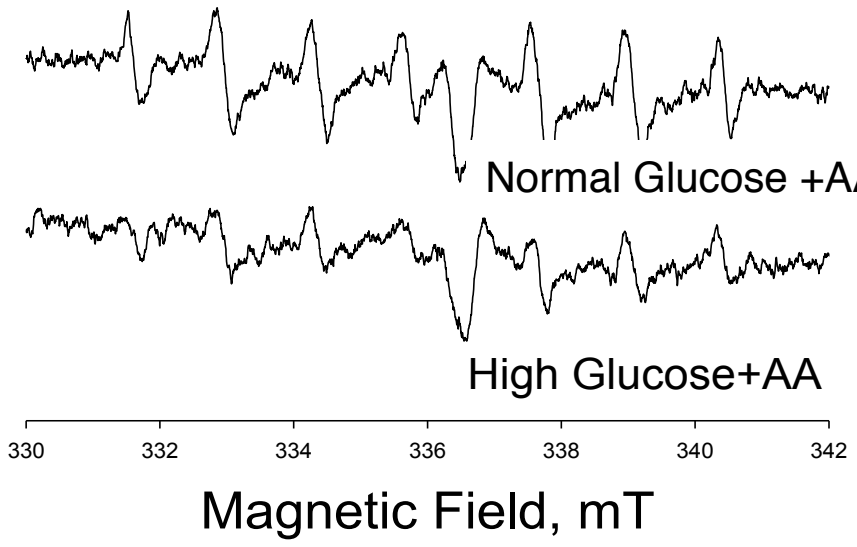
Supplemental Figure 1.

Imaging of glomerular, liver and heart superoxide production in normal, STZ-diabetic (DM) and F1 Akita-diabetic (F1 AKITA) mice. (**A)** Slice imaging of frozen kidneys from DHE-injected B6 control (CTRL) and STZ mice (DM) exhibited DHE oxidation in glomeruli, as identified by immunostaining with the podocyte specific antibody, podocin (green) (original magnification,63X). Confocal imaging of perfused organs from DHE-injected F1(DBA/2 x C57BL/6) wild-type control group (Control) and F1(DBA/2 x C57BL/6) -*Ins2*^{Akita} (F1 Akita) mice exhibited DHE oxidation in **(B)** glomerulus (white arrow), (**D**) liver and **(F)** heart (confocal images representative of n = 6 mice per group) (original magnification, 100x for kidney, original magnification 25x for liver and Heart). **(C, E and G)**, (n = 6 each for control and diabetic groups, *$p<0.05$ vs control).

A


Control plus Antimycin A
Normal Glucose +AA
High Glucose+AA
330
332
334
336
338
340
342
Magnetic Field, mT

B

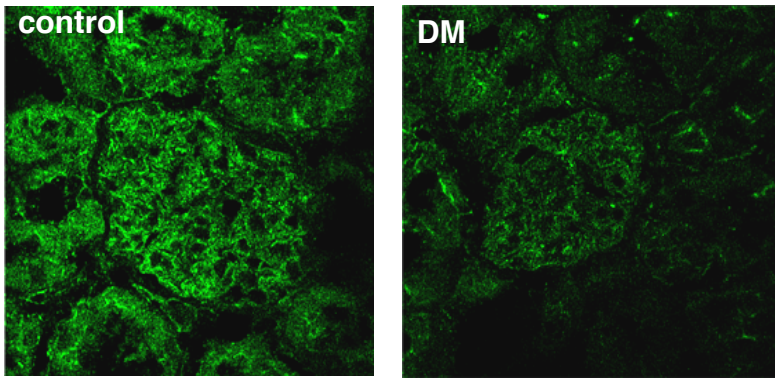

DM plus Antimycin A
Normal Glucose +AA
High Glucose+AA
330
332
334
336
338
340
342
Magnetic Field, mT

Supplemental Figure 2.

EPR spectra in control and diabetic kidney mitochondria treated with the mitochondrial Complex III inhibitor, Antimycin-A (AA). Spectra from control **(A)** and diabetic (DM) **(B)** samples after addition of the mitochondrial Complex III inhibitor, antimycin-A (AA), showing the expected increase in superoxide in both sets of samples, confirming the ability to detect increased mitochondrial superoxide production, if present.

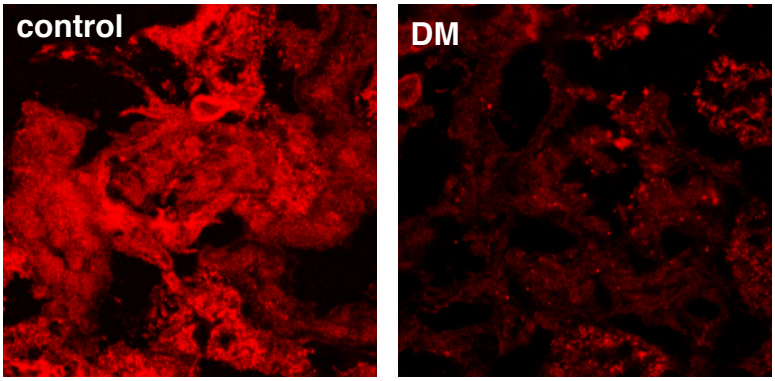
A

PGC1a



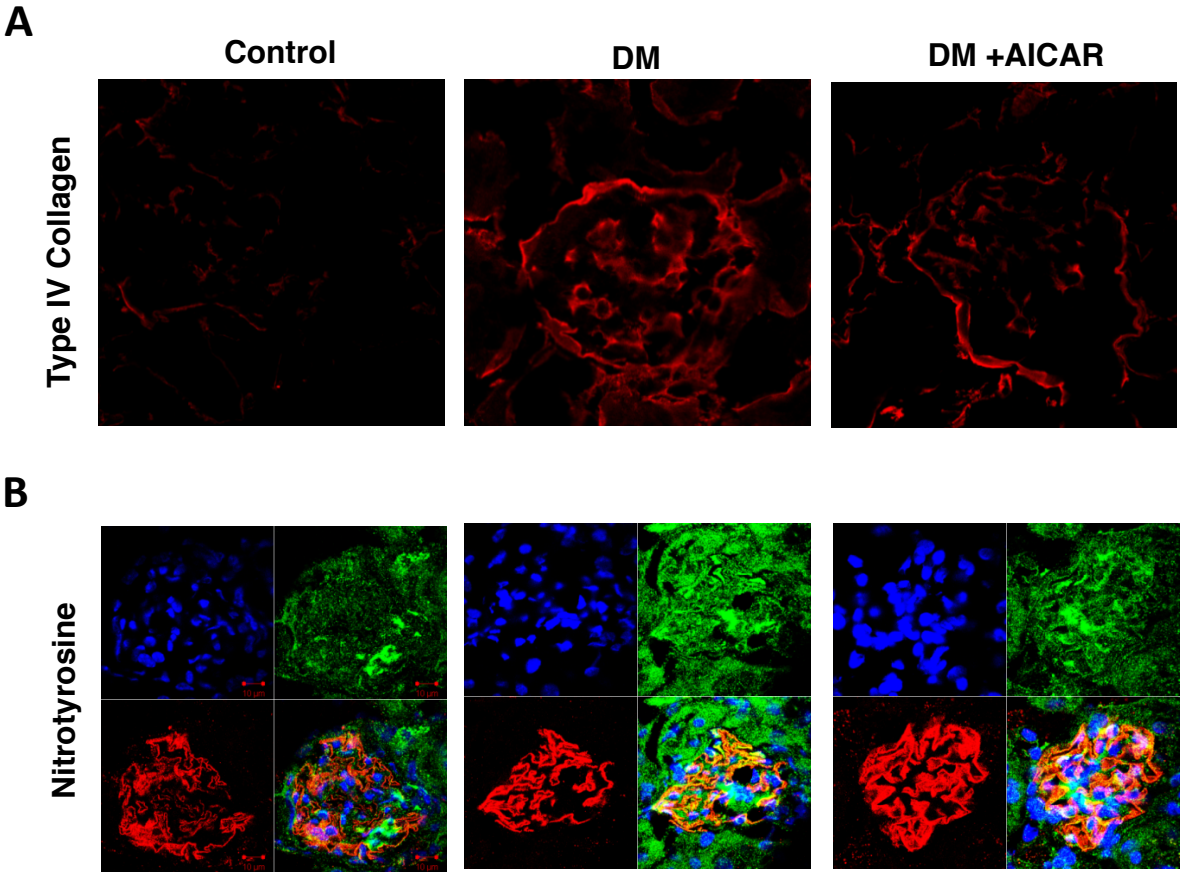
B

P-AMPK



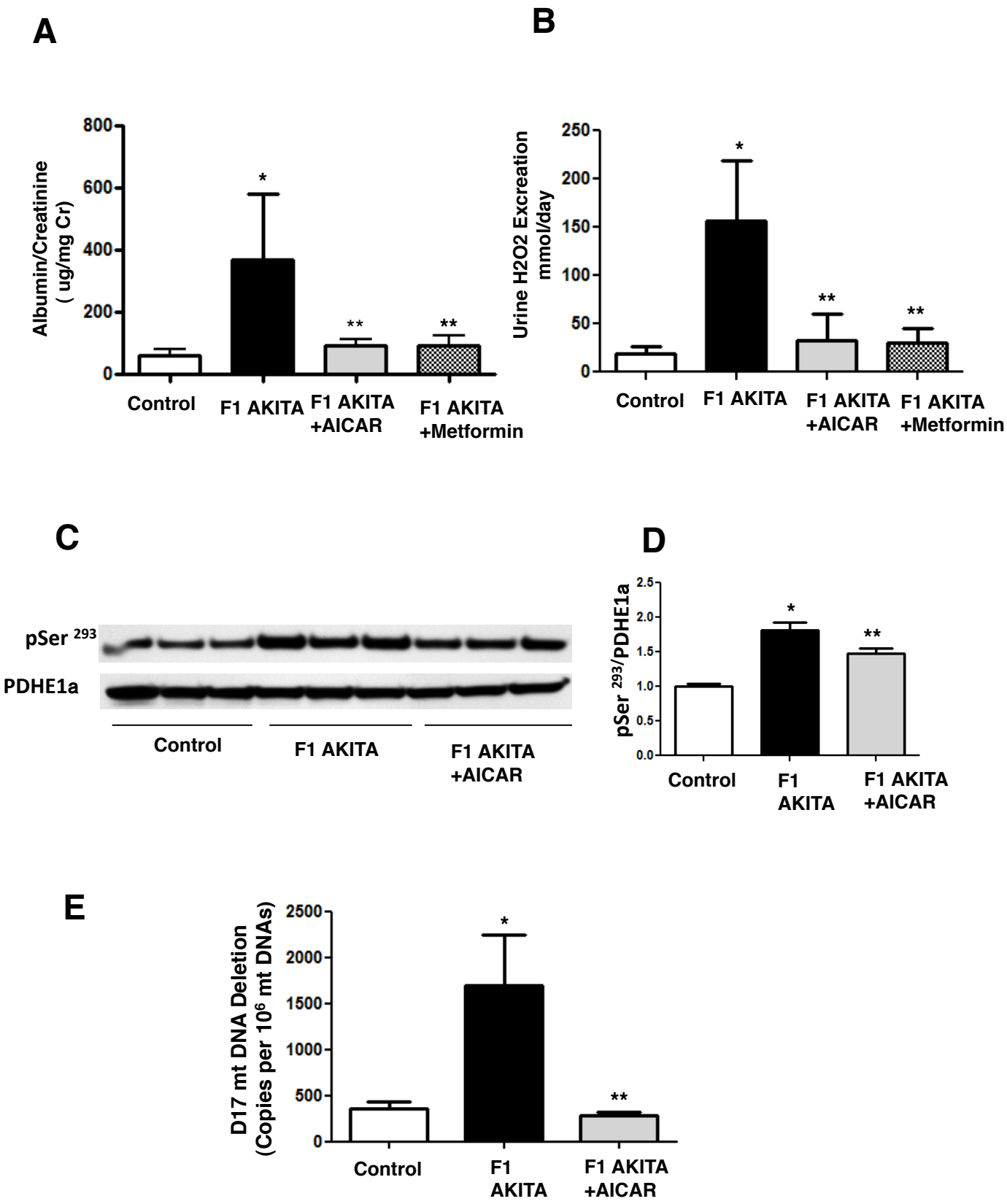
Supplemental figure 3.

PGC1a and phospho-AMPK decreased in diabetic kidney. Immunofluorescence image with anti- PGC1a (Green) **(A),** and phospho-Thr172 of the AMPKa subunit (Red) (B) antibodies in glomeruli from control, STZ –diabetic (DM) (n = 3 mice per group, original magnification, 63x).


A
Control
DM
DM +AICAR
Type IV Collagen
B
Nitrotyrosine

Supplemental figure 4.

AMPK activation by AICAR decreased type IV collagen and Nitrotyrosine in diabetic kidney. Immunofluorescence image with anti- type IV collagen (Red) **(A),** and Nitrotyrosine (green) (podocin staining in red) **(B)** antibodies in glomeruli from control, STZ –diabetic (DM) and STZ-diabetic mice treated with AICAR for two weeks (DM-AICAR). (n = 3 mice per group, Original magnification, 63x).


A
Albumin/Creatinine (ug/mg Cr)
800
600
400
200
0
*
**
**
Control
F1 AKITA
F1 AKITA +AICAR
F1 AKITA +Metformin
B
Urine H2O2 Excreation mmol/day
250
200
150
100
50
0
*
**
**
Control
F1 AKITA
F1 AKITA +AICAR
F1 AKITA +Metformin
C
pSer 293
PDHE1a
Control
F1 AKITA
F1 AKITA +AICAR
D
pSer 293/PDHE1a
2.5
2.0
1.5
1.0
0.5
0.0
*
**
Control
F1 AKITA
F1 AKITA +AICAR
E
D17 mt DNA Deletion (Copies per 10^6 mt DNAs)
2500
2000
1500
1000
500
0
*
**
Control
F1 AKITA
F1 AKITA +AICAR

Supplemental Figure 5.

AICAR and metformin reduced albuminuria and hydrogen peroxide (H_2O_2) excretion, mtDNA deletion and PDH phosphorylation in F1 Akita diabetic mice. **(A)** AICAR and Metformin reduced the urine albumin/creatinine ratio, **(B)** hydrogen peroxide (H_2O_2) excretion in the F1 Akita diabetic mice. Mice were divided into four groups: F1(DBA/2 x C57BL/6) wild-type control group (Control), vehicle treated F1(DBA/2 x C57BL/6) - *Ins2*^{Akita} (Akita), AICAR treated, and metformin -treated F1 Akita-diabetic group (*n*=6 per group). AICAR (500 mg/kg) or Metformin (150 mg/kg) was administered by daily intraperitoneal injection for 2 weeks. **(C)** Immunoblot analysis of phosphorylated PDHE1a -pSer^{293} and total PDHE1a (lower panel) in kidney cortex from control and diabetic mice. **(D)** Quantitative analysis of PDH phosphorylation in immunoblot, and **(E)** D17 mtDNA deletion in kidney DNA measured in F1 control, F1 AKITA-diabetic (DM), and F1 AKITA -diabetic mice treated with AICAR (DM-AICAR). ($n \geq 6$ per group, *$p<0.05$ vs control, **$p<0.05$ vs corresponding diabetic group).