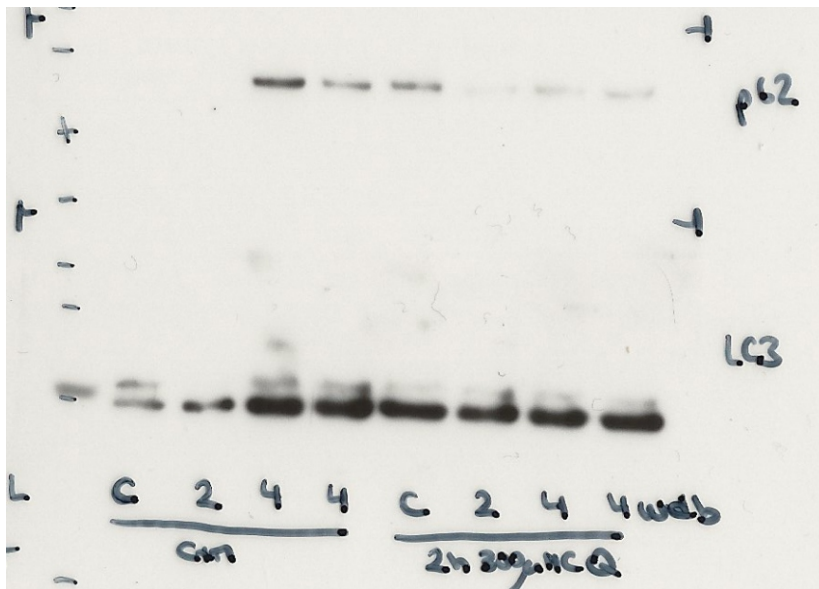


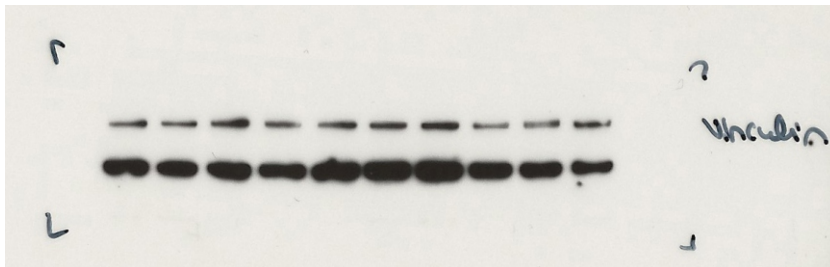
Supplementary Figure 1. Lipid profile in $\beta V59M$ mice

Alanine aminotransferase (ALT) activity (A), total cholesterol (B), HDL cholesterol (C), LDL/VLDL cholesterol (D), free fatty acids (E), and triglyceride levels (F) in control mice (black bars), $\beta V59M$ mice 2-4 weeks after diabetes onset, or after 2-4 weeks of diabetes followed by 2 weeks of glibenclamide therapy (hatched bars). Data are mean \pm SEM, n=7-20 per genotype.

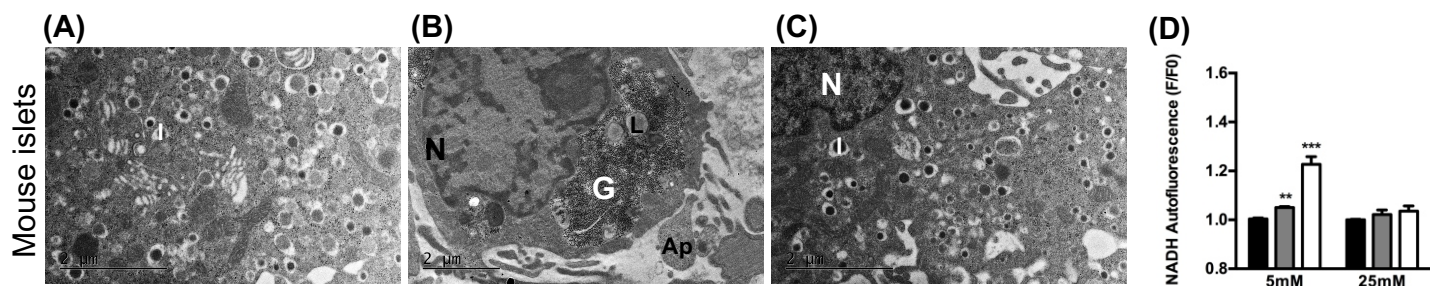
(A)



(B)



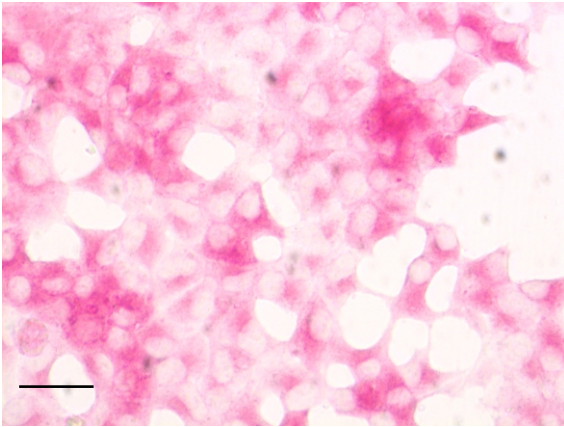
Supplementary Figure 2. Original Western blot images for Figure 5E
(A) Western blot image for p62 and LC3B. (B) Western blot image for vinculin.



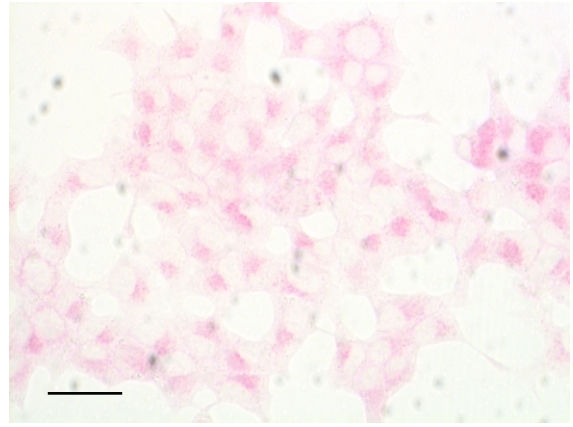
Supplementary Figure 3. Control mouse islets accumulate glycogen *in vitro*

(A-C) Representative electron micrographs of isolated islets from control mice following 48 hours culture in 5mM glucose (A), 25mM glucose (B), or 48h hours in 25mM glucose followed by 24 hours in 5mM glucose (C). Data are representative of islets from 3 patients. I, insulin granule. N, nucleus. Ap, apoptotic body. G, glycogen granules. L, lysosome. Scale bars 2 μ m. (D) Mean (\pm SEM) NAD(P)H autofluorescence produced by 1mM (black bars) 6mM (grey bars) and 20mM glucose (white bars) in islets isolated from control mice and cultured at 5mM glucose or 25mM glucose for 72 hours prior to the experiment (n=4-5).

(A)

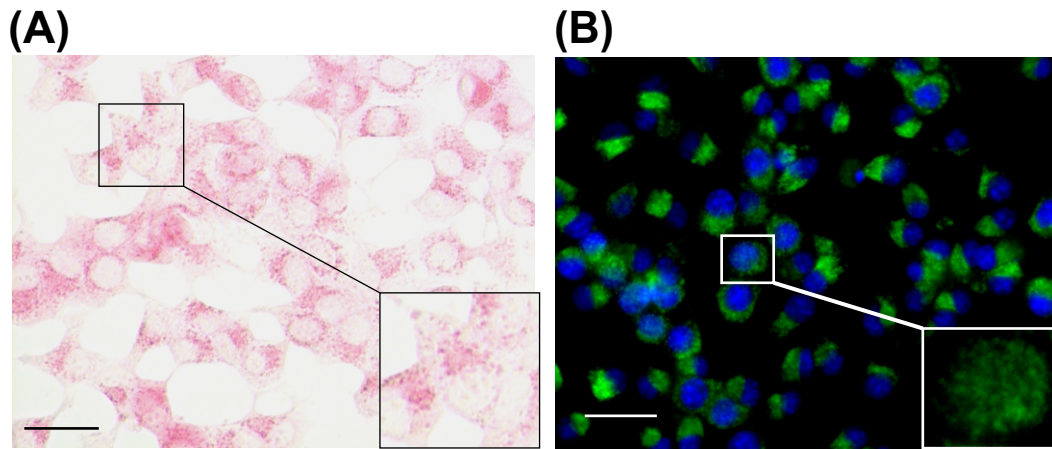


(B)

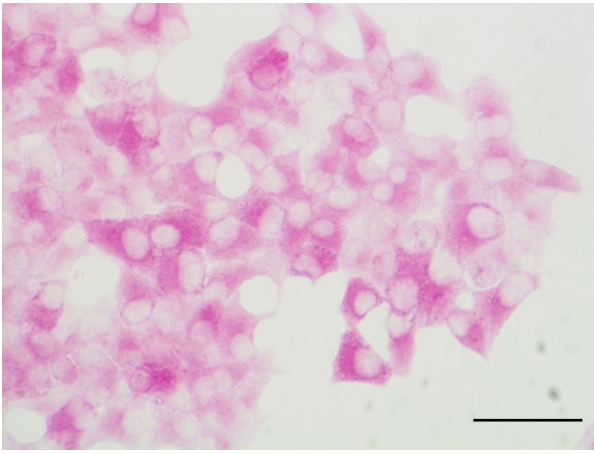
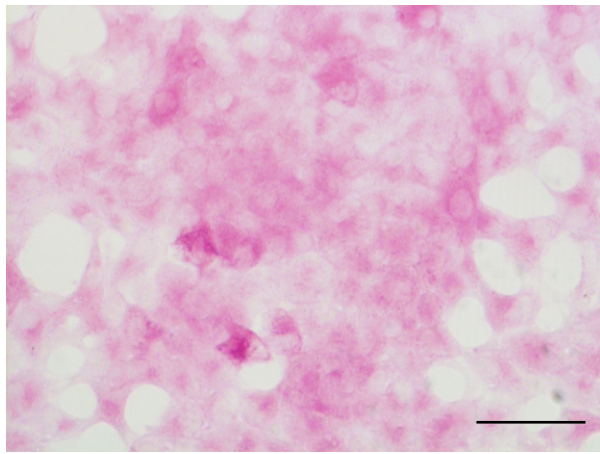
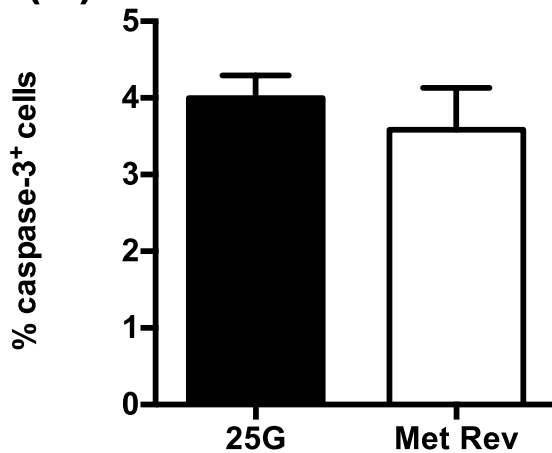


Supplementary Figure 4. Glycogen dissipates from INS-1 cells upon return to low glucose

(A,B) Representative images of INS1 cells following 48 hours culture in **(A)** 25mM glucose and **(B)** 48 hours culture in 25mM glucose followed by 24 hours at 5mM glucose. Scale bar, 200 μ m. Data are representative of >3 separate experiments.



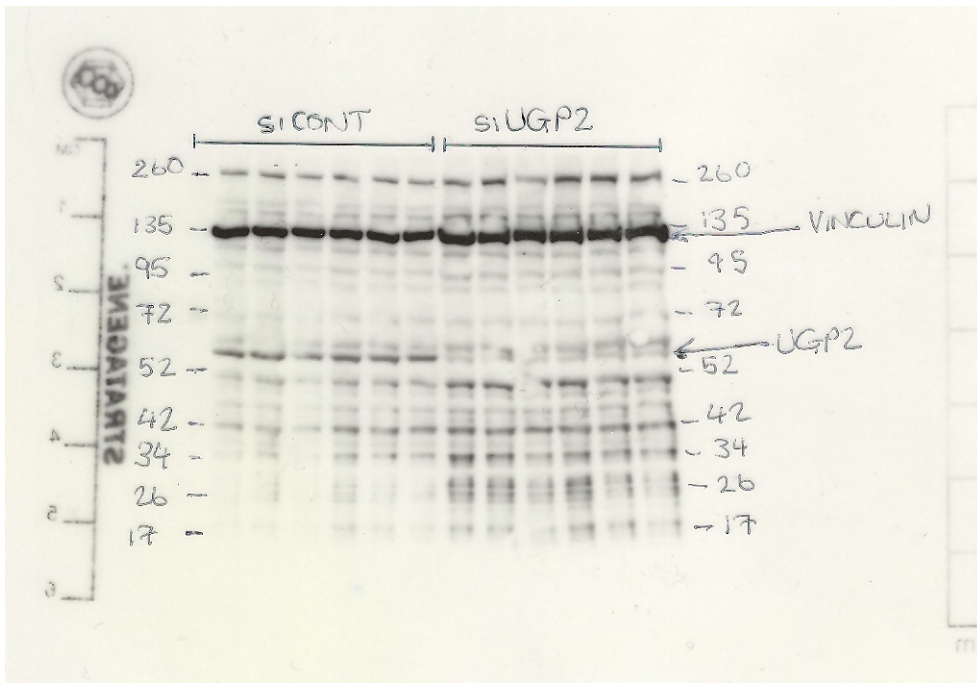
Supplementary Figure 5. Glycogen accumulates in lysosomes in INS-1 cells
(**A,B**) Representative images of INS-1 cells following 48 hours culture in 25mM glucose plus the lysosomal inhibitors pepstatin A (10 μ g/ml) and E-64d (10 μ g/ml). (**A**) PAS-staining for glycogen. (**B**) Immunofluorescence staining for the lysosomal marker Lamp-2 (green). Inset shows Lamp-2 positive punctae. Scale bar, 200 μ m. Data are representative of >3 separate experiments.

(A)**(B)****(C)**

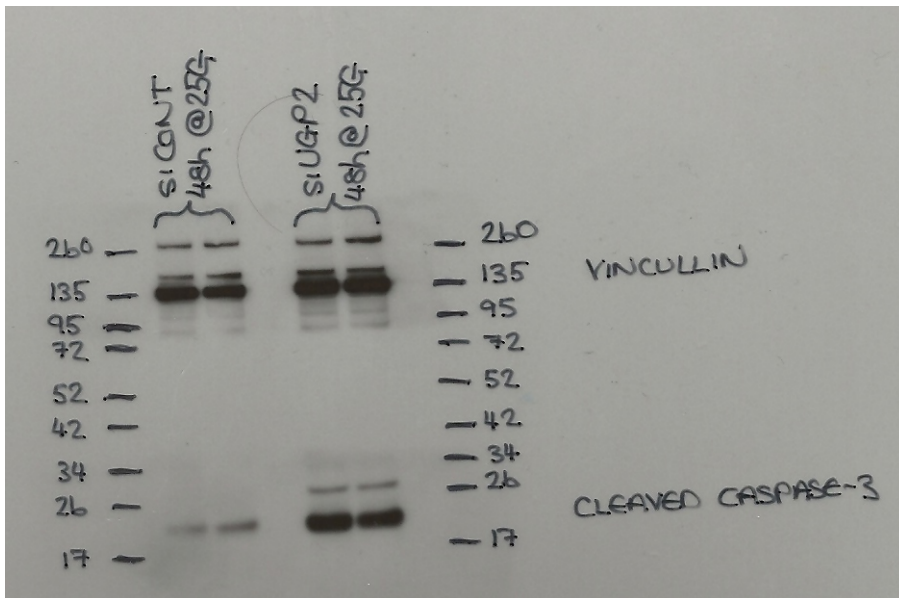
Supplementary Figure 6. Metformin treatment does not reverse glycogen formation

(A,B) Representative images of INS-1 cells following 48 hours culture in (A) 25mM glucose or (B) 48 hours at 25mM glucose then 24-hours with 25mM glucose plus metformin (0.5mM). Scale bar, 200 μ m. Data are representative of >3 separate experiments. (C) Mean \pm SEM number of cleaved-caspase-3 positive INS-1 cells as a percentage of the total number of INS-1 cells (n=25 fields of view from 3 experiments) in cells cultured for 48 hours in 25mM glucose (black bars), or 48 hours at 25mM glucose then 24-hours with 25mM glucose plus metformin (white bars).

(A)

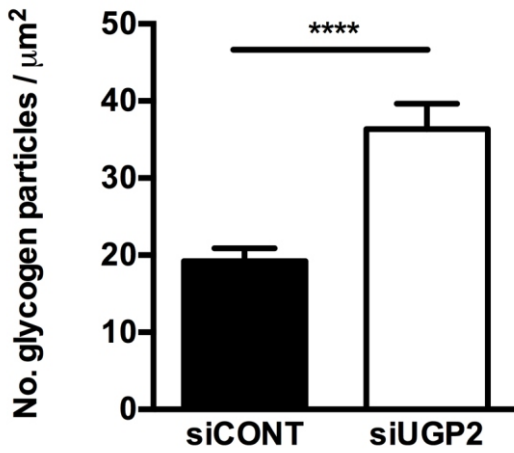


(B)



Supplementary Figure 7. Original Western blot images for Figure 7

(A) Western blot image for UGP2 and vinculin. (B) Western blot image for cleaved caspase-3 and vinculin.



Supplementary Figure 8. Silencing UGP-2 increases glycogen content

Mean (\pm SEM) number of glycogen particles identified from $n=31$ cells using electron microscopy in INS-1 cells 72h post UGP2 knockdown that were cultured for 48h at 25mM glucose. siCONTROL (black bar) and siUGP2 (white bar) treated cells.

*** $p < 0.001$ (Mann-Whitney test).

(A)

Gene Symbol	Gene Name	Control	2wk	Fold change
Aldob	Aldolase B, fructose-bisphosphate	389	5496	14.4
Fbp1	Fructose bisphosphatase 1	986	3851	4.3
Pfkfb3	6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 3	289	1206	4.2
Pdk1	Pyruvate dehydrogenase kinase, isoenzyme 1	770	2770	3.6
Fbp2	Fructose bisphosphatase 2	191	556	2.8
Acaca	Acetyl-Coenzyme A carboxylase alpha	334	929	2.8
Ppp1r3c	Protein phosphatase 1, regulatory (inhibitor) subunit 3C	219	470	2.2
Pgm2l1	Phosphoglucomutase 2-like 1	255	544	2.1
Idh1	Isocitrate dehydrogenase 1 (NADP+), soluble	1475	2995	2.1

(B)

Gene Symbol	Gene Name	Control	2wk	Fold change
Cox6a2	Cytochrome c oxidase, subunit VI a, polypeptide 2	2896	333	6.3
Eno2	Enolase	1471	742	2.0
Fah	Fumarylacetoacetate hydrolase	1345	708	1.9
Pfkfb2	6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 2	2592	1420	1.8
G6pc2	Glucose-6-phosphatase, catalytic, 2	13186	7235	1.8
ATP6	ATP synthase F0 subunit 6 /// predicted gene 10925	2226	1286	1.8
Ogdhl	Oxoglutarate dehydrogenase-like	2293	1328	1.7

Supplementary Table 1. Summary of microarray data

Selected metabolic genes that are significantly up-regulated **(A)** or down-regulated **(B)** in β V59M mice after 2 of weeks of diabetes compared to littermate controls.

Taqman Primers	
Gene	Catalogue number (Applied Biosystems)
<i>Actb</i>	Mm00607939_s1
<i>ATP6</i>	Mm03649417_g1 Rn03296710_s1
<i>Becn1</i>	Mm01265461_m1
<i>Cox6a2</i>	Mm00438295_g1
<i>Fhl1</i>	Mm01321349_m1
<i>Fbp1</i>	Mm00490181_m1 Rn00561189_m1
<i>Fbp2</i>	Mm00484280_m1
<i>G6pc2</i>	Mm00491176_m1 qRnoCIP0033113 (Bio-Rad)
<i>G6pd2</i>	Mm00658204_s1
<i>Gsk3b</i>	Mm00444911_m1 Rn01444108_m1
<i>Gys1</i>	Mm01962575_s1 Rn01476417_m1
<i>Gys2</i>	Mm0523953_m1 Rn00565296_m1
<i>Ogdhl</i>	Mm01221916_m1
<i>Pdk1</i>	Mm00554306_m1
<i>Pfkfb2</i>	Mm00435575_m1
<i>Pgm2l1</i>	Rn01508647_m1
<i>Ppp1r3c</i>	Mm01204084_m1
<i>Pygl</i>	Mm01289790_m1
<i>Pygm</i>	Mm00478582_m1
<i>Ugp2</i>	Rn01434170_m1

Supplementary Table 2: Taqman primer assay ID for the indicated genes.

Antibody	Concentration	Source	Application	Source
<i>Guinea pig anti-insulin</i>	1:500	Made in house	Immunohistochemistry	Made in house
<i>Mouse anti-glucagon</i>	1:500	Sigma (2645)	Immunohistochemistry	Sigma (2645)
<i>Rabbit anti-cleaved caspase-3</i>	1:100, 1:1000	Cell signalling (9664)	Immunohistochemistry, Western blot	Cell signalling (9664)
<i>Rabbit anti-LAMP2</i>	1:200	Sigma (L0668)	Immunohistochemistry	Sigma (L0668)
<i>Mouse anti-ubiquitin</i>	1:100	MBL (Clone IB3)	Immunohistochemistry	MBL (Clone IB3)
<i>Rabbit anti-p62</i>	1:500	MBL (PM045)	Immunohistochemistry, Western Blot, Immuno-gold labelling	MBL (PM045)
<i>Rabbit anti-LC3B</i>	1:1000	Abcam (ab48394)	Western Blot	Abcam (ab48394)
<i>Rabbit anti-vinculin</i>	1:5000	Abcam (ab18058)	Western Blot	Abcam (ab18058)
<i>Rabbit anti-UGP2</i>	1:500	Abcam (ab10627)	Western Blot	Abcam (ab10627)
<i>Anti-guinea pig Texas red</i>	1:50	Vector Laboratories (TI-7000)	Immunohistochemistry	Vector Laboratories (TI-7000)
<i>Anti-mouse Alexa 633</i>	1:500	ThermoFisher (A-21046)	Immunohistochemistry	ThermoFisher (A-21046)
<i>Anti-rabbit Alexa 488</i>	1:200	ThermoFisher (A-11034)	Immunohistochemistry	ThermoFisher (A-11034)
<i>ECL Anti-rabbit IgG, HRP linked</i>	1:2500	GE Healthcare (NA934V)	Western Blot	GE Healthcare (NA934V)

Supplementary Table 3: Antibodies.