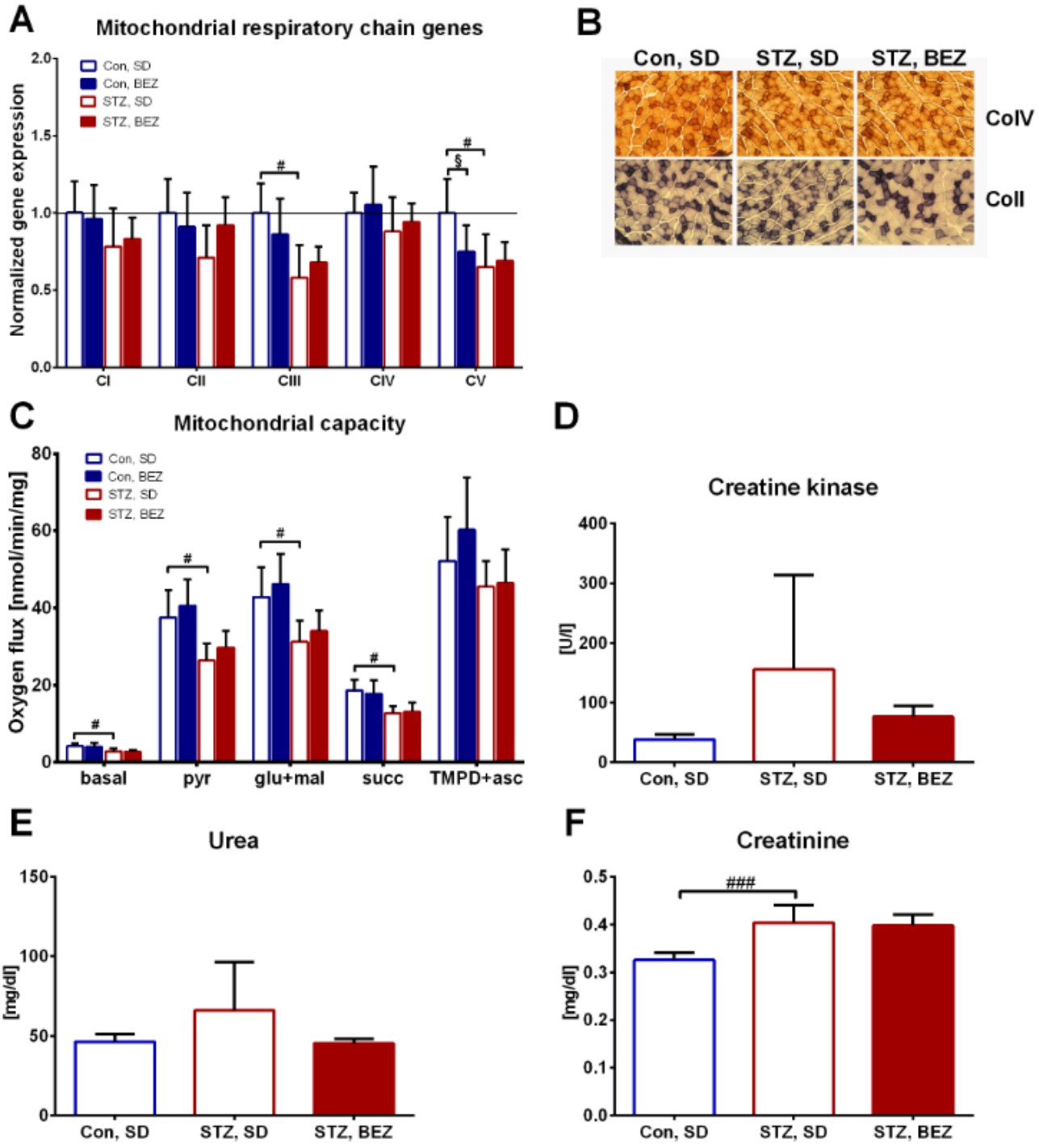
SUPPLEMENTARY DATA

Supplementary Figure 1. Mitochondrial function in skeletal muscle and plasma parameters of STZ mice

A Expression of representative subunits of the mitochondrial respiratory chain was analyzed by real time PCR in *tibialis cranialis* muscle. C denotes mitochondrial complexes I-V. Gene expression was normalized to housekeeping gene and Con, SD group. **B** Histochemical staining representing Complex IV (CoIV, brown staining, upper panels) and Complex II (CoII, blue staining, lower panels) activities in situ, images were acquired by 200x magnifications in *gastrocnemius* muscle. Representative areas are shown. **C** Oxygen consumption in saponin skinned *soleus* fibers was measured by high-resolution respirometry (Oroboros) with the denoted substrates added to the chambers. basal:pyruvate was used in the absence of ADP; pyr:ADP; glu:glutamate; mal:malate; succ:succinate; TMPD: tetramethylphenylendiamin; asc:ascorbate. A, C represent n=4-8 animals, while B represents n=3 animals. **D-F** Plasma parameters measured by clinical chemistry. **#** denotes significant differences between STZ, SD vs. Con, SD; #$p<0.05$; ###$p<0.001$, **§** denotes significant differences between Con, BEZ vs. Con, SD; §$p<0.05$,

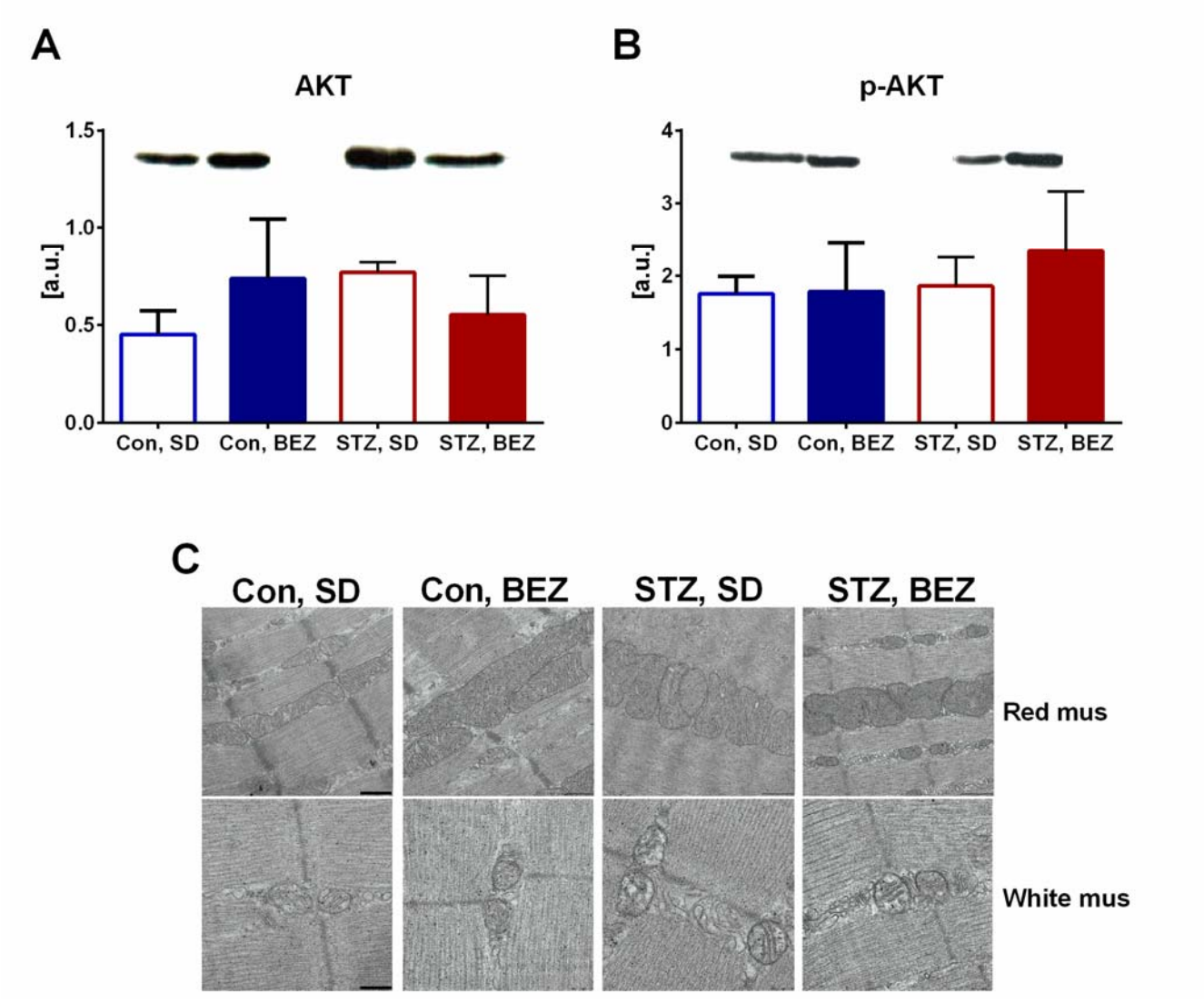
SUPPLEMENTARY DATA



SUPPLEMENTARY DATA

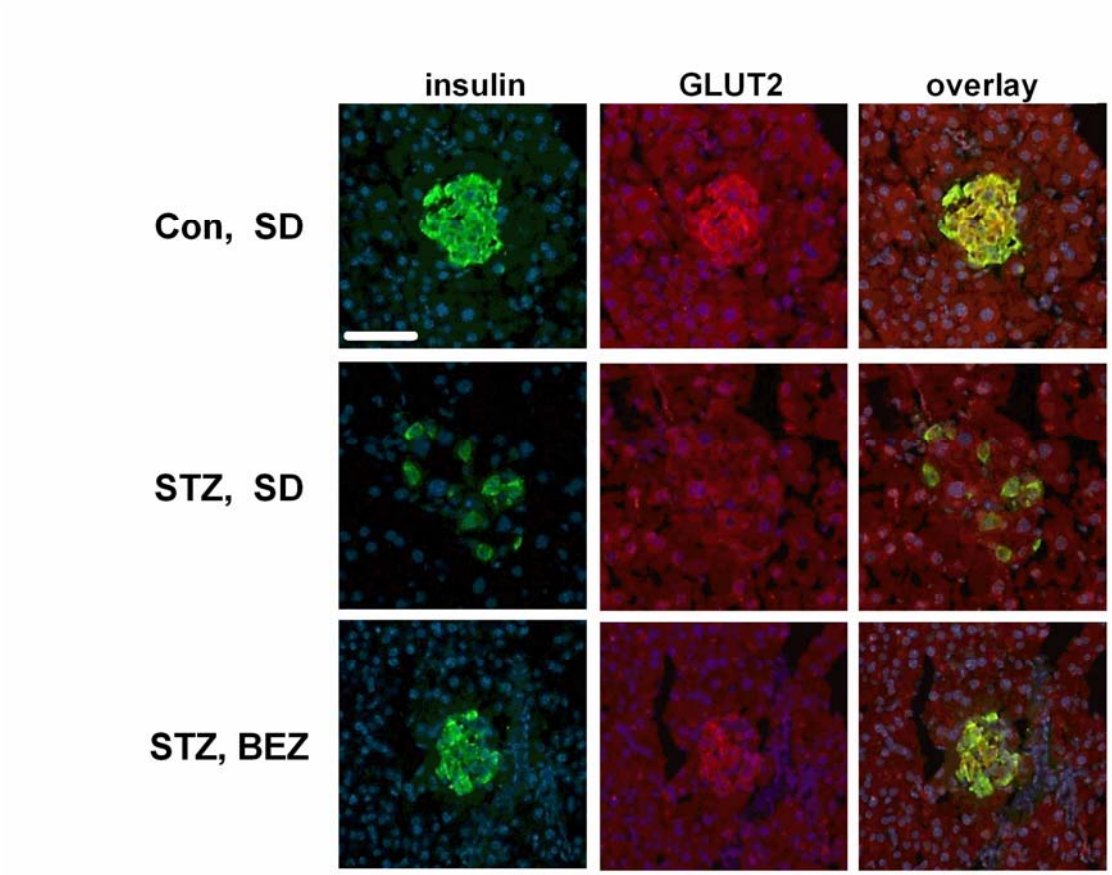
Supplementary Figure 2. Phospho-AKT levels and mitochondrial mass in skeletal muscle of STZ mice

A anti-AKT and **B** anti-phospho-473-AKT antibodies were used in Western blot to visualize protein levels from *quadriceps* muscles. **C** Mitochondrial morphology and mass was assessed by transmission EM from *quadriceps* muscles. Upper panels represent red, lower panels represent white muscle fibers at 10.000x and 20.000x magnification, respectively. Black bars denote 500 nm in the upper and 200 nm in the lower panels, respectively. Representative areas are shown. Columns represent averages+standard deviations; n=4-5 animals.



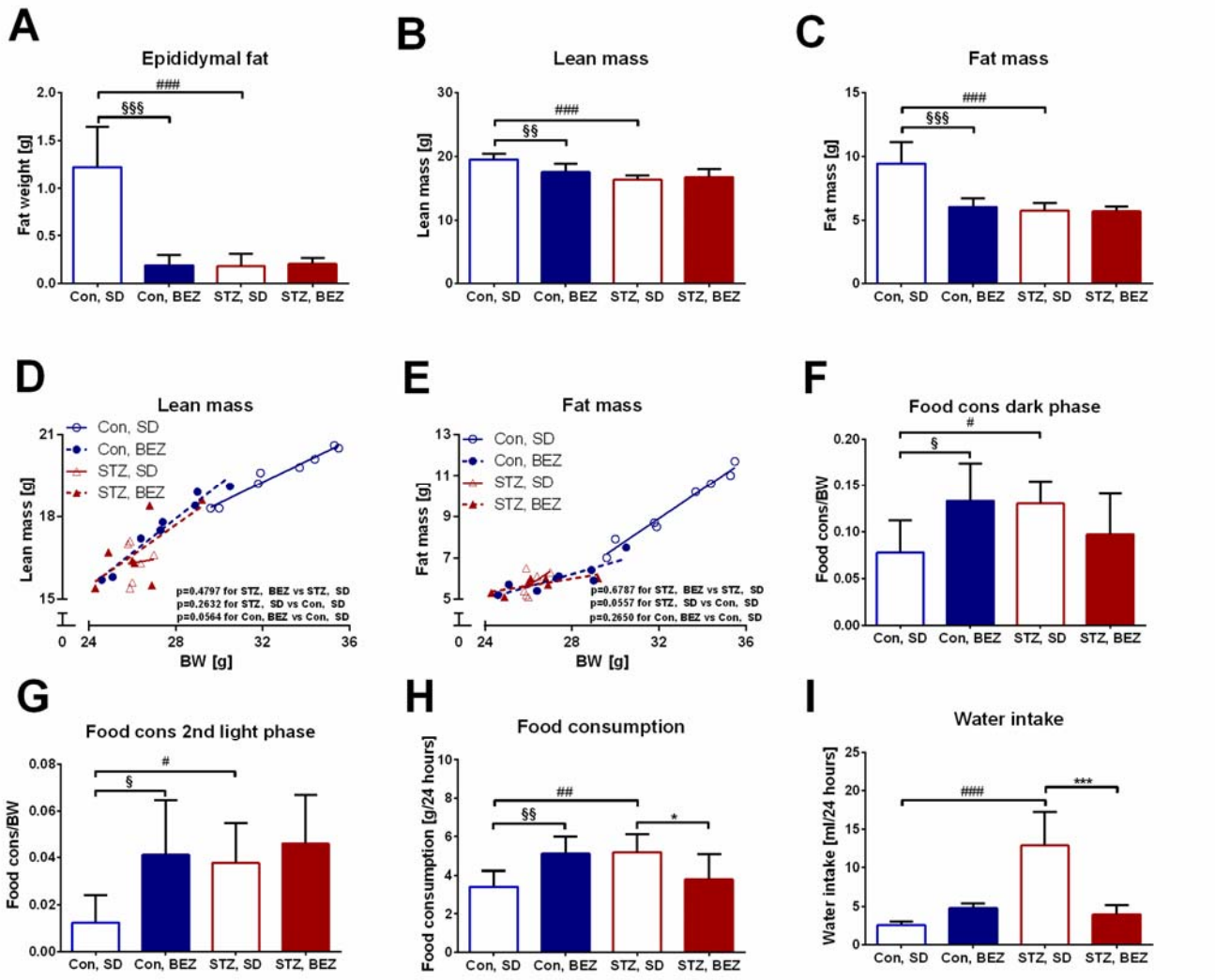
SUPPLEMENTARY DATA

Supplementary Figure 3. Insulin and GLUT2 staining in pancreata of STZ mice
Pancreata were stained with anti-insulin (green) and anti-GLUT2 (red) antibodies and visualized by fluorescent microscopy. Cell nuclei were stained with DAPI (blue). White bar represents 50 µm. Representative areas are shown from n=3 animals.



SUPPLEMENTARY DATA

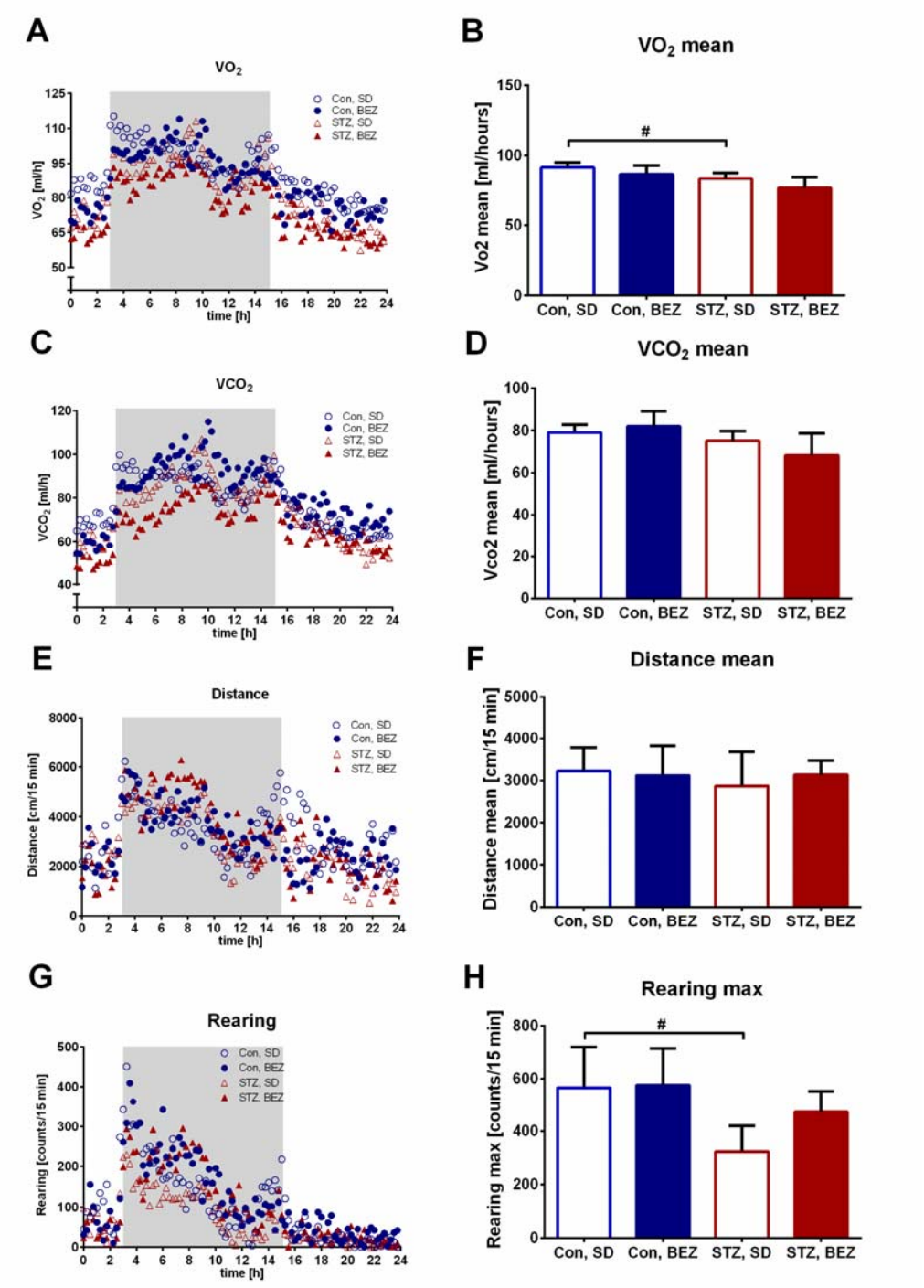
Supplementary Figure 4. Body composition and indirect calorimetry in STZ mice
A Epididymal fat weight. **B** Lean and **C** fat mass were measured by qNMR and these values were **D-E** normalized to body weight. **F** Food consumption in the dark and **G** second light phase. **H** Food consumption and **I** water intake. Columns represent averages+standard deviations; n=6-8 animals. For calculating p-values ANOVA and Holm-Sidak´s tests were applied for A-C and F-I. For D-E linear regression analysis were applied and calculated p-values are indicated in the figures. ***** denotes significant differences between STZ, BEZ vs. STZ, SD; *p<0.05, ***p<0.001; **#** denotes significant differences between STZ, SD vs. Con, SD; #p<0.05, ##p<0.01, ###p<0.001; **§** denotes significant differences between Con, BEZ vs. Con, SD; §p<0.05, §§p<0.01, §§§p<0.001.



SUPPLEMENTARY DATA

Supplementary Figure 5. Indirect calorimetry in STZ mice

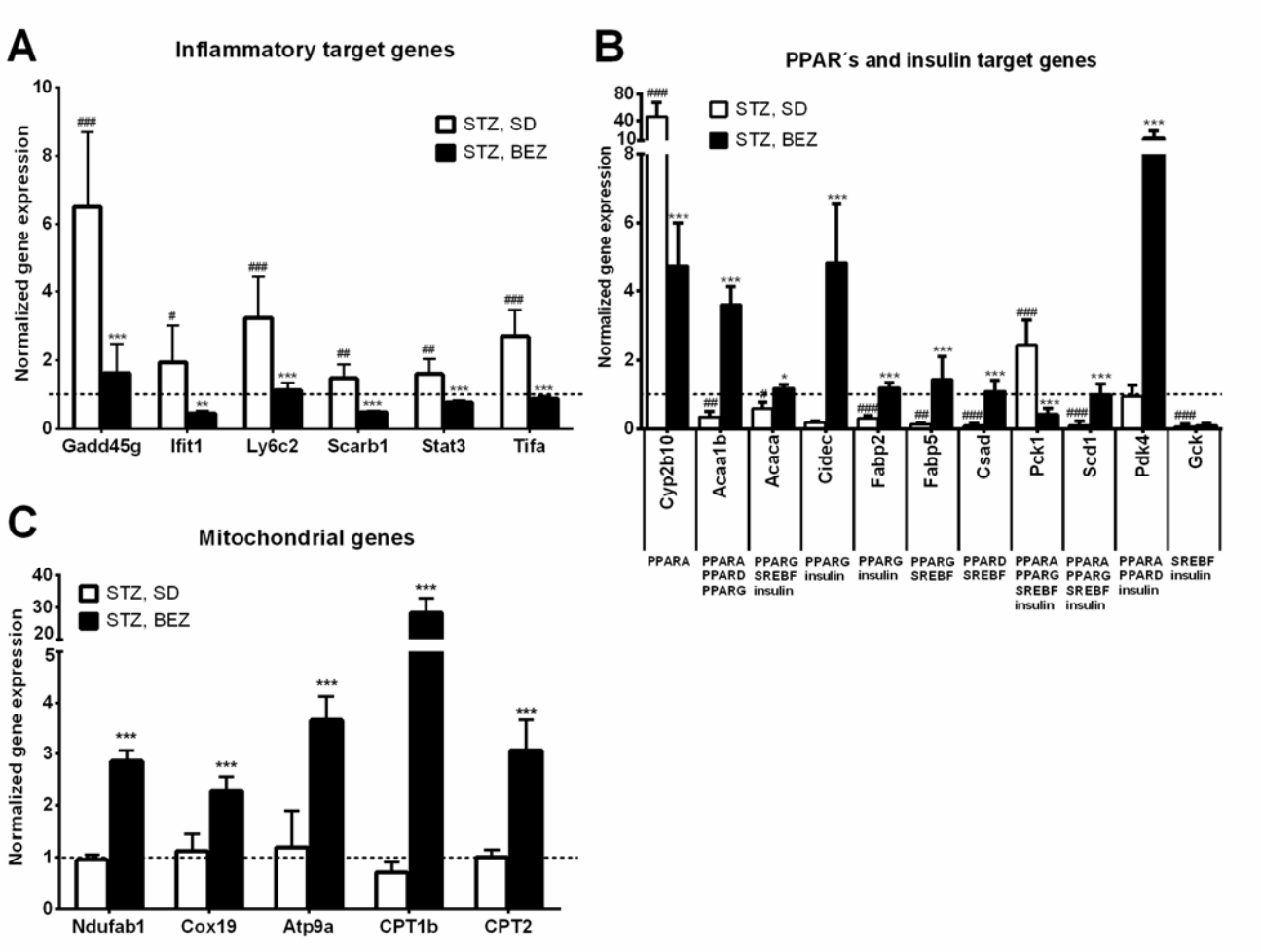
A Oxygen consumption (VO_2), **C** carbon dioxide production (VCO_2), **E** run distance and **G** rearing were measured and appropriate mean as well as maximum values were calculated **B, D, F, H**. Gray rectangle represents 12 hours dark phase (0 time point represents 3 p.m.). Columns represent averages+standard deviations; n=7-8 animals. # denotes significant differences between STZ, SD vs. Con, SD; #p<0.05.



SUPPLEMENTARY DATA

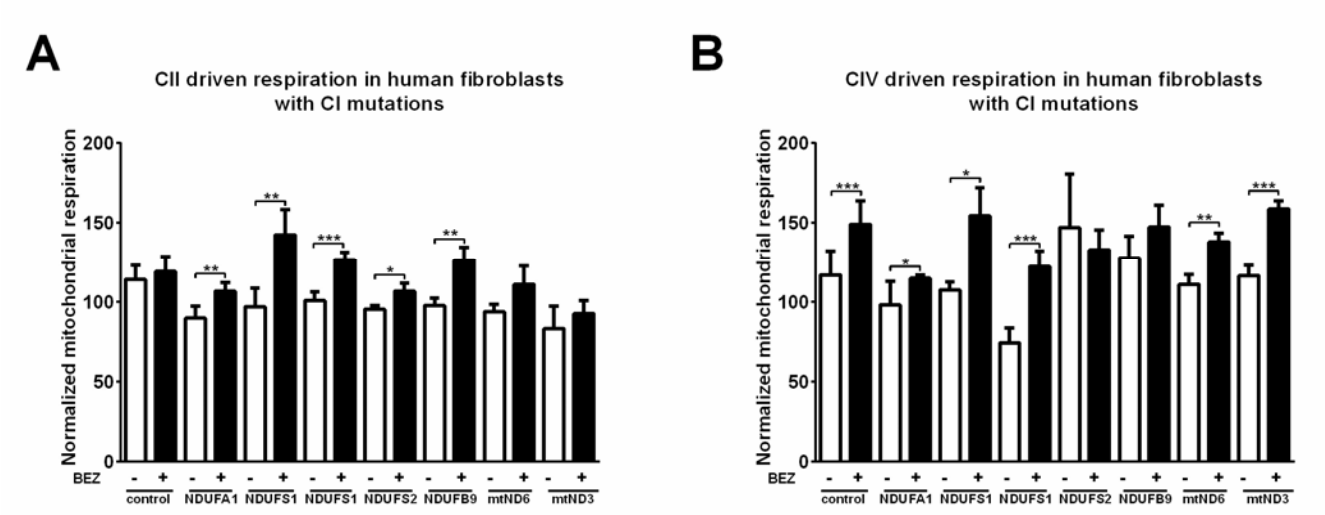
Supplementary Figure 6. Hepatic gene expression in STZ mice

Hepatic gene expression was studied by real-time PCR. Gene expression data were normalized to Con, SD, denoted at 1 with dashed line. Gene names are given in Suppl. Table 1. **A** Genes for inflammatory pathways. **B** Target genes for PPAR and insulin pathway. The possible upstream regulators were taken from Ingenuity database and are denoted under the graphic. **C** Mitochondrial genes. Columns represent averages+standard deviations; n=5-7 animals. ***** denotes significant differences between STZ, BEZ vs. STZ, SD; *p<0.05, **p<0.01, ***p<0.001; # denotes significant differences between STZ, SD vs. Con, SD; #p<0.05, ##p<0.01, ###p<0.001.



SUPPLEMENTARY DATA

Supplementary Figure 7. Mitochondrial function in human fibroblasts treated with BEZ
Mitochondrial respiration was determined using high resolution respirometry and **A** succinate as complex II substrate or **B** TMPD as complex IV substrates; subsequently potassium cyanide was applied the loci of the mutation for the appropriate subunits of complex I are indicated under the figure. Data are normalized to the lowest value of untreated control samples. For control fibroblasts n=7-33, for patients fibroblasts n=3-11 replicates were performed and students t-tests were used for calculating p-values. ***** denotes significant differences between BEZ treated and untreated fibroblasts; *p<0.05, **p<0.01, ***p<0.001.



SUPPLEMENTARY DATA

Supplementary Table 1. Primer sequences used for liver real-time PCR

Symbol	Gene	Entrez	5´primer	Tm	3´primer	Tm	Length
Acaa1b	acetyl-Coenzyme A acyltransferase 1B	235674	CTGCTTCAAGGACACCACCC	60.89	GAGATGTCTCCCAGCTGCTC	59.9	99
Acaca	acetyl-Coenzyme A carboxylase alpha	107476	ACACCTGAAGACCTTAAAGCCA	59.56	CCAGCCCACACTGCTTGTA	59.93	152
Atp9a	ATPase, class II, type 9A	11981	CCTCCCTCTGCCACTCAAAG	60.04	ACAGCACCTGGGCTGACATT	62.07	82
Cidec	cell death-inducing DFFA-like effector c	14311	AAGCGCATCGTGAAGGAGAT	59.82	CATGTAGCTGGAGGTGCCAA	60.04	87
Cox19	COX19 cytochrome c oxidase assembly homolog (S. cerevisiae)	68033	GTCGACCGCAATGAACTTCG	59.91	ACATTCACCGAAGTGGTCCAG	60.27	88
Csad	cysteine sulfinic acid decarboxylase	246277	CTGCTCCCTCTGCTTCTGTC	60.11	GGATGAAATCTTCCAGCTCAGG	58.79	109
Cyp2b10	cytochrome P450, family 2, subfamily b, polypeptide 10	13088	GCTTTGAGTACACAGACCGTCA	60.55	AGAGAAGAGCTCAAACATCTGG	57.79	104
Fabp2	fatty acid binding protein 2, intestinal	14079	GGACTGGACCTCTGCTTTCC	60.04	TCTACTTTCCACGTGCCGTC	60.04	72
Fabp5	fatty acid binding protein 5, epidermal /// fatty acid binding protein 5-like 2	16592	CATGGCCAAGCCAGACTGTA	60.04	GGTGCAGACCGTCTCAGTTT	60.25	154
Gadd45g	growth arrest and DNA-damage-inducible 45 gamma	23882	AGTCCTGAATGTGGACCCTG	59.01	GCAGAACGCCTGAATCAACG	60.18	112
Gck	glucokinase	103988	TTGCAACACTCAGCCAGACA	60.11	TGCTCTACCAGAGTCAACGAC	59.46	147
Ifit1	interferon-induced protein with tetratricopeptide repeats 1	15957	TCTGCTCTGCTGAAAACCCA	59.53	CACCATCAGCATTCTCTCCCAT	60.16	70
Ly6c2	lymphocyte antigen 6 complex, locus C2 /// lymphocyte antigen 6 complex, locus C1	100041546	ACGCTACAAAGTCCTGTTTGC	59.4	CTGCAGTCCCTGAGCTCTTC	60.11	71
Ndufab1	NADH dehydrogenase (ubiquinone) 1, alpha/beta subcomplex, 1	70316	CACCCCCACTGACGTTAGAC	60.04	ACGGAGAGCTTTTCTGGATCA	59.1	88
Pck1	phosphoenolpyruvate carboxykinase 1, cytosolic	18534	ATGAAAGGCCGCACCATGTA	60.03	GGGCGAGTCTGTCAGTTCAA	59.97	93
Pdk4	pyruvate dehydrogenase kinase, isoenzyme 4	27273	TTTCCAGGCCAACCAATCCA	59.81	GGCCCTCATGGCATTCTTGA	60.4	87
Scarb1	scavenger receptor class B, member 1	20778	TGATGCCCCAGGTTCTTCAC	59.96	TGTCTTCAGGACCCTGGCT	60.15	108
Scd1	stearoyl-Coenzyme A desaturase 1	20249	CAGGTTTCCAAGCGCAGTTC	60.04	ACTGGAGATCTCTTGGAGCA	57.76	142
Stat3	signal transducer and activator of transcription 3	20848	GTGTGACACCATTCATTGATGC	58.5	TCCTCACATGGGGGAGGTAG	60.03	132
Tifa	TRAF-interacting protein with forkhead-associated domain	211550	AAGTCCCCAGGAGAGGAGACAA	62.19	GGCCAGGATGGTAAATGGTCA	60.06	153

Symbol	Gene	Entrez	Qiagen Assay name	Qiagen Cat. No.
Cpt1b	carnitine palmitoyltransferase 1b, muscle	12895	Mm_Cpt1b_1_SG	QT00172564
Cpt2	carnitine palmitoyltransferase 2	12896	Mm_CPT2_1_SG	QT00304717

SUPPLEMENTARY DATA

Supplementary Table 2. Blood parameters in random fed mice

	Con, SD	Con, 0.25% BEZ	Con, 0.5% BEZ	STZ, SD	STZ, 0.25% BEZ	STZ, 0.5% BEZ
TG [mg/dl]	**112.2**±38.6	**29.86**±5.9§§§	**40.11**±7.1§§	**149.1**±79.3	**29.93**±3.7***	**34.2**±3.8***
NEFA [mmol/l]	**0.41**±0.09	**0.35**±0.08	**0.43**±0.13	**0.63**±0.23#	**0.42**±0.07*	**0.42**±0.04*
BG [mg/dl]	**147.7**±11.1	**144.9**±13.5	**127.9**±13.8	**534.7**±58.1###	**399.0**±87.3***	**320.4**±78.8***

Triglyceride (TG) and non-esterified fatty acids (NEFA) were measured by routine clinical chemistry data from plasma and blood glucose (BG) from tail blood. Numbers represent averagesstandard deviations; n=4-7 animals. * denotes significant differences between STZ, BEZ vs. STZ, SD; *p<0.05, ***p<0.001; # denotes significant differences between STZ, SD vs. Con, SD; #p<0.05, ###p<0.001; denotes significant differences between Con, BEZ vs. Con, SD; p<0.01, p<0.001.

SUPPLEMENTARY DATA

Supplementary Table 3. Expression of hepatic genes involved in fatty acid oxidation normalized to STZ, SD group and depicted as fold changes

Gene symbol	Gene name	STZ, BEZ/ STZ, SD
ACAA1b	acetyl-Coenzyme A acyltransferase 1B	**4.87**
ACAA2	acetyl-Coenzyme A acyltransferase 2 (mitochondrial 3-oxoacyl-Coenzyme A thiolase)	**1.22**
ACADL	acyl-Coenzyme A dehydrogenase, long-chain	**1.89**
ACADM	acyl-Coenzyme A dehydrogenase, medium chain	**1.68**
ACADS	acyl-Coenzyme A dehydrogenase, short chain	**1.39**
CPT1B	carnitine palmitoyltransferase 1b, muscle /// cDNA sequence BC090627	**14.51**
CPT2	carnitine palmitoyltransferase 2	**1.92**
EHHADH	enoyl-Coenzyme A, hydratase/3-hydroxyacyl Coenzyme A dehydrogenase	**3.48**
FABP1	fatty acid binding protein 1, liver	**2.68**
FABP2	fatty acid binding protein 2, intestinal	**3.28**
FABP3	fatty acid binding protein 3, muscle and heart	**28.82**
FABP4	fatty acid binding protein 4, adipocyte	**3.20**
HADHA	hydroxyacyl-Coenzyme A dehydrogenase (trifunctional protein), alpha subunit	**1.74**
HADHB	hydroxyacyl-Coenzyme A dehydrogenase (trifunctional protein), beta subunit	**2.26**

Genes involved in fatty acid oxidation were selected from liver microarray data, comparing BEZ treated STZ mice to STZ, SD controls. Array data has been submitted to the GEO database at NCBI (GSE39752, GSE79008).

SUPPLEMENTARY DATA

Supplementary Table 4. Fold changes of plasma metabolite levels (33 out of 52), which show inverse regulation between STZ, BEZ vs STZ, SD and STZ, SD vs Con, SD comparisons

Metabolites	STZ, SD/Con, SD	STZ, BEZ/STZ, SD	
Creatinine	**-1.1**	**1.2**	
Putrescine	**-1.5**	**2.2**	
Trp	**-1.5**	**1.5**	
Orn/Arg	**-1.3**	**2.2**	
PC aa C30:0	**-1.6**	**1.5**	
PC aa C32:0	**-1.7**	**1.7**	
PC aa C32:1	**-10.1**	**9.0**	
PC aa C32:2	**-2.7**	**2.4**	
PC aa C34:1	**-3.6**	**4.0**	
PC aa C34:3	**-1.5**	**1.9**	
PC aa C36:1	**-2.2**	**1.9**	
PC aa C36:3	**-1.7**	**2.4**	
PC aa C38:3	**-2.1**	**2.1**	
PC aa C38:5	**-1.5**	**1.6**	
PC aa C40:3	**-3.7**	**2.1**	
PC aa C40:4	**-2.2**	**1.9**	
PC ae C32:1	**-1.9**	**2.2**	
PC ae C34:1	**-2.2**	**2.3**	
PC ae C34:2	**1.8**	**-2.2**	
PC ae C36:2	**2.1**	**-2.2**	
PC ae C38:4	**2.0**	**-2.1**	
PC ae C40:3	**-1.5**	**1.6**	
PC ae C40:6	**1.7**	**-3.2**	
PC ae C42:0	**-2.4**	**1.7**	
PC ae C42:4	**1.6**	**-2.3**	*****
SM (OH) C16:1	**1.8**	**-1.8**	
SM C20:2	**-1.4**	**1.8**	
SM C24:1	**-1.6**	**2.7**	
PUFA (PC) / MUFA (PC)	**3.8**	**-4.1**	*****
PUFA (PC) / SFA (PC)	**1.5**	**-1.3**	*****
PUFA (LPC) / MUFA (LPC)	**3.9**	**-4.4**	*****
Total AC / C0	**1.6**	**-1.5**	*****
Total SM-OH / Total SM-non OH	**1.4**	**-1.5**	*****

STZ treatment significantly altered the level of 85 metabolites and metabolite ratios compared to Con, SD animals (left column). On the other hand, BEZ treatment of STZ mice significantly altered 78 metabolites and metabolite ratios compared to STZ, SD mice (right column). Among these comparisons there were 54 common metabolites and metabolite ratios, 52 of them showed inverse regulation. Numbers denote fold changes calculated by dividing the appropriate means of groups. The original data are shown as Suppl. Table 5.

SUPPLEMENTARY DATA

AC:acylcarnitine, numbers after PC or SM denote the length of carbon chain, the numbers after : denote the number of double bounds, LPC:lysophosphatidyl choline, MUFA:monounsaturated fatty acid, SFA:saturated fatty acid, PUFA:polyunsaturated fatty acid, PC:phosphatidyl choline, SM:sphingomyelin, C0: free carnitine, aa:acyl-acyl, ae:acyl-ether. * denotes values, which were lower than 3-times zero values.