Supplemental Acknowledgments

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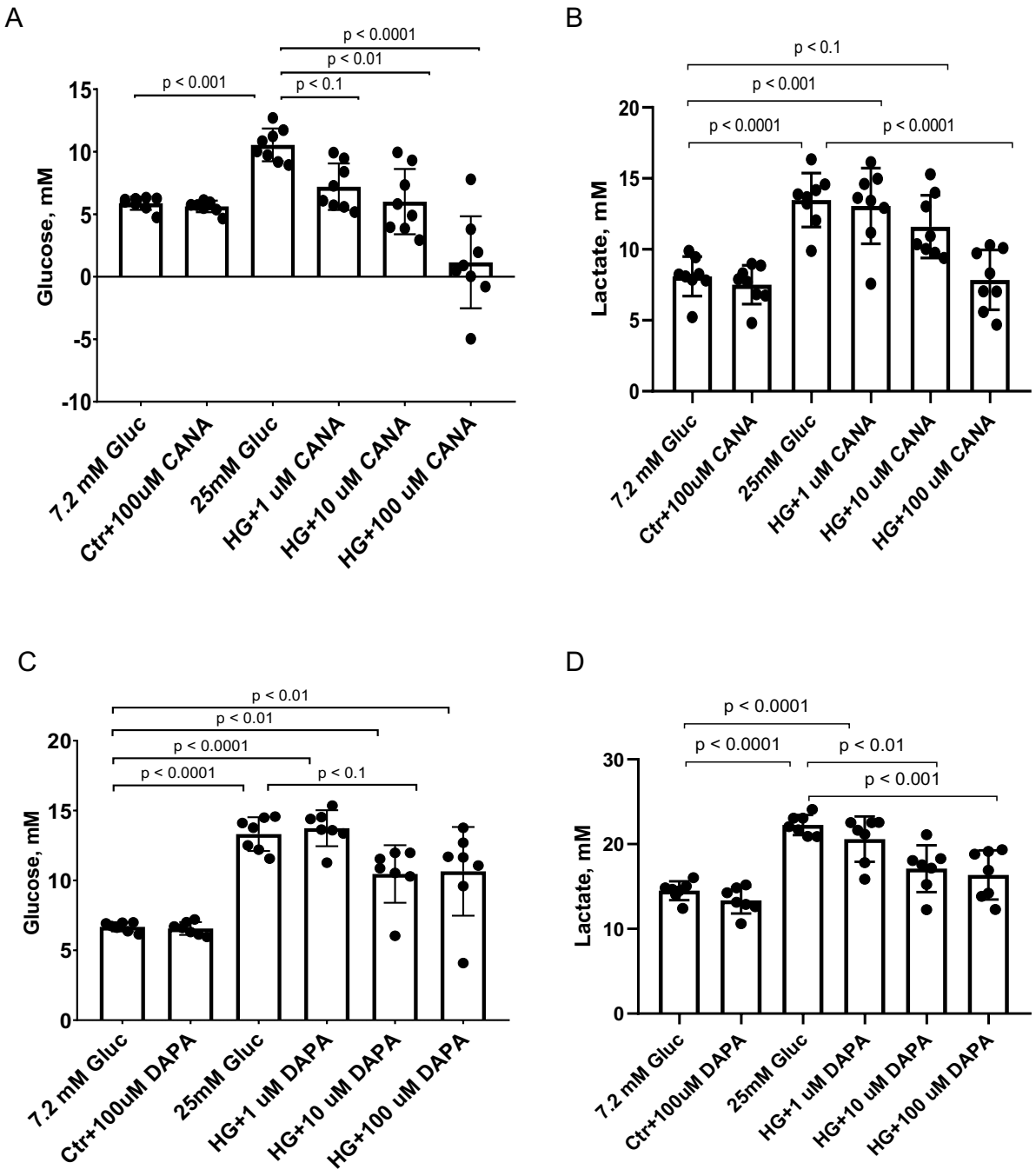
Supplemental Table 1: Demographic and baseline characteristics of living donors and patients with DKD from KPMP data.

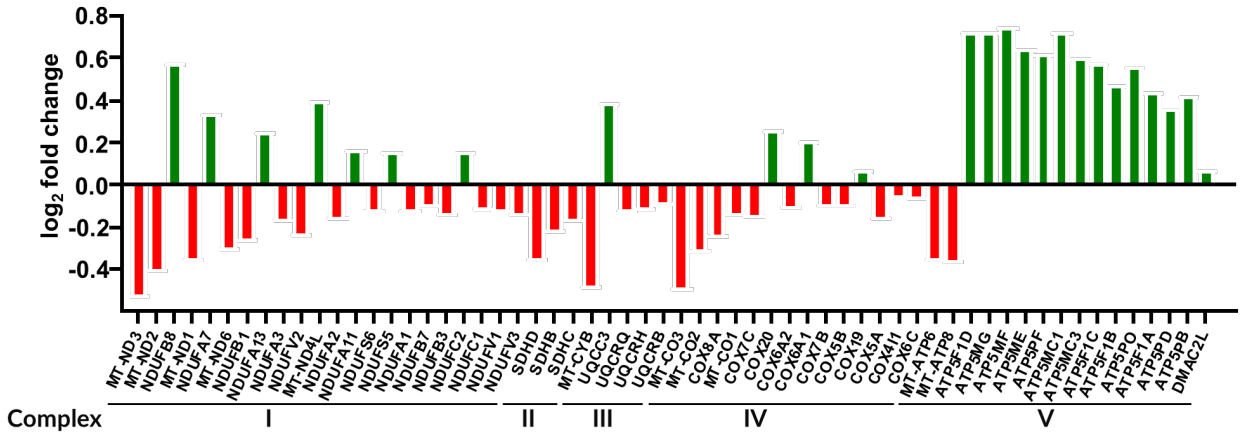
	LD (n=20)	DKD (n=11)
Age, n (%)		
30-39 years	6 (30%)	2 (18.2%)
40-49 years	6 (30%)	0
50-59 years	7 (35%)	1 (9.1%)
60-69 years	1 (5%)	4 (36.4%)
70-70 years	0	4 (36.4%)
Sex, n (%)		
Male	7 (35%)	3 (27.3%)
Female	13 (65%)	8 (72.7%)
Diabetes Duration, n (%)		
0-4 years	-	1 (9.1%)
5-9 years	-	1 (9.1%)
10-14 years	-	3 (27.3%)
20-24 years	-	4 (36.4%)
25-29 years	-	1 (9.1%)
30-34 years	-	1 (9.1%)
HbA1c, n (%)		
<6.5%	-	1 (9.1%)
6.5% to <7.5%	-	5 (45.5%)
7.5% to <8.5%	-	0
<8.5%	-	2 (18.2%)
Unavailable data	20 (100%)	3 (27.3%)
eGFR, n (%)	Not available	
20-60 ml/min/1.73m^2	-	8 (72%)
>60 ml/min/1.73m^2	-	3 (28%)
UACR, n (%)		
<30 mg/g	-	2 (18.2%)
30 to <300 mg/g	-	1 (9.1%)
500 to <1000 mg/g	-	1 (9.1%)
>=1000 mg/g	-	2 (18.2%)
Unavailable data	20 (100%)	5 (45.5%)
Use of RAAS blockade, n (%)	Not available	
Yes	-	6 (54.5%)
No	-	5 (45.5%)
History of hypertension, n (%)	Not available	

Yes	-	10 (90.9%)
No	-	1 (9.1%)

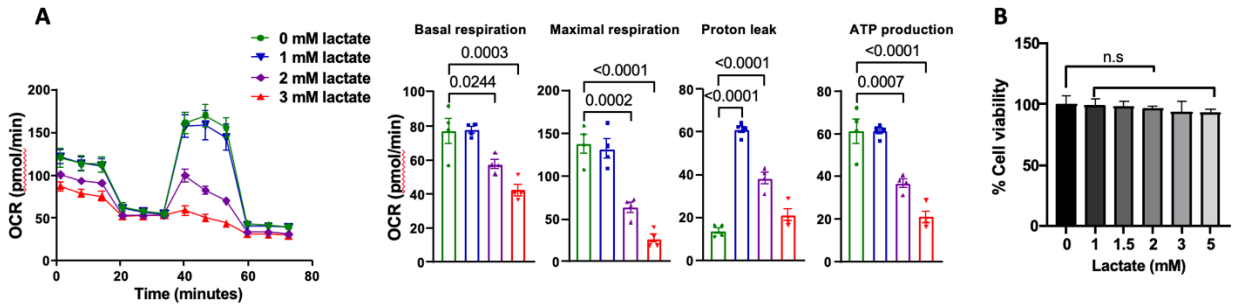
DKD, diabetic kidney disease; LD living donor; HbA1c, hemoglobin A1c; eGFR, estimated glomerular filtration rate; UACR, urine albumin-to-creatinine ratio; RAAS, renin-angiotensin-aldosterone system.



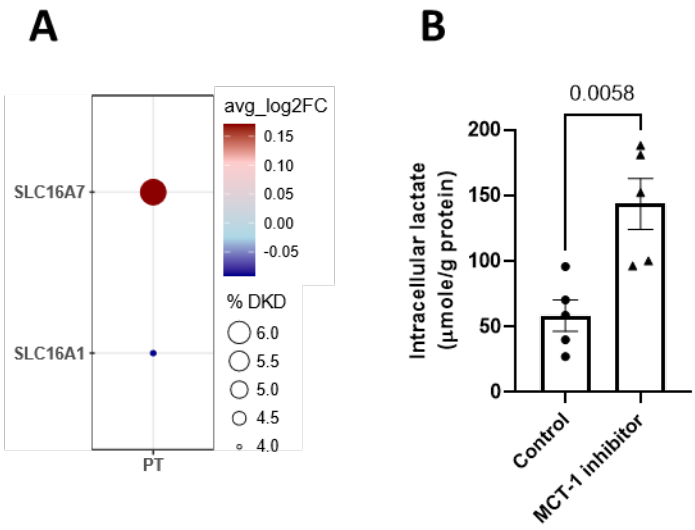
Supplemental Figure 1: Glucose induced increase in lactate in kidney sections is reduced by canagliflozin and dapagliflozin. Mouse kidney sections from 10–12-week-old male C57Blk/6J mice have a SGLT2 dependent increase in glucose (Gluc) uptake from normal glucose (NG) to high glucose (HG) (panel A, C) and lactate production (panel B, D). The SGLT2 inhibitor, Canagliflozin (CANA) and Dapagliflozin (DAPA) exhibit a dose dependent effect to reduce glucose uptake and lactate secretion compared to control (CTR).



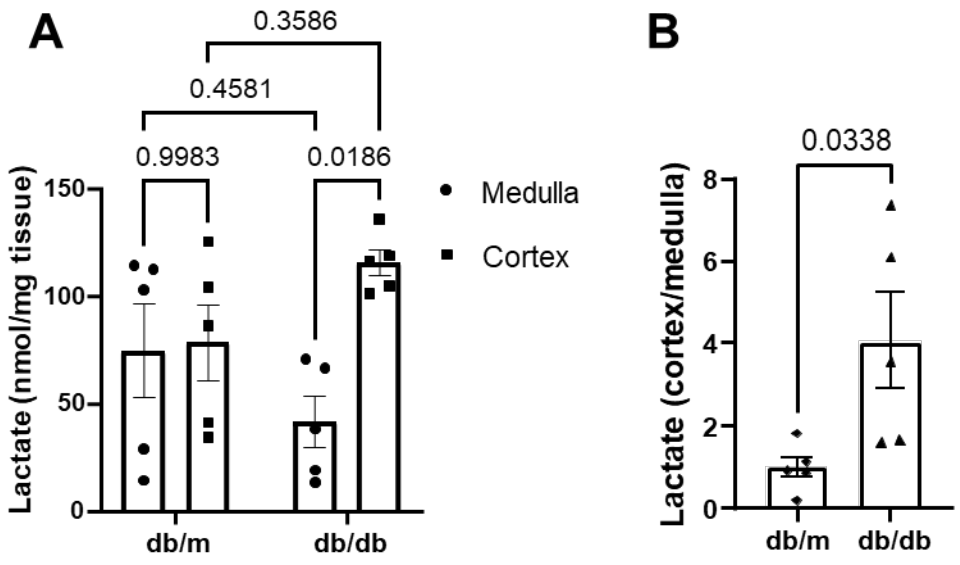
Supplemental Figure 2. **Expression of respiratory genes in the proximal tubular (PT) cells of patients with diabetic kidney disease (DKD).** Log2 fold-change calculated between average of normalized gene expression values form the living donors (LD; n=20) and DKD patients (n=11) in PT cells. Compared to LD, positive log2 fold-change indicate upregulated and negative values indicate downregulated genes in DKD.



Supplemental Figure 3. Extracellular lactate inhibits OCR in isolated mouse proximal tubular cells in a dose-dependent manner without cytotoxicity. OCR was measured in mouse primary renal tubular epithelial cells using Seahorse extracellular flux analyzer with 1-hour preincubation with different concentration (0-3mM). Basal respiration, maximal respiration, proton leak and ATP production linked OCR were calculated from the above traces (panel A). MTT assay in HK2 cells treated with various concentration of lactate for 24h (n=4) (panel B).



Supplemental Figure 4. Inhibition of lactate transporter accumulates intracellular lactate in kidney cortical sections. Dot plot of regulated lactate transporters, MCT-1(SLC16A1) and MCT2 (SLC16-A7) in the proximal tubular (PT) cells of patients with diabetic kidney disease (DKD). Log2 fold-change calculated between the average of normalized gene expression values from the living donors (LD; n=20) and DKD patients (n=11) in PT cells. % DKD circle size shows the percentage of cells in which the gene was detected within in DKD biopsies (panel A). Kidney sections from 10–12-week-old male C57Blk/6 mice were treated with 2 µm of MCT-1 inhibitor (SR13800, Sigma) for 24h and measured the cellular lactate level (panel B).



Supplemental Figure 5. Kidney lactate level in diabetic mice. Lactate levels and cortex/medulla lactate ratio in kidney medulla and cortex were compared between 6-month-old db/m and db/db mice (n=5/group). Two-way ANOVA followed by Tukey's multiple comparison test was performed for statistical analysis (panel A). Student 't' test was performed for statistical analysis (panel B).