# Supplemental Information

## Table S1

| DAG | T2D | T2D + VLCD |
|---|---|---|
| PO C18_1 C16 | 46.6±6.7 | 31.6±5.0 |
| AE C20_4 C20_5 | 107.3±7.2 | 67.3±4.8*** |
| AP C16 C20_4 | 5.1±0.4 | 3.3±0.2** |
| AS C18 C20_4 | 3.7±0.2 | 2.5±0.2** |
| SS C18,C18 | 3.9±0.7 | 3.8±0.3 |
| LS C18_2,C18 | 11.8±1.7 | 7.8±0.9 |
| OS C18_2,C18 | 5.0±0.8 | 3.9±0.7 |
| PP C16,C16 | 14.1±3.2 | 12.7±2.2 |
| SP C18,C16 | 7.0±1.1 | 5.8±0.7 |
| OO C18_1 | 33.5±4.7 | 25.1±4.8 |
| OL C18_1,C18_1 | 57.8±9.5 | 38.0±7.0 |
| LL C18_2,C18_2 | 81.8±16.4 | 60.0±11.7 |
| PL C16,C18_2 | 119.4±16.5 | 76.8±9.8 |
| **Total DAG** | **497.1±57.3** | **343.4±37.8** |
| | | |
| **Ceramide** | **T2D** | **T2D + VLCD** |
| C16 | 50.1±5.0 | 54.4±2.8 |
| C18 | 8.5±0.9 | 9.9±0.8 |
| C20 | 42.8±10.9 | 47.8±11.7 |
| C22 | 39.6±4.7 | 44.7±4.5 |
| C24:1 | 15.0±1.3 | 16.7±0.9 |
| C24 | 50.2±5.0 | 56.4±2.7 |
| **Total ceramide** | **206.2±23.4** | **229.8±22.1** |

**Table S1, related to Fig. 1**. Individual DAG and ceramide species. Data are the mean±S.E.M. of n=6 per group, with *$P$<0.05, **$P$<0.01 and ***$P$<0.001 by the 2-tailed unpaired Student's t-test.

# Figure S1

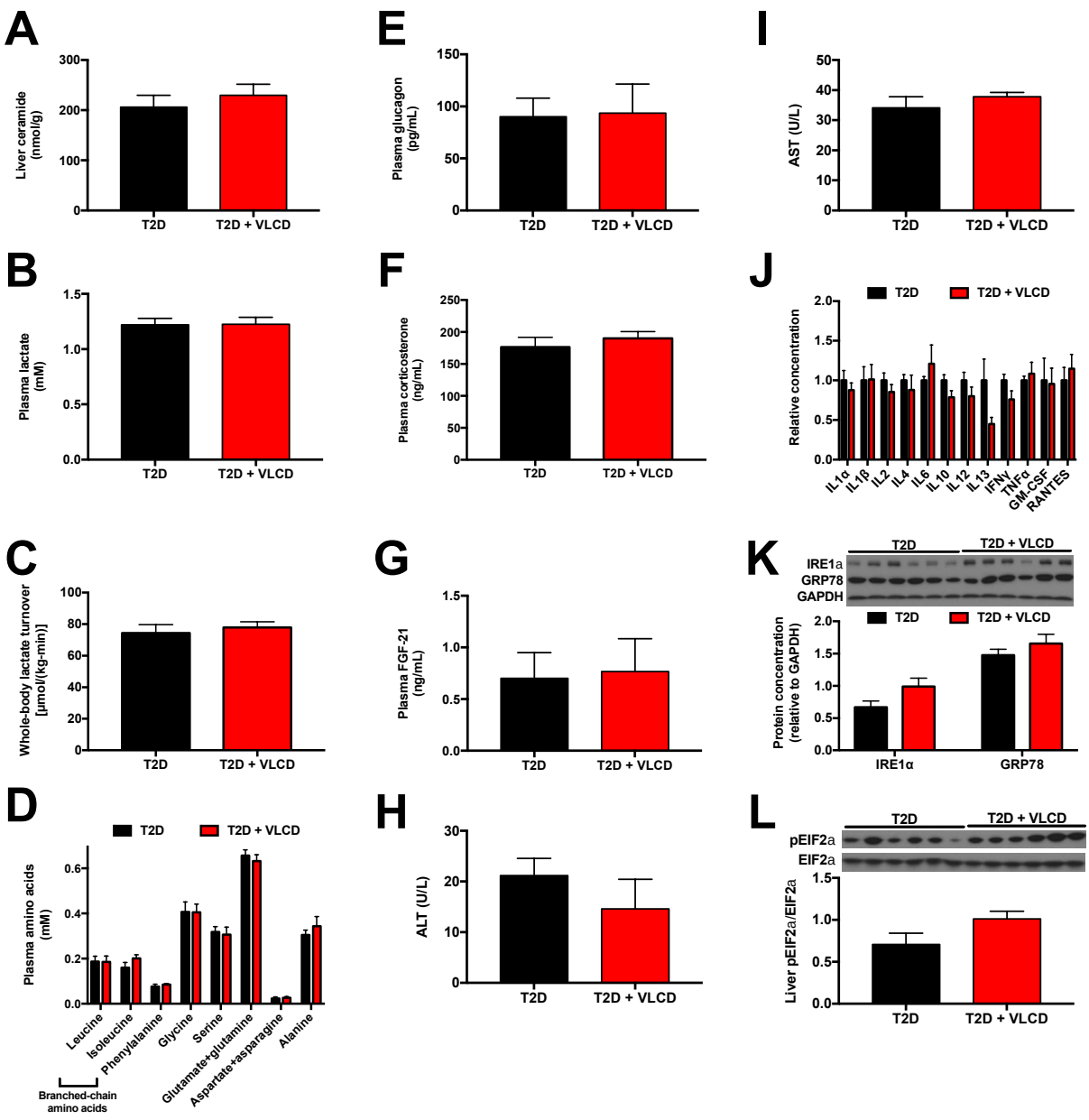


**Fig. S1, related to Fig. 1.** Caloric restriction reverses fasting hyperglycemia in a rat model of T2D without any alterations in gluconeogenic substrates (lactate, alanine, amino acids), gluconeogenic hormones (corticosterone, glucagon), FGF-21 or hepatic ceramide content. (A) Liver ceramide content. (B)-(C) Plasma lactate and whole-body lactate turnover. (D) Plasma amino acid concentrations. (E)-(G) Plasma glucagon, corticosterone, and FGF-21. (H)-(I) Plasma ALT and AST. (J) Liver inflammatory cytokine concentrations. (K)-(L) ER stress markers. In all panels, data are the mean±S.E.M. of n=6 per group, with no differences by the 2-tailed unpaired Student's t-test.

# Figure S2

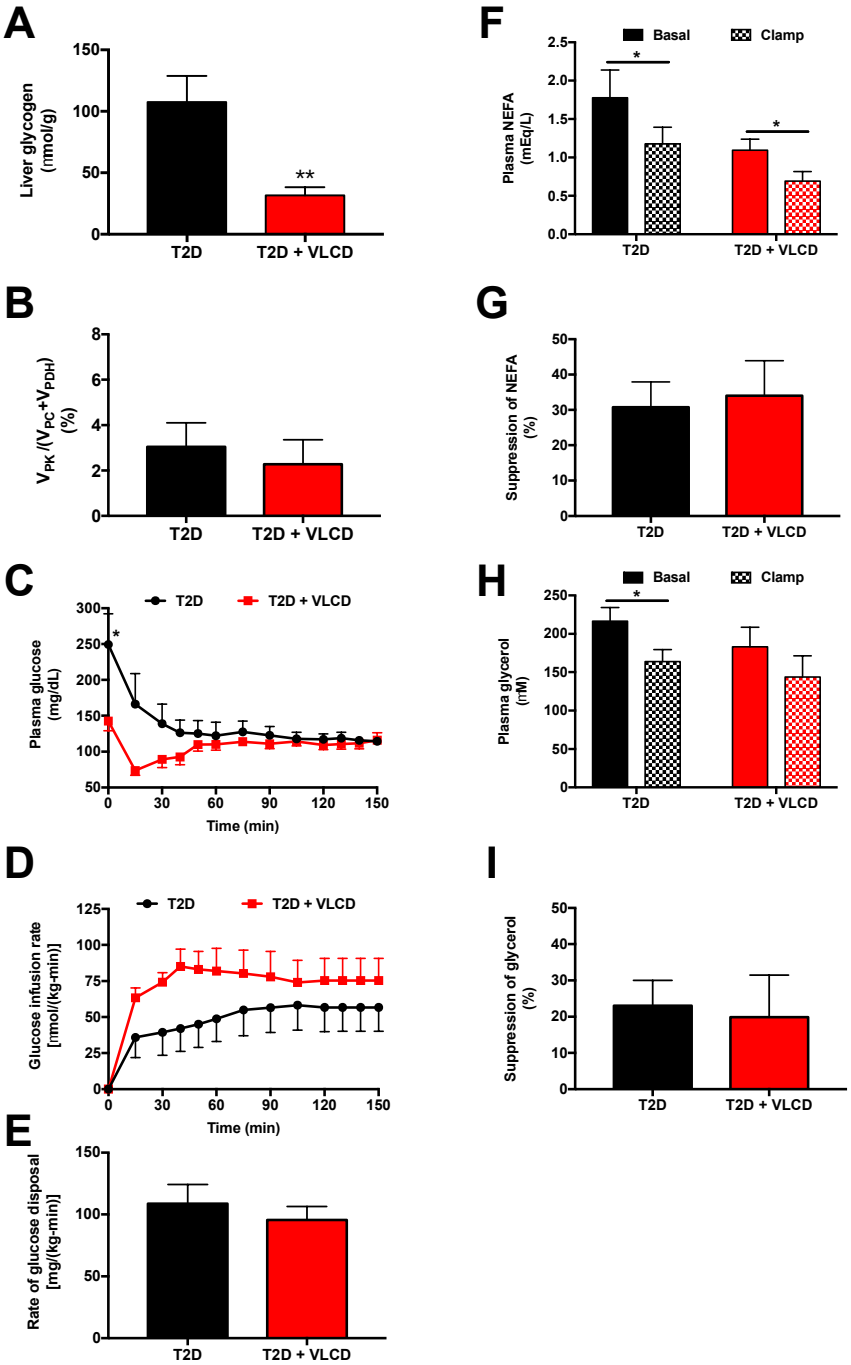


**Fig. S2, related to Fig. 2.** Liver glycogen content is reduced and hepatic insulin sensitivity is improved in VLCD rats. (A) Liver glycogen in 8 hr fasted rats. ***P*<0.01 by the 2-tailed unpaired Student's t-test. n=6 per group. (B) Ratio of hepatic pyruvate kinase flux to the sum of pyruvate carboxylase and pyruvate dehydrogenase flux. n=5 per group. (C)-(D) Plasma glucose and glucose infusion rate required to maintain euglycemia during a hyperinsulinemic-euglycemic clamp. In panels (C)-(I), n=6 per group. (E) Insulin-stimulated glucose disposal rate. (F)-(G) Plasma NEFA and suppression of NEFA concentrations during the clamp. In panels (F) and (H), **P*<0.05 by the 2-tailed paired Student's t-test. (H)-(I) Plasma glycerol and suppression of glycerol concentrations during the clamp. In all panels, data are the mean±S.E.M.

# Figure S3

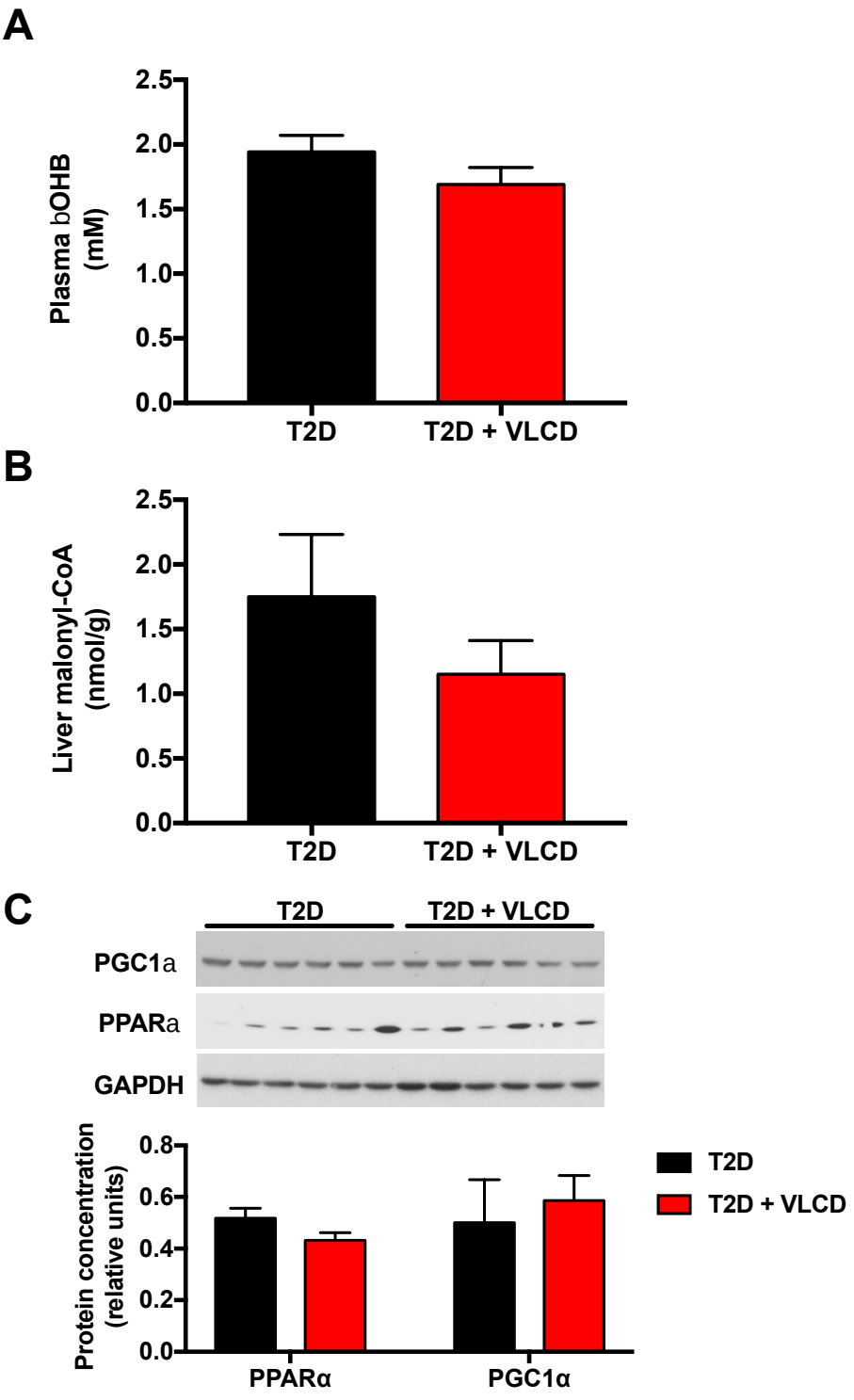


**Fig. S3, related to Fig. 3.** A very low calorie diet does not alter hepatic mitochondrial oxidation. (A) Plasma βOHB. (B) Liver malonyl-CoA. (C) Hepatic PPARα and PGC1α protein expression, normalized to GAPDH. In all panels, data are the mean±S.E.M. of n=6 per group. No significant differences were observed with the 2-tailed unpaired Student's t-test.

# Figure S4

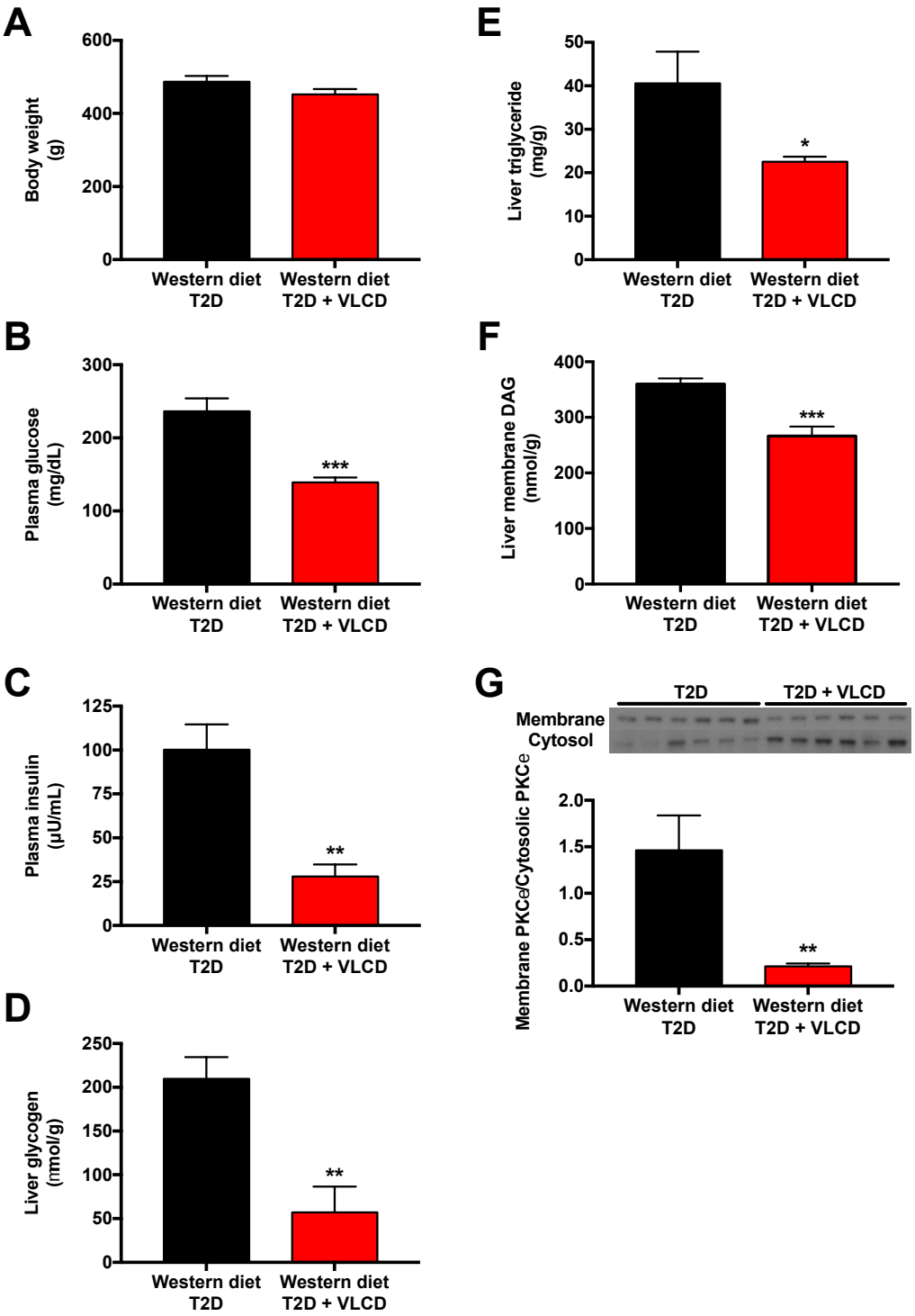


**Fig. S4, related to Fig. 4.** VLCD reverses hyperglycemia in Western diet fed rats. (A) Body weight. (B)-(C) Plasma glucose and insulin concentrations following an 8 hr fast. (D) Liver glycogen concentrations. (E)-(G) Hepatic TAG, DAG, and membrane/cytosol PKCε protein expression. Data are the mean±S.E.M. of n=6 per group. In all panels, **P*<0.05, ***P*<0.01, ****P*<0.001 by the 2-tailed unpaired Student's t-test.