Supplemental Table 1. Clinical Features Distinguishing Nutritional Ketosis from Ketoacidosis

Feature	**Nutritional Ketosis**	**Ketoacidosis**
Clinical state	Physiological	Pathological
Serum insulin	Low to moderate (Sufficient)	Absent/very low (Deficient)
Blood glucose	< 120 mg/dL	> 250 mg/dL[1]
Blood ketones (βOHB)	0.5-5.0 mM	> 3- 5 mM[2]
Urine ketones (acetoacetate)	Variable[3]	Present
Ketone production	Regulated	Unregulated
Venous pH	> 7.3[4]	≤ 7.3
Serum bicarbonate	> 18mEq/L[4]	≤ 15-18mEq/L

[1] "Euglycemic" ketoacidosis (BG < 250 mg/dL) may occur in patients with T1D (in various states associated with starvation) and in T2D, and is more common in those taking SGLT2 inhibitors.
[2] βOHB concentration of ≥ 5.3 mM in children with hyperglycemia (on a conventional diet) provides optimal accuracy for predicting ketoacidosis (1).
[3] With adaptation to nutritional ketosis, urinary excretion of ketone bodies decreases.
[4] See Gomez-Arbelaez et al., Sheikh-Ali et al., and Dhatariya et al. (2-4).
Abbreviations: βOHB, β-hydroxybutyrate

Supplemental Table 2: A Research Agenda to Study Carbohydrate Restriction for the Treatment of Diabetes. Key scientific questions listed according to study type, with potential characteristic design aspects noted.

STUDY TYPE	Duration	Focus of Validity[1]	Setting	Participant number
Mechanistic	Days to weeks	Internal	Metabolic ward	10 to 20
• What insulin regimen(s) provide(s) the best balance of glycemic control and safety with a VLC diet for T1D? • Does the presence of ketones on a VLC diet protect against symptomatic hypoglycemia? • Do ketones modulate pathophysiological processes (e.g., related to chronic inflammation, oxidative stress) of relevance to diabetic complications? • How do VLC diets with normal (15 - 20%) vs high (≥25%) protein content affect glycemic control, metabolic and safety parameters?				
Efficacy	3 to 12 months	Internal	Outpatient with food provision	50 to 200
• Does a VLC improve measures of glycemic control in T1D and T2D? • Does a VLC diet improve adiposity, insulin resistance and other components of the metabolic syndrome? • How do VLC diets affect risk for symptomatic hypoglycemia and diabetic ketoacidosis in T1D? • How do VLC diets affect LDL cholesterol and small-dense LDL particles? • Do VLC diets adversely affect growth and/or pubertal development in children with T1D? • Do VLC diets increase risk for other clinically important adverse events in T1D or T2D? • Does a MC or LC diet, with a simultaneous focus on reducing GI, produce similar benefits to a VLC diet?				
Behavioral aspects	Various	Internal / External	Various	Various
• How do CR diets affect hunger, satiety and eating behavior? • Which behavioral methods will enhance long-term adherence to a CR diet? • Which environmental interventions will enhance long-term adherence to a CR diet? • How do CR diets affect quality of life and well-being? • What are the financial costs of a VLC diet (e.g., potentially increased for food, decreased for insulin)?				
Effectiveness (Surrogate outcomes)	1 to 2 years	External	Outpatient	100 to 500
• How do CR vs conventional diabetes diets affect glycemic control over the long-term for T1D and T2D? • How do CR vs conventional diabetes diets affect CVD risk factors over the long-term for T1D and T2D? • Do certain patients respond especially well to a CR diet? And if so, can they be identified in advance?				
Effectiveness (Clinical outcomes)	≥2 years	External	Outpatient	≥500
• Do CR vs conventional diabetes diets prevent microvascular disease in T1D and T2D? • Do CR vs conventional diabetes diets prevent CVD, kidney disease or limb amputation in T1D and T2D? • Do CR vs conventional diabetes diets prevent premature mortality in T1D and T2D? • Does a CR diet prevent T2D in individuals at risk? • Does a CR diet reduce direct medical and total (including lost productivity) costs associated with diabetes? • Does CR from time of diagnosis extend honeymoon period in T1D?				

Abbreviations: CR; carbohydrate-restricted; CVD, cardiovascular disease; GI, glycemic index; LC, low carbohydrate (10-25% energy intake); MC, moderate carbohydrate (26-45% energy intake); T1D, type 1 diabetes; T2D, type 2 diabetes; VLC, very-low-carbohydrate (<10% energy intake)

[1] Internal validity (experimental control over intervention) vs external validity (practicality and generalizability)

Supplemental References

1. Tremblay ES, Millington K, Monuteaux MC, Bachur RG, and Wolfsdorf JI. Plasma beta-Hydroxybutyrate for the Diagnosis of Diabetic Ketoacidosis in the Emergency Department. *Pediatr Emerg Care.* 2020.
2. Dhatariya KK, Glaser NS, Codner E, and Umpierrez GE. Diabetic ketoacidosis. *Nat Rev Dis Primers.* 2020;6(1):40.
3. Gomez-Arbelaez D, Crujeiras AB, Castro AI, Goday A, Mas-Lorenzo A, Bellon A, et al. Acid-base safety during the course of a very low-calorie-ketogenic diet. *Endocrine.* 2017;58(1):81-90.
4. Sheikh-Ali M, Karon BS, Basu A, Kudva YC, Muller LA, Xu J, et al. Can serum beta-hydroxybutyrate be used to diagnose diabetic ketoacidosis? *Diabetes Care.* 2008;31(4):643-7.