University of East Anglia

Norfolk and Norwich University Hospitals NHS
NHS Foundation Trust

Update on Measuring Ketones

The why, when, and how

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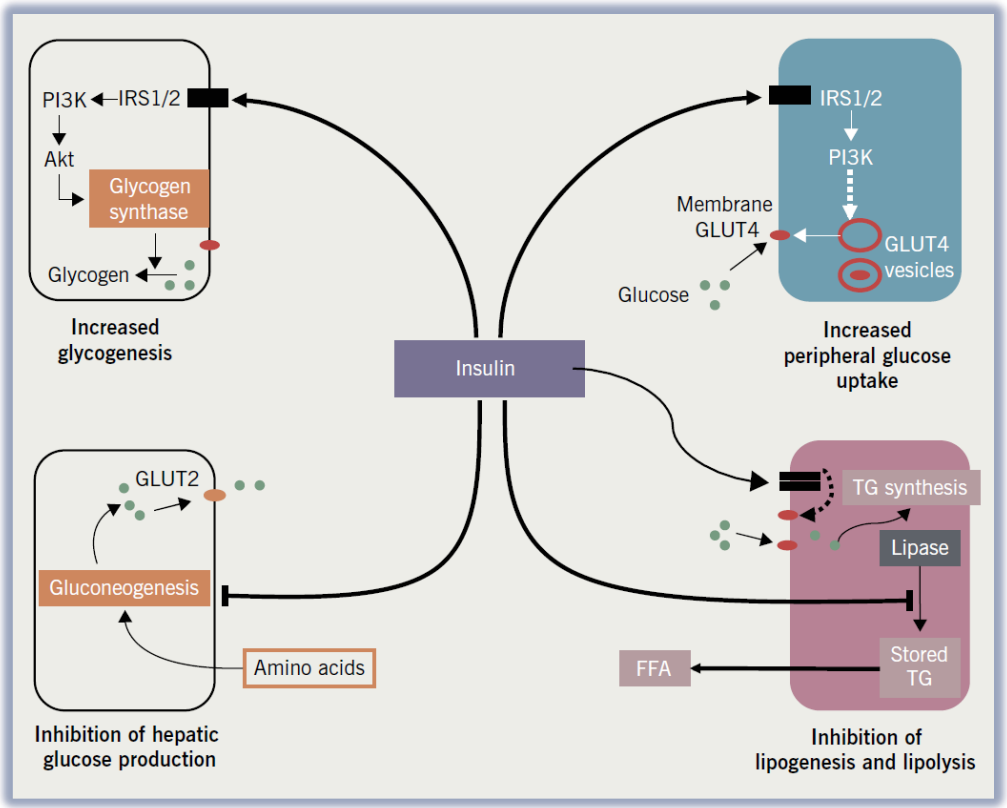
Disclosures

- In the last 12 months I have received honoraria, travel or fees for advisory boards from
  - AstraZeneca
  - Novo Nordisk
  - Boehringer-Ingelheim
  - Eli Lilly

Topics to be Covered

- What are ketones?
- Why are they important?
- When might you encounter them?
- Diagnosing diabetic ketoacidosis
- Measurement: Urine vs Blood vs Breath?
- Euglycemic DKA
- Drug induced ketosis

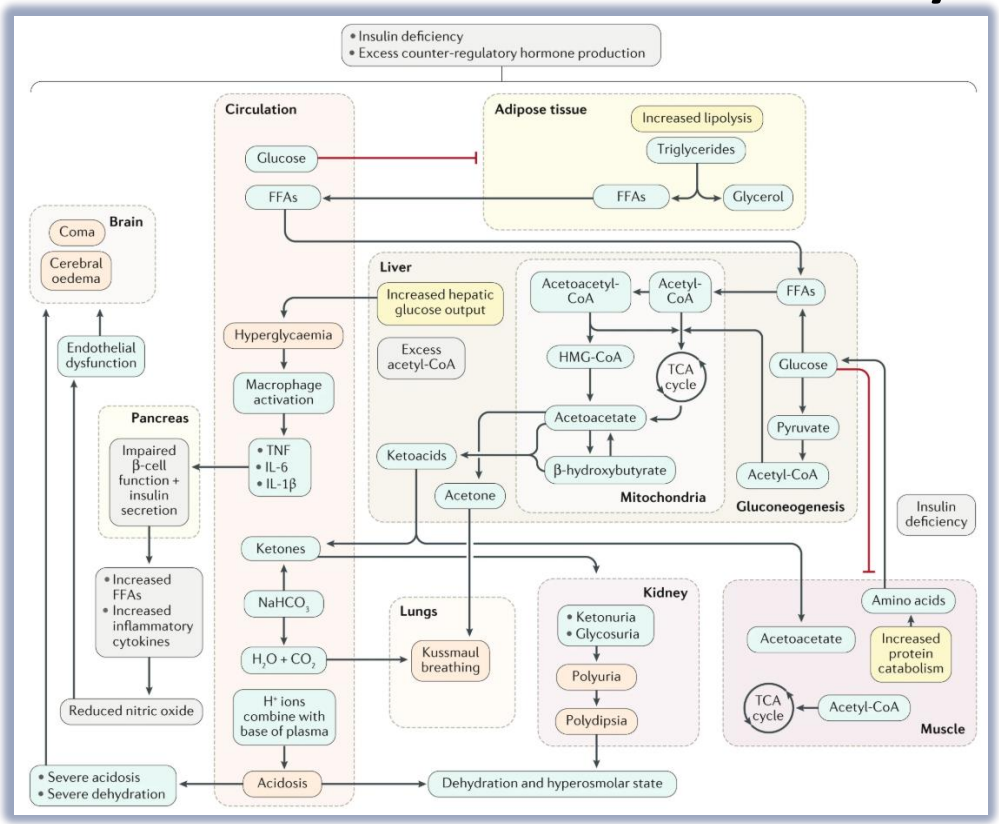
Back to Basics



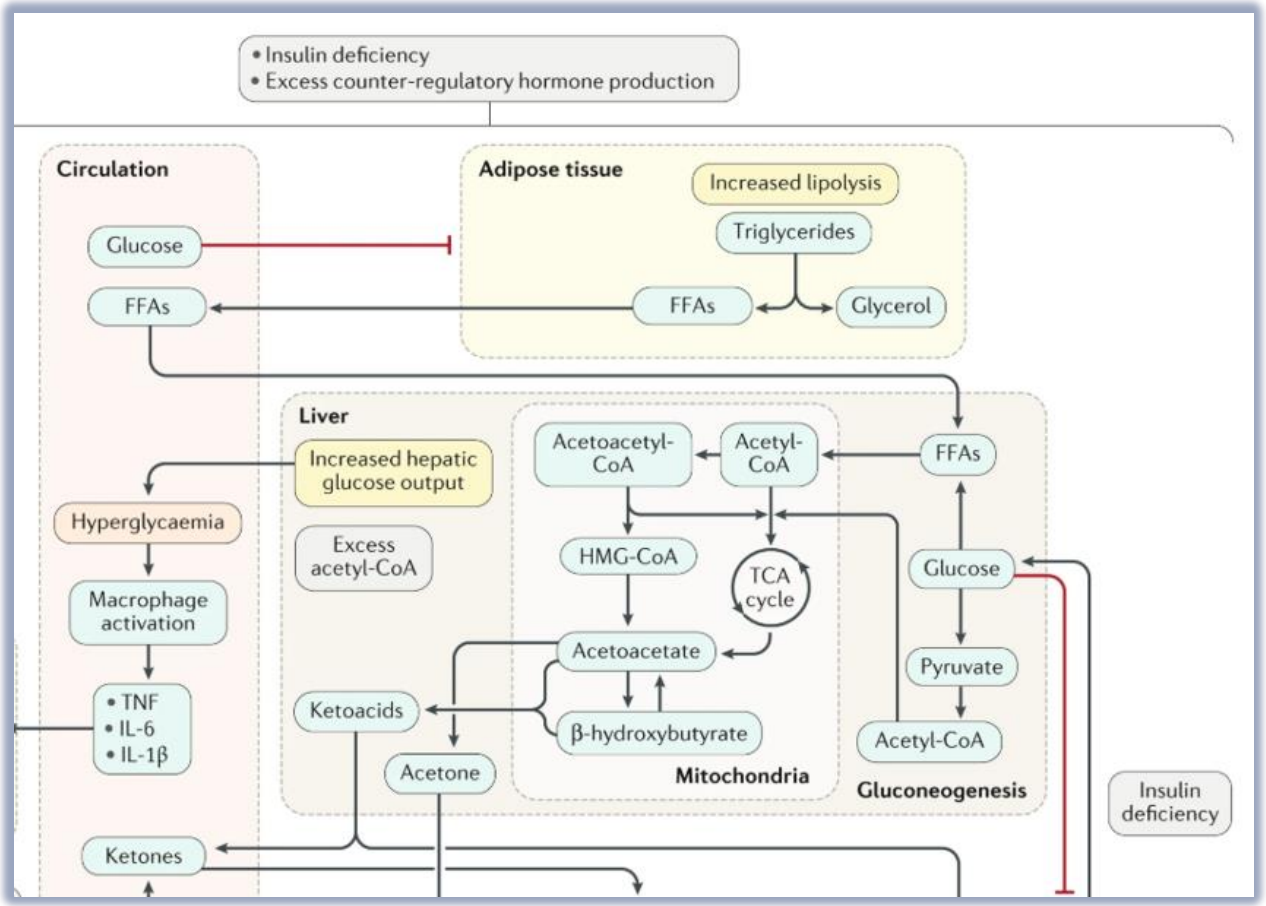
- At different plasma concentrations, insulin has different effects
  - At the very lowest concentrations, insulin suppresses ketogenesis
  - Then it stops gluconeogenesis and skeletal muscle catabolism
  - Then it causes glucose uptake and glycogen synthesis
  - Finally, it is an anabolic hormone

Barwell ND et al Br J Cardiol 2011;18(5/6):224-228

Ketones – What are They?



Dhatariya KK et al Nat Rev Dis Primers 2020:6;40

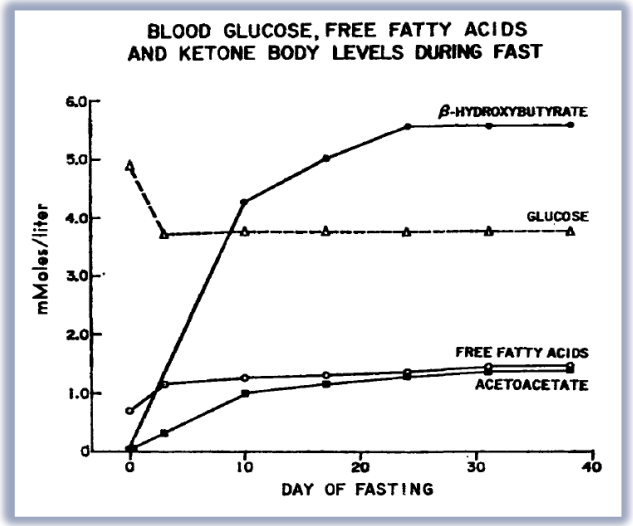


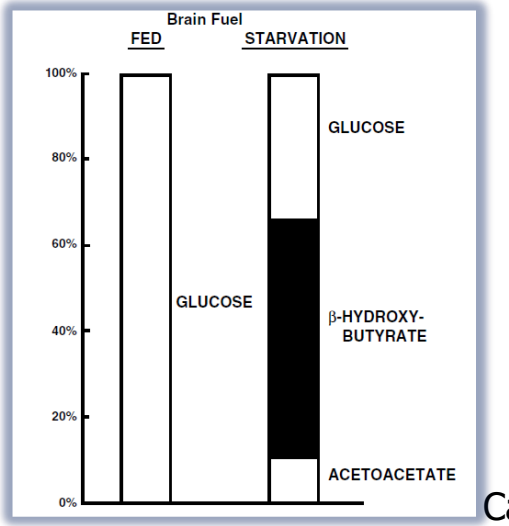
Dhatariya KK et al Nat Rev Dis Primers 2020:6;40

Ketones – Why Are They Important?

TABLE 2. *Levels of Circulating Substrates.*

Period of Observation	Glucose	Free Fatty Acids	Acetoacetate	β-Hydroxy-butyrate	Glycerol	Amino Acids	Lactate	Pyruvate
	mg/100 ml			*mM*				
Post-absorptive	80	0.5	0.01	0.01	0.06	4.5	0.6	0.1
After 1-wk fast	65	1.5	1.0	4.0	0.1	4.5	0.6	0.1
After fast of 4-5 wk	65	1.5	1.5	6.0	0.1	3.5	0.6	0.1





- Evolution!

Cahill GF NEJM 1970;282(12):668-675
Cahill GF Diabetes 1971;20(12):785-799
Cahill GF Ann Rev Nutr 2006;26(1):1-22

Conditions in Which They are Raised

- Diabetic ketoacidosis (with or without raised glucose)
- Starvation
- Pregnancy
- Excess alcohol intake
- SGLT2 inhibitor use

Their presence represent states of absolute or relative insulin insufficiency

Part of Defining and Diagnosing DKA

	DKA		
	Mild (plasma glucose >250 mg/dl)	Moderate (plasma glucose >250 mg/dl)	Severe (plasma glucose >250 mg/dl)
Arterial pH	7.25–7.30	7.00 to <7.24	<7.00
Serum bicarbonate (mEq/l)	15–18	10 to <15	<10
Urine ketone	Positive	Positive	Positive
Serum ketone	Positive	Positive	Positive
Effective serum osmolality	Variable	Variable	Variable
Anion gap	>10	>12	>12
Mental status	Alert	Alert/drowsy	Stupor/coma

DIAGNOSIS:

Ketonaemia $\geq$ 3.0mmol/L **or** significant ketonuria (more than 2+ on standard urine sticks)

Blood glucose > 11.0mmol/L or known diabetes mellitus (200 mg/dL)

Bicarbonate (HCO_3^-) < 15.0mmol/L **and/or** venous pH < 7.3

ADA, American Diabetes Association; DKA, diabetic ketoacidosis; JBDS, Joint British Diabetes Societies.

Kitabchi AE, *et al. Diabetes Care* 2009;32:1335–1343;

Association of British Clinical Diabetologists. Joint British Diabetes Societies (JBDS) for Inpatient Care Group.

The management of diabetic ketoacidosis (DKA) in adults | ABCD (Diabetes Care) Ltd

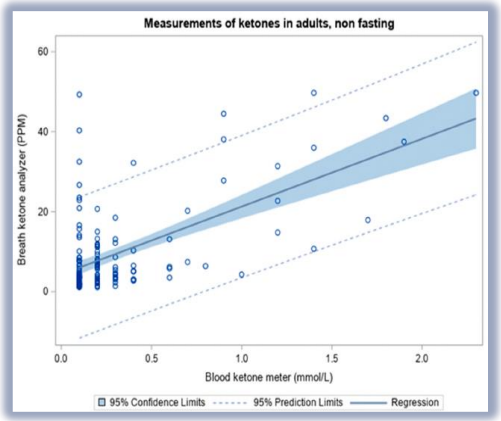
Measurement: Urine vs Blood?

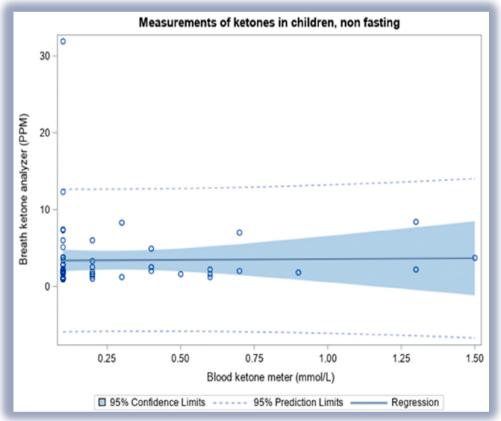
Plasma ketones		Urine ketones	
Advantage	**Disadvantage**	**Advantage**	**Disadvantage**
Measures the current plasma ketone concentration, allowing diagnostic certainty, and subsequent management plan			Reading is an average of urine ketone concentration since last void; management may be delayed
Allows for timely change of treatment as necessary			Length of time to resolution of DKA may be overestimated
Fast, immediate measurement			Urine sample collection may be delayed due to dehydration
Greater sensitivity and specificity for DKA			Lower sensitivity and specificity for DKA
Measures beta-hydroxybutyrate, the predominant ketone in DKA			Measures only acetoacetic acid, not beta-hydroxybutyrate
	Potentially painful	Painless	
	Equipment (meter) needed	Readings can be read off the bottle	
	Meter needs regular quality assurance testing	No quality assurance needed	
	Staff who can use the meter required (if in hospital)	No technical skill required to use the equipment	
Individually wrapped ketone strips have a long shelf life			Ketone strips have a relatively short shelf life
	Relatively expensive	Relatively cheap	
	Meter may be inaccurate at readings outside the range it is designed for		
	Interference caused by other substances (e.g. vitamin C), giving inaccurate results		Interference caused by other substances (e.g. vitamin C), giving inaccurate results

Dhatariya KK Rev Diabet Studies 2016;13(4):217-225

Breath Ketones

- Breath acetone concentrations vary from 1ppm in healthy non fasting states, to over 1250ppm in DKA
- There is debate over whether breath ketones are a true reflection of plasma ketones - particularly in children





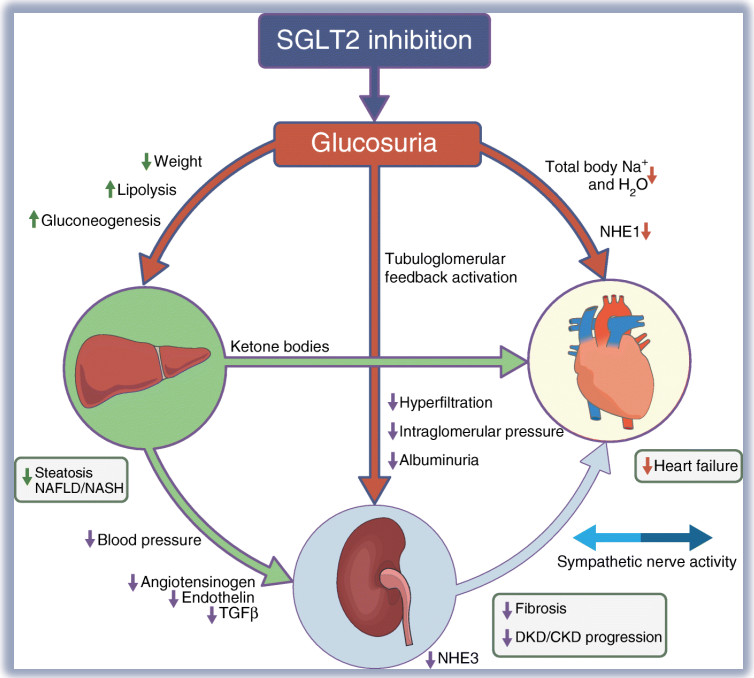
Qiao Y et al Biomed Res Int 2014;869186
Akturk HK et al J Diab Comp 2021;35(11):108030

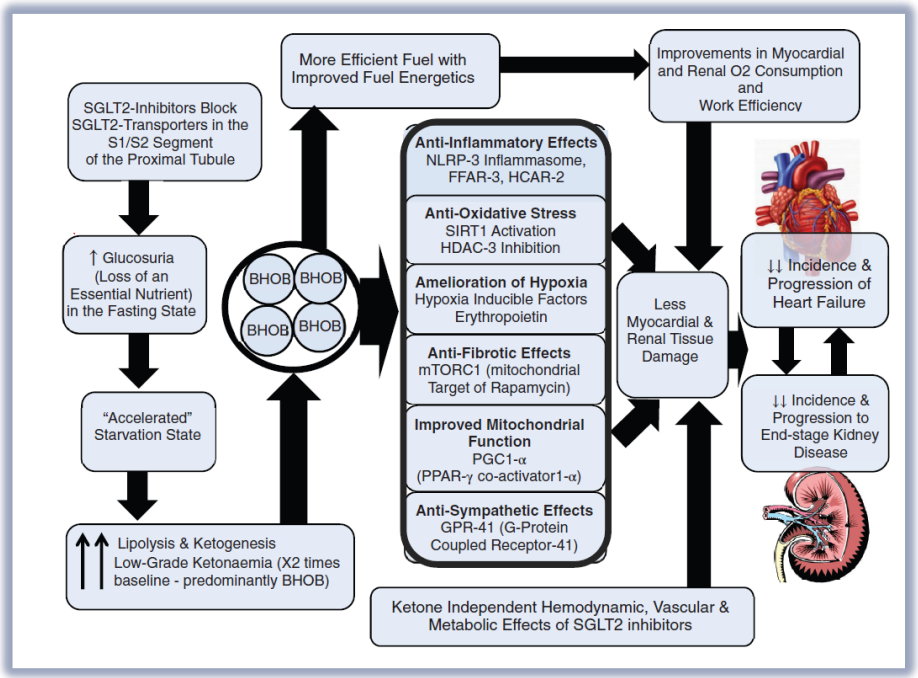
Breath Ketones

- As the technology improves, the devices may prevent DKA admissions
- Issues around affordability, reliability, accuracy, sustainability, readability and suitability have been raised

Brew-Sam N et al PLOS One 2022;17(7):e269925

SGLT2 Induced Ketosis / Ketoacidosis





Wanner C et al Diabetologia 2018;61(10):2134-2139
Ekanayake P et al DOM 2022;24(1):3-11

Euglycaemic DKA?

TABLE. Prevalence of Euglycemic Diabetic Ketoacidosis in People With Type 1 Diabetes in the United Kingdom[a]

	Number	Admission glucose <11.0 mmol/L (200 mg/dL)[1]	Admission glucose <13.9 mmol/L (250mg/dL)[2]	Admission glucose <16.7 mmol/L (300 mg/dL)[3]
National survey (2014)[4]	277	6	14	23
Local audit (2015)[5]	57	4	4	6
	334	10	18	29
		3.0%	5.4%	8.7%

[a]Data from a national survey[4] and local audit.[5] Data are divided into different thresholds of "euglycemia."

Munro JF et al BMJ 1973;2(5866):578-5880
Kitabchi AE et al Diab Care 2009;32(7):1335-1343
Dhatariya K et al Diab Med 2016;33(2):252-260
Macfarlane J et al Mayo Clin Proc 2019;94(9):1909-1910

Immune Checkpoint Inhibitors

Up to 75% of people who develop ICP-induced hyperglycaemia, present with DKA
But animal data suggest that ketone bodies enhance the anticancer effects of PD-1 blockade

Type of Systemic Anti-Cancer Therapy	Drug Examples	Risk of Diabetes/Hyperglycaemia (Range of any grade)	Type of diabetes most likely to develop
Targeted therapy			
Immune Checkpoint Inhibitors			
PD-1	Nivolumab [27]	<1%	T1DM
	Pembrolizumab [28]	1-2.2%	
CTLA-4	Ipilumumab [27]	0.02%	
	Combination ICP [77]	4%	

Joharatnam-Hogan N et al. Diab Med 2022;39(1):e14636
Ferrere G et al JCI Insight 2021;6(2):e145207

In Summary

- Ketones are an evolutionary adaptation to prolonged starvation
- Their presence can be beneficial or harmful – depending on the rate of appearance in the circulation
- Measurement of plasma is better than urine – but both have limitations; breath is not yet ready for ‘prime time’
- Newer diabetes and anti-cancer agents can precipitate DKA

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