Clinical utility of ketone testing

Eric S. Kilpatrick
Consultant in Chemical Pathology
Wythenshawe Hospital, Manchester
Honorary Professor in Clinical Biochemistry,
Hull York Medical School, UK

NHS
Manchester University
NHS Foundation Trust

H·Y·M·S

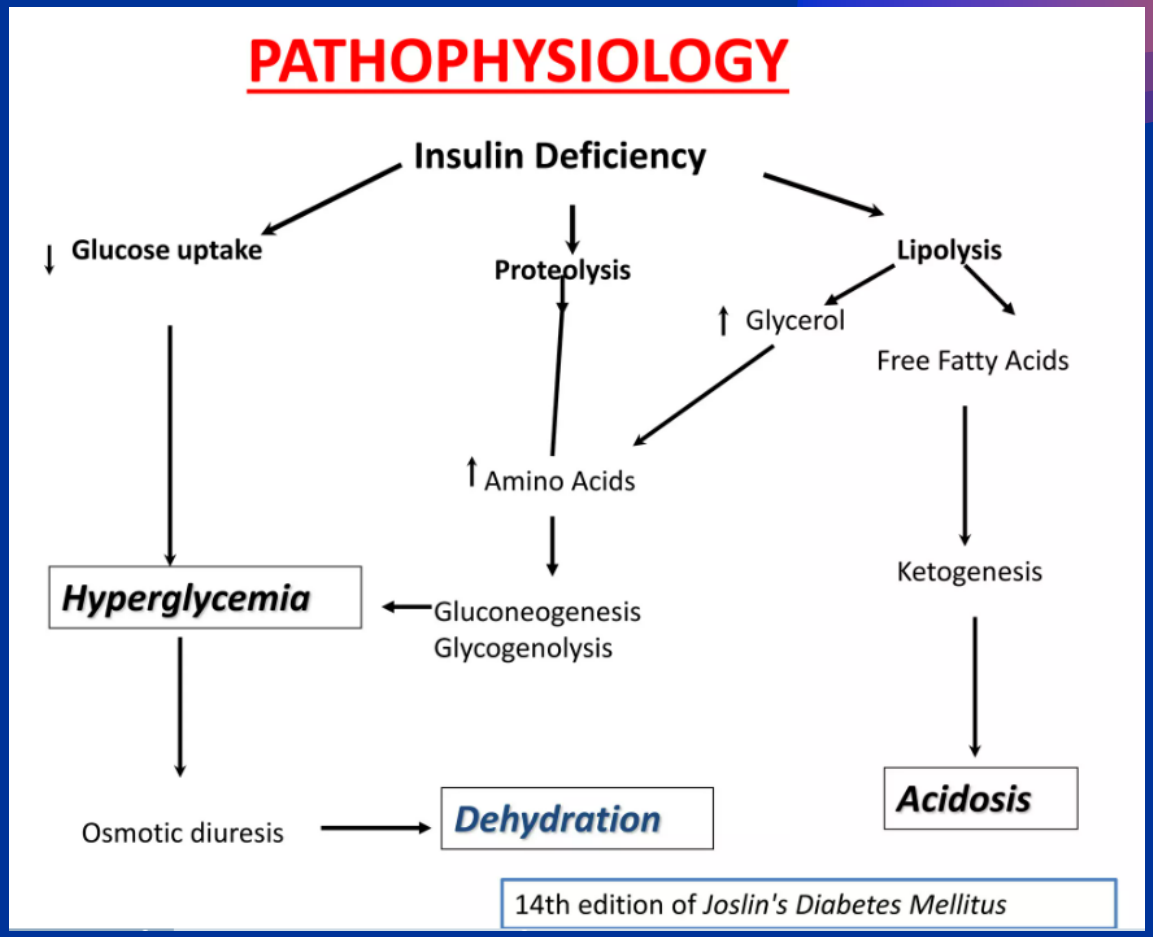
Clinical utility of ketone testing

- Causes of ketonaemia
- Diabetic ketoacidosis (DKA) guidelines
- Ketone targets
- Ketone analytical performance specifications (APS)
- Remaining uncertainties

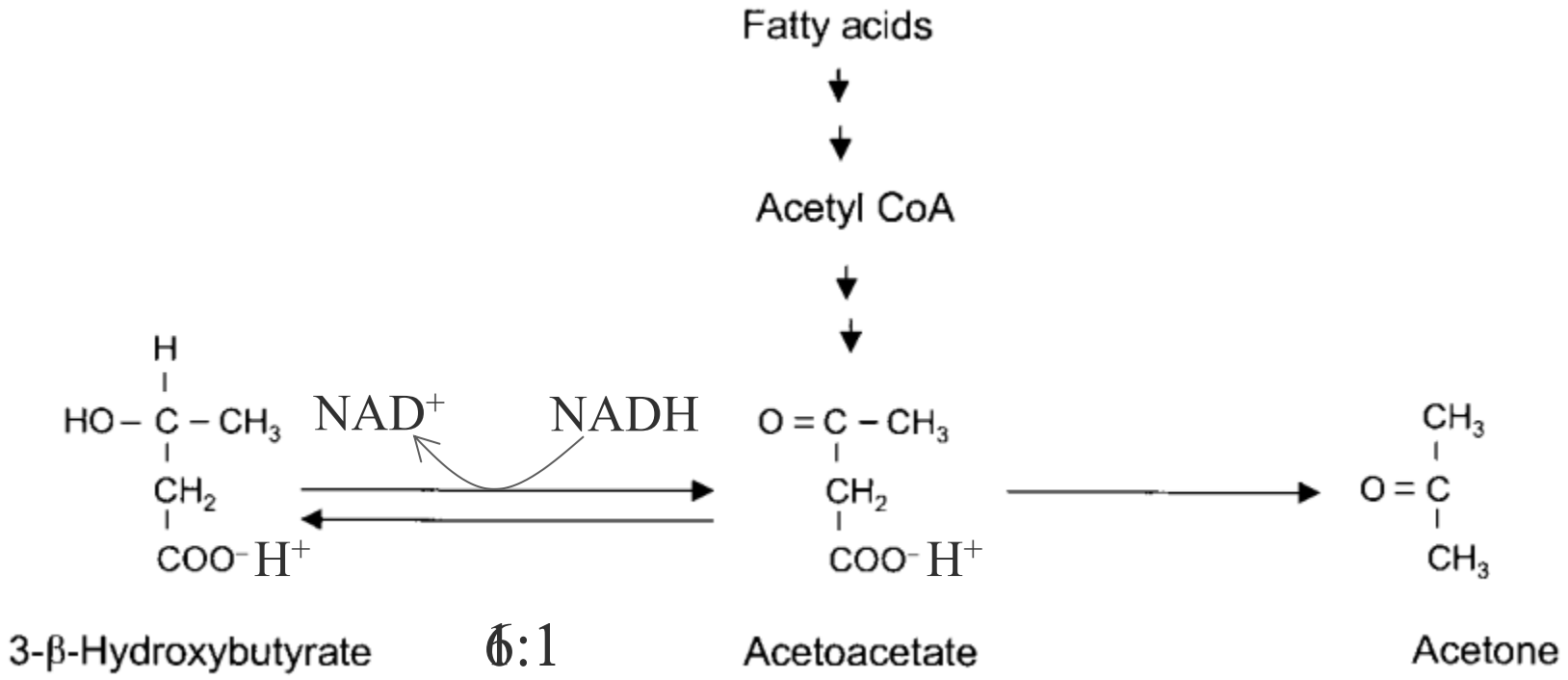
Causes of ketonaemia

- Diabetic ketoacidosis
- Starvation/Ketogenic diet
- Alcoholic ketoacidosis
- Metabolic disorders e.g MMA, PA
- SGLT-2 inhibitors in type 2 diabetes

Development of Diabetic Ketoacidosis (DKA)



Ketone formation



Diabetes Metab Res Rev 1999; 15: 412-26

Diagnosing DKA

- Diabetic Hyperglycaemia
- Ketosis Ketonaemia/Ketonuria
- Acidosis Metabolic acidosis

DKA diagnostic criteria

	DKA Diagnostic Criteria		
	Glucose	Ketones	Acidosis
American Diabetes Association (ADA), 2009	Glucose >250mg/dL (13.9mmol/L) by nitroprusside reaction	Urine or serum ketones 'positive' by nitroprusside reaction	pH<7.3 Bicarbonate <18mmol/L
American Association of Clinical Endocrinologists (AACE) et al. 2017		Elevated serum or urine ketones (greater than the upper limit of the normal range).	Serum bicarbonate <15mmol/L or blood pH <7.3
International Society for Paediatric and Adolescent Diabetes (ISPAD), 2018	Glucose >200mg/dL (11.1mmol/L)	BOHB ≥3 mmol/L or moderate/large ketonuria Blood measured whenever possible,	Venous pH <7.3 and/or Bicarbonate <15mmol/L
Joint British Diabetes Societies (JBDS), 2021	Glucose >11.1mmol/L (200mg/dL)	Capillary or blood ketones >3mmol/L or urine ketones ≥2+	Venous pH <7.3 and/or Bicarbonate <15mmol/L
ADA/EASD/JBDS/AACE/DTS 2024	Glucose >200mg/dL (11.1mmol/L)	Capillary or blood ketones >3mmol/L or urine ketones ≥2+	pH<7.3 and/or Bicarbonate <18mmol/L

BOHB ~~Blood ketone~~ measurement

Degrees of ketonaemia

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<0.6 mmol/L	Normal
0.6 to 1.5 mmol/L	Ketonaemia
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Treatment of DKA	
JBDS	>0.5 mmol/L/hr fall in BOHB
ISPAD	Approximately 0.5 mmol/L/hr fall in BOHB

Ketone questions

PRACTICE

RATIONAL TESTING

Distinguishing between type 1 and type 2 diabetes

Alexandra E Butler,[1] David Misselbrook[2]

Check for updates

1 Diabetes Research Center, Qatar Biomedical Research Institute Hamad Bin Khalifa University, Qatar Foundation, Doha, Qatar
2 Department of Family Medicine, Royal College of Surgeons in Ireland - Bahrain, Adliya, Kingdom of Bahrain
Correspondence to A E Butler abutler@rcsi.edu.qa

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What you need to know

- In patients with new onset hyperglycaemia where the type of diabetes is ambiguous, diabetes specific autoantibodies are the diagnostic test of choice to distinguish between type 1 and type 2 diabetes
- Patients with newly diagnosed diabetes who are over 40 and respond well to oral anti-hyperglycaemic therapy do not need to undergo testing to distinguish between type 1 and type 2 diabetes
- Glycated haemoglobin (HbA1c) is not recommended as a diagnostic test for patients with possible or suspected type 1 diabetes because it may not reflect a recent rapid rise in blood glucose and results take longer than with serum glucose testing

A 33 year old man with no notable medical history attends his general practitioner reporting two months of fatigue, with no other symptoms. His mother has hypothyroidism. His body mass index is 25 kg/m² and he has a pulse rate of 72 beats/min and blood pressure 135/88 mmHg with no postural drop. Examination is unremarkable. A random blood glucose test shows 14 mmol/L (250 mg/dL). Urinalysis is normal. The next day the patient returns, and a repeat fasting glucose test finds 14 mmol/L.

This article is intended to help primary care doctors to differentiate between type 1 and type 2 diabetes when first diagnosing diabetes in a patient where the distinction is unclear.

Differentiating between type 1 and type 2 diabetes

For people who fit the classic pattern of type 2 diabetes (table 1), and where two glucose test results are in the diabetic range (box 1), no further testing is required for diagnosis, and management should follow current guidelines.[1] Follow-up testing of glycated haemoglobin (HbA1c) is useful to assess glycaemia over time and to tailor treatment.[1]

Table 1 | Clinical features at presentation that help to distinguish type 1 and type 2 diabetes

	Type 1 diabetes	Type 2 d…
Weight loss	Yes (though not always at presentation)	

Ketone questions

- Where did the blood ketone thresholds come from?
- What's this about using the nitroprusside reaction to measure blood ketones instead of measuring BOHB?
- Is everyone not using meters already?

Ketone controversies

Diabetes Care Volume 45, February 2022

Check for updates

Controversies Around the Measurement of Blood Ketones to Diagnose and Manage Diabetic Ketoacidosis

Eric S. Kilpatrick,[1] Alexandra E. Butler,[2] Linda Ostlundh,[3] Stephen L. Atkin,[2] and David B. Sacks[4]

Diabetes Care 2022;45:267–272 | https://doi.org/10.2337/dc21-2279

Ketone questions

1. Should blood ketone measurement be used for diagnosing and treating DKA?
2. What is the preferred test to measure blood ketones: the nitroprusside reaction or beta-hydroxybutyrate (BOHB)?
3. Should measurement be performed in the laboratory or as a POCT?
4. What is the evidence for current diagnostic and management ketone thresholds?

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Blood ketone measurement

	BOHB (Quantitative)	Nitroprusside (Semiquantitative)
UK	100%	0%
US	68%	32%

EQA/CAP PT, hospital and laboratory settings 2020

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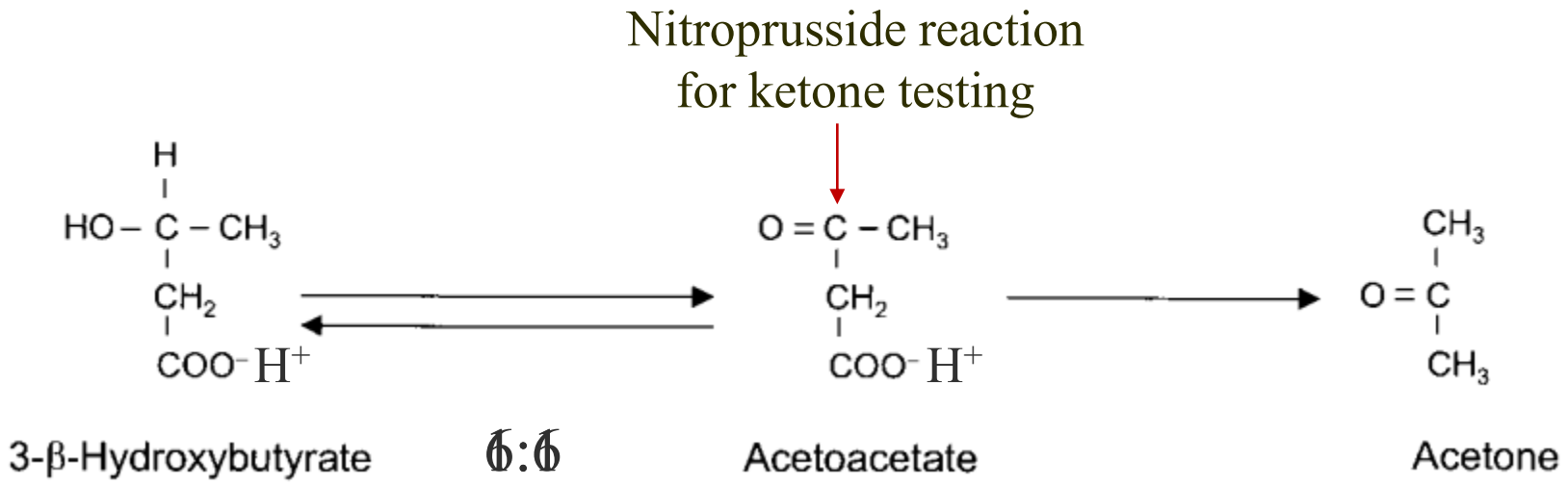
Ketone measurement



Diabetes Metab Res Rev 1999; 15: 412±426

Recommendation

- Given the likely clinical advantages …… BOHB measurement should be the preferred blood ketone test.

Diabetes Care 2022;45:267–272

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Recommendations

- While convenient and rapid, point of care blood ketone measurement [needs] careful planning … prior to … implementation.
- Recommendations for ... BOHB APS would help ensure meters/instruments provide clinically acceptable results.

Clinically, how well do we need a ketone meter to perform?

United Kingdom Accreditation Service (UKAS)

Finding 219216-03-E01082-002

- ‘IQC summary results for blood ketone assays consistently exceed the laboratory's target for acceptable performance.’

- CV 10.5% at a mean of 2.9mmol/L

Response to UKAS

- Laboratory targets derived from trimmed data. IQC data presented as untrimmed.
- Manufacturer quotes ‘typical’ or ‘representative’ performance data, not their *claims* for analytical performance.
- What performance is required clinically anyway?

Desirable assay performance

Analytical Performance Specifications options

1 Clinical outcome studies

2 Biological variation

3 ‘State of the art’

Clin Chem Lab Med 2015; 53(6): 833–835

Desirable assay performance

Hierarchy

1 Clinical outcome studies
   Direct outcome studies
   Indirect outcome studies
      simulating impact of clinical decisions

2 Biological variation

3 ‘State of the art’

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Desirable ketone performance

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Degrees of ketonaemia

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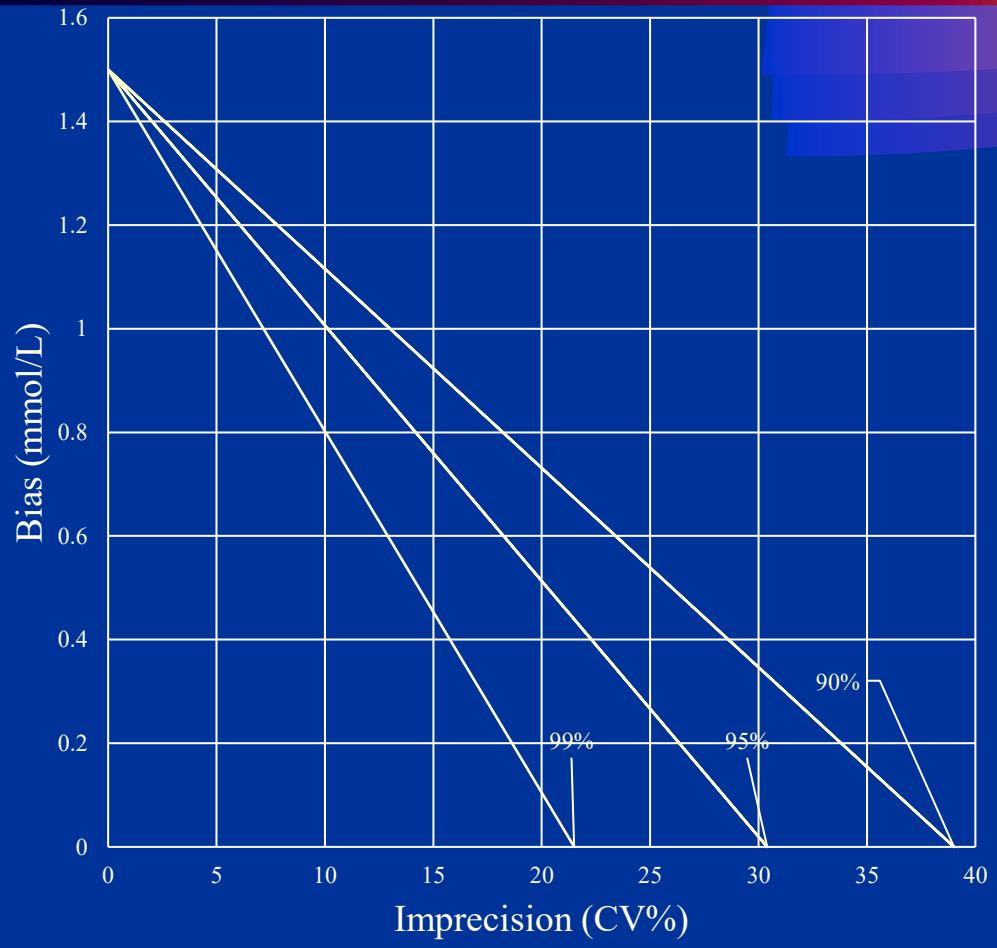
Any assay with a CV < 21%
can tell non-adjacent groups apart
with > 99% certainty

Effect of bias on allowable CV



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Blood ketone measurement

1 hr

True
3.0 mmol/L

True
≥3.0 mmol/L

Blood ketone measurement

1 hr

True
3.0 mmol/L

True
≤2.5 mmol/L

Rounding errors

0.4 – 0.6

True
2.96 – 3.05

True
2.46 – 2.55

Target CVs for a 0.5mmol/L fall

	Initial BOHB concentration						
	0.5 mmol/L	1.0 mmol/L	1.5 mmol/L	2.0 mmol/L	2.5 mmol/L	3.0 mmol/L	6.0 mmol/L
Probability	Target CV (%)						
90% Minimal	54.6	27.3	18.2	13.6	10.9	9.1	4.5
95% Desirable	42.2	21.1	14.1	10.5	8.4	7.0	3.5
99% Optimal	29.3	14.6	9.8	7.3	5.9	4.9	2.4

CV 10.5% at a mean of 2.9mmol/L
'consistent with minimum specification'

Blood BOHB APS

- Clinical guidelines can define pragmatic BOHB assay performance specifications
- Informs test users how much reliance can be placed on BOHB measurement
- Advises meter or assay manufacturers where their products could be further improved

Ketone questions

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3. *Should measurement be performed in the laboratory or as a POCT?* EITHER, SO LONG THEY MEET THE APS
4. What is the evidence for current diagnostic and management ketone thresholds?

Spreading the word

Clinical Chemistry 69:5
519–524 (2023)

Endocrinology and Metabolism

Establishing Pragmatic Analytical Performance Specifications for Blood Beta-Hydroxybutyrate Testing

Eric S. Kilpatrick,[a,*] Alexandra E. Butler,[b] Stephen L. Atkin,[b] and David B. Sacks [c]

BACKGROUND: Currently, no authoritative guidelines exist recommending the analytical performance specification (APS) of blood beta-hydroxybutyrate (BOHB) testing in order to meet the clinical needs of patients. This study has applied existing diabetic ketoacidosis (DKA) BOHB diagnostic thresholds and the recommended rates of fall in BOHB concentrations during DKA treatment to establish pragmatic APSs for BOHB testing.

METHODS: Required analytical performance was based

for urine ketones in guidelines and in clinical practice (1). The most commonly recommended test is beta-hydroxybutyrate (BOHB) which is the predominant ketone formed during DKA. Diagnostic BOHB thresholds now exist to define patients who have either developed DKA or are at a high risk of doing so (2, 3). If a diagnosis is made, there now exist recommended rates of fall in BOHB concentrations to help guide the success, or otherwise, of DKA treatment (4, 5).

Currently, there are no authoritative guidelines re-

Ketone questions

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BOHB	
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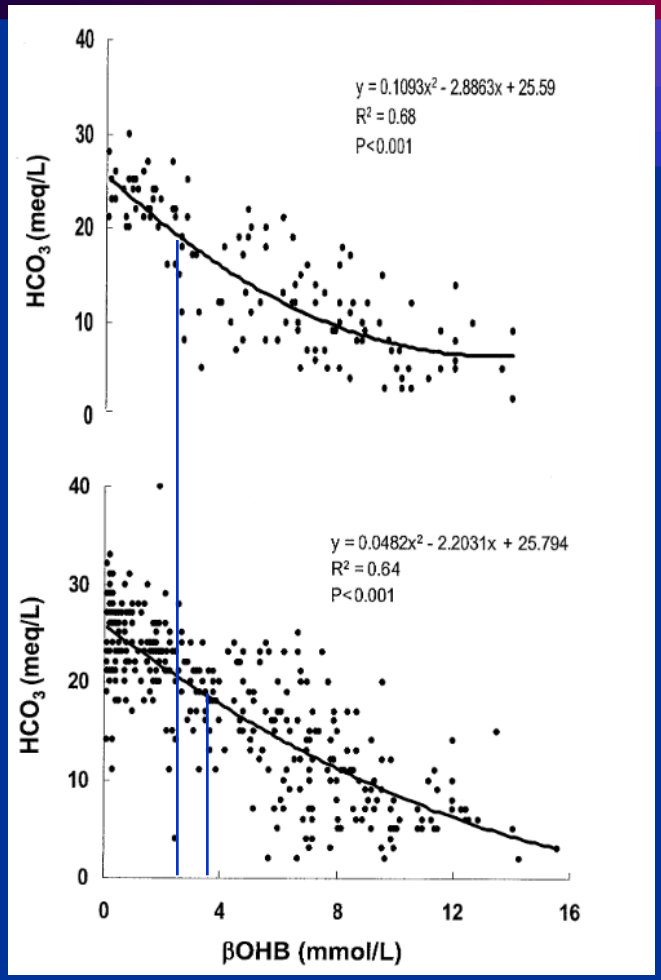
1.6 to 2.9 mmol/L	Impending DKA
≥3 mmol/L	Probable DKA

Initially based on 14 patients with DKA:
'> 3 mmol/L necessitates medical review'

Diabetic Medicine 2001, 18: 640-645

Relationship between HCO_3 and BOHB

Children (n=129)



Adults (n=337)

18mmol/L HCO_3 ≈ 3mmol/L BOHB

18mmol/L HCO_3 ≈ 3.8mmol/L BOHB

Diabetes Care 31:643–647, 2008

Degrees of ketonaemia

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Abbott/Medisense package inserts

Ketone intermediate thresholds

The diagnosis of diabetic ketoacidosis was based on:

- venous blood pH <7.25 or bicarbonate <16mmol/L
- and
- BOHB >1.5mmol/L

Diabetes Care. 1997;20:1347-1352

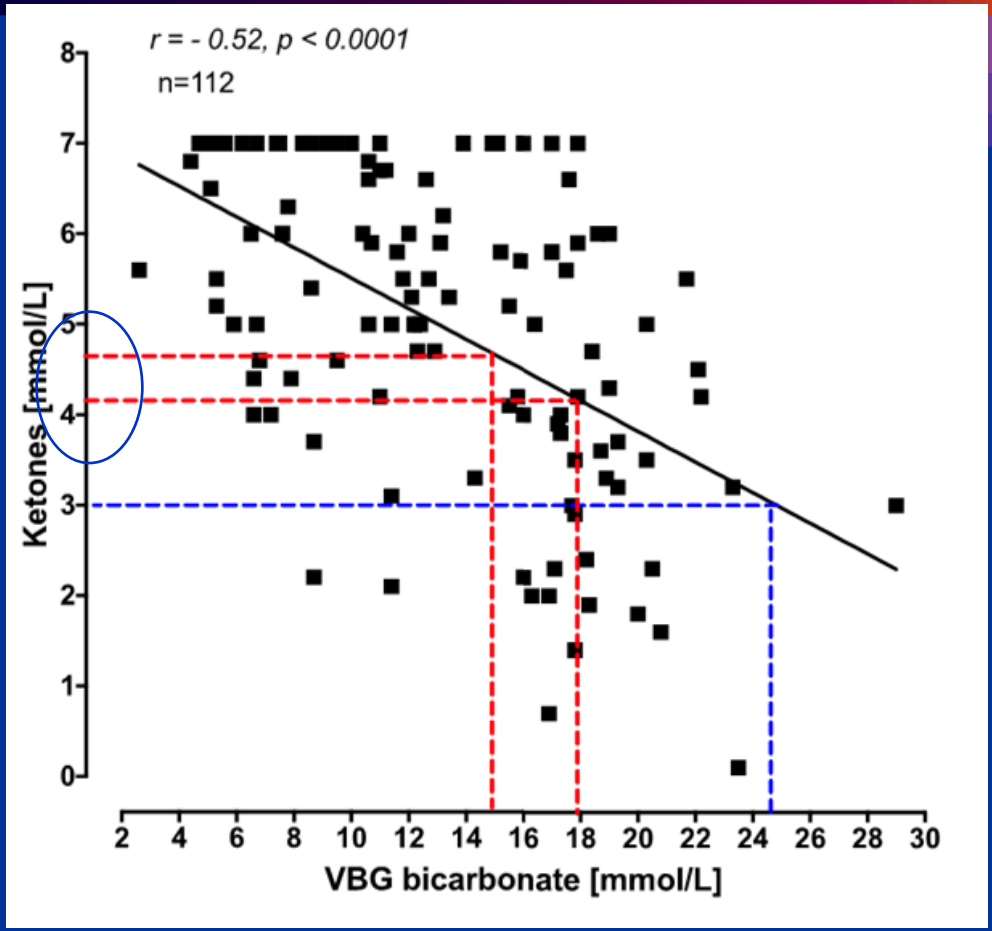
Recomendations

- ‘There is value in further studies verifying or disproving [the 3 mmol/L cut-off] as well as the normal threshold.’

DKA threshold study

- First results from ED admission
- 161 presumptive episodes of DKA in 95 patients
  (42F, 53M, age range 14-89 years)
- All had a complete dataset of Glucose, BOHB, pH and HCO_3
- BOHB and Glucose predominantly measured using meters

Results


r = - 0.52, p < 0.0001
n=112
Ketones [mmol/L]
VBG bicarbonate [mmol/L]
0
1
2
3
4
5
6
7
8
2
4
6
8
10
12
14
16
18
20
22
24
26
28
30

Results

Of the 133 of 161 events with HCO_3<18mmol/L:

- 8 were not hyperglycaemic (>13.9mmol/L)
- 9 were not ketonaemic (≤3mmol/L, n=9)
- 5 were neither

22 episodes might have been missed
with a D-K-A strategy

Summary

- A BOHB DKA cut-off of 3mmol/L could not be verified
- Using real-world data, acid-base status was poorly predicted by both ketones and glucose
- pH and/or HCO_3 should also be tested in any patient suspected of DKA (AKD instead of DKA?)

Diabetol Metab Syndr. 2023;15:198

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4. *What is the evidence for current diagnostic and management ketone thresholds?* LESS THAN YOU MIGHT IMAGINE

Conclusions

- Blood ketone measurement has largely supplanted urine ketone testing
- The provenance of many blood ketone recommendations is not obvious
- It is hard to know what BOHB cutoffs should be used
- Desirable assay performance has been established