

INVESTIGATION OF MARKERS TO INDICATE AND DISTINGUISH DEATH DUE TO ALCOHOLIC KETOACIDOSIS, DIABETIC KETOACIDOSIS AND HYPEROSMOLAR HYPERGLYCEMIC STATE

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Introduction

Recent information from the International Diabetes Federation (IDF) states that the number of people diagnosed with and dying from diabetes continues “on a relentlessly upward trajectory” with no signs of abating. Worldwide one person dies every 7 seconds from diabetes and by 2030 one adult in ten will be diabetic. ⁽¹⁾

Diabetes is the fifth most common cause of death globally and is one of the most challenging problems faced by the NHS accounting for approximately 10% of their entire budget. ⁽²⁾

One third to one half of diabetics are undiagnosed at any given time and, therefore, many deaths due to diabetes may go unrecognised. ⁽³⁾

The two main conditions causing death directly as a result of diabetes are **Diabetic Ketoacidosis (DKA)** and **Hyperglycemic Hyperosmolar State (HSS)**. Mortality rates are 2–5% for DKA and 15% for HHS. ⁽⁴⁾

FIG. 1: Typical diagnostic features of AKA, DKA and HHS

AKA:	DKA:	HHS:
<ul style="list-style-type: none"> Acidosis Ketosis Hypoglycemia or normal glucose 	<ul style="list-style-type: none"> Acidosis Ketosis Hyperglycemia 	<ul style="list-style-type: none"> No significant ketosis or acidosis Hyperglycemia
<ul style="list-style-type: none"> - High Ketones^a - Low/Normal Glucose 	<ul style="list-style-type: none"> - High Ketones^a - High Glucose^b 	<ul style="list-style-type: none"> - Low/Normal Ketones - High Glucose^b

^aHigh ketones: Blood beta-hydroxybutyrate (βHB) concentration greater than 250 µg/ml

^bHigh glucose: Vitreous humor glucose concentration greater than 6.9 mmol/L

RELATIONSHIP BETWEEN βHB AND GLUCOSE

Vitreous humor glucose was measured in 102 cases and was >6.9 mmol/L in 31 cases:

- 25 cases with βHB >250 µg/mL indicating DKA.
- 6 cases with βHB < 250 µg/mL indicating possible HHS.
- 11 cases (35%) with glucose >6.9 mmol/L had no known history of diabetes.

TABLE 2: Cases with glucose <6.9 mmol/L and βHB <250 µg/mL indicating possible HHS.

Case	Vitreous humor glucose (mmol/L)	Blood βHB (µg/mL)	Blood acetone (mg/dL)	Case history
1	52.9	<50	Not detected	Mental health problems.
2	47.6	107	5	Passing blood in urine.
3	42.6	78	Not detected	Severe abdominal pain.
4	38.4	196	8	Died in hospital.
5	34.3	87	Not detected	Type 2 diabetes.
6	12.2	<50	Not detected	Died in hospital.

REFERENCES

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Aims

A study was undertaken to investigate the markers to identify and distinguish between **HHS**, **DKA** and ketoacidosis from other causes e.g. Alcoholic Ketoacidosis (**AKA**). ⁽⁵⁾

Blood beta-hydroxybutyrate (βHB) and vitreous humor glucose (where available) concentrations were measured in 191 post-mortem cases. Blood acetone was also detected in these cases during routine screening for ethanol using headspace-gas chromatography (HS-GC).

RELATIONSHIP BETWEEN βHB AND ACETONE

Unlike βHB, acetone does not dissociate to hydrogen ions and therefore is not a contributory factor to acidosis. In addition, endogenous acetone accounts for only 2% of all ketone bodies and the source of acetone detected could be extrinsic e.g. intoxication with acetone based solvent. ⁽⁶⁾

Therefore, whilst acetone is relatively quick and easy to detect it should not be used in isolation to diagnose ketoacidosis.

βHB accounts for 78% of the total ketone body concentration and is the main compound responsible for the elevated anion gap seen in ketotic patients and so is a better marker of ketoacidosis. ⁽⁶⁾

FIG. 2: Relationship between βHB and acetone

Acetone was detected in 71 cases:

- Alcoholics: 5-52 mg/dL
- Diabetics: 8-66 mg/dL
- Alcoholic Diabetics: 6-44 mg/dL
- Unknown: 13-95 mg/dL.

βHB was greater than 250 µg/mL in 61 of these cases, elevated (50-250 µg/mL) in 9 cases and normal (<50 µg/mL) in 1 case.

There were no cases with βHB detected at significant concentration (>250 µg/mL) without acetone also being detected.

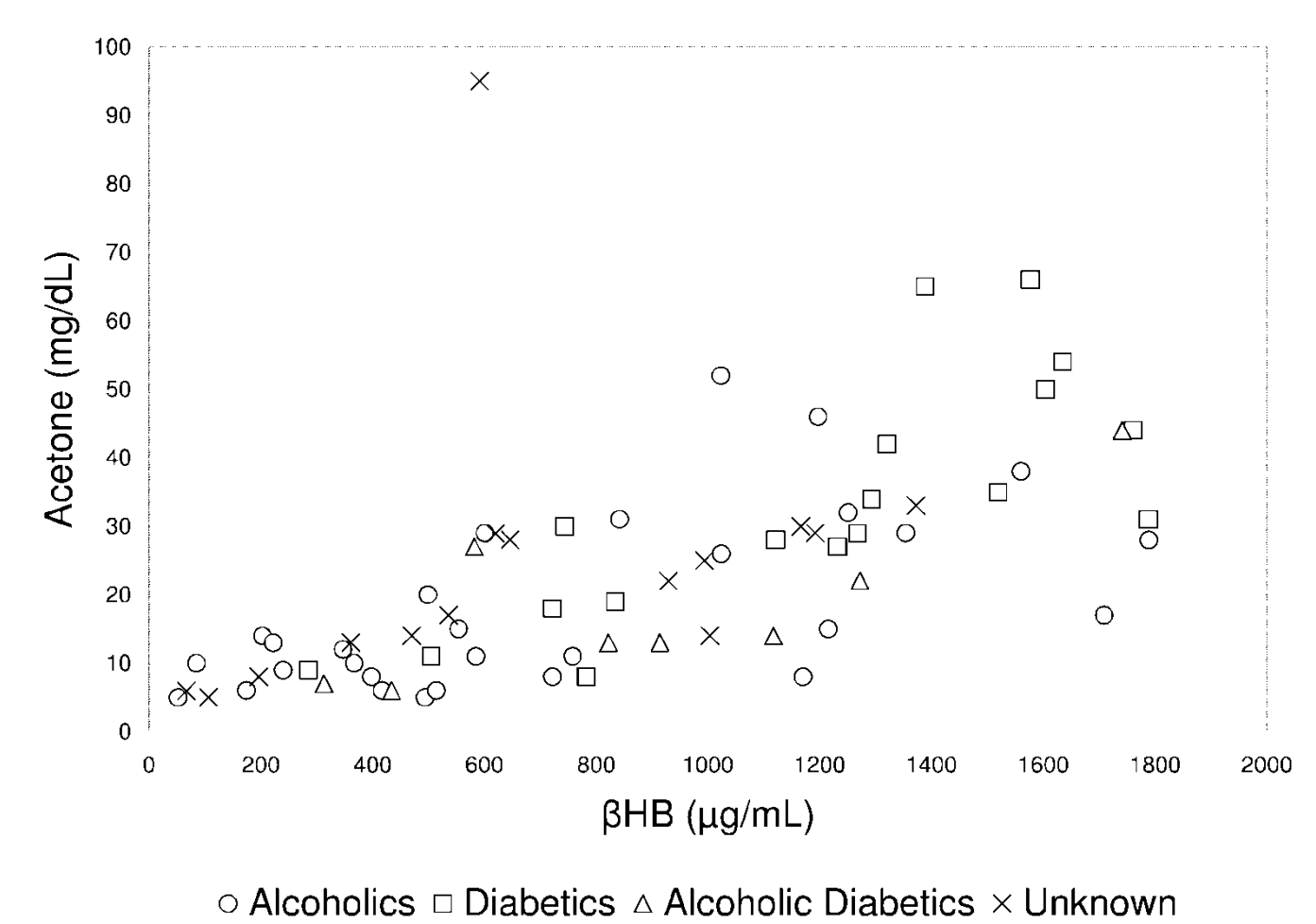


TABLE 1: Cases with blood acetone at 2 mg/dL.

Case	Blood acetone (mg/dL)	Blood βHB (µg/mL)	VH Glucose (mmol/L)
1	2	>50	>1.4
2	2	90	N/A
3	2	242	>0.3
4	2	330	N/A
5	2	879	18.4

Whilst there is good correlation between βHB and acetone concentration there is also variation.

Cases analysed subsequent to the study demonstrate the variation in βHB results at the limit of detection (2 mg/dL).

A limit of detection of 2 mg/dL is essential to ensure all cases of ketoacidosis are recognised.

CONCLUSION

- βHB is the preferred marker of ketoacidosis.
- Acetone can be used as an indicator and all cases involving ketoacidosis will be identified providing analysis for ethanol using HS-GC is carried out.
- βHB only needs to be measured if acetone is detected >2 mg/dL.
- Vitreous humor glucose should be routinely measured to distinguish DKA from ketoacidosis of other causes and to identify HHS.