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Alcoholic Ketoacidosis at Autopsy

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ABSTRACT: Total ketone bodies (acetone, acetoacetate, and β-hydroxybutyrate) were measured in 105 medicolegal autopsies (71 non-alcoholics, 22 chronic alcoholics, and 12 diabetics) using a coupled enzymatic head-space gas chromatographic method. Samples included vitreous humour, pericardial fluid, and blood from the femoral vein, inferior vena cava (IVC), superior vena cava (SVC), and aorta. Vitreous ketone levels showed good correlation with blood and pericardial fluid levels, suggesting that vitreous could be used as an alternative autopsy specimen for this analysis. This opens up the possibility of using simpler clinical laboratory methodologies which cannot be applied to autopsy blood due to hemolysis. In 71 non-alcoholics (age 18 to 96, median 67) total ketones (mM/L) were: vitreous 0.19 to 3.35, median 0.49; pericardial fluid 0.02 to 1.54, median 0.35; femoral blood 0.23 to 8.08, median 1.00; aortic blood 0.25 to 9.96, median 0.90; IVC blood 0.30 to 6.49, median 1.27; SVC blood 0.32 to 6.00, median 1.07. Eleven outliers (>2.5 mM/L in femoral blood) mostly had prolonged illness prior to death. The 22 alcoholics (age 36 to 83, median 62) included four extreme outliers with femoral blood total ketone levels of 129.9 (also diabetic), 39.4 (no anatomical cause of death), 38.5 (suicidal hanging), and 18.6 (hypothermia), suggesting that while alcoholic ketoacidosis may be a previously overlooked potential cause of death, interpretation must be guarded and made within the total case context. The other 18 alcoholics had ketone levels not statistically different from non-alcoholics, suggesting that ketoacidosis is a significant factor in at most a small minority of alcoholic deaths. Three of 12 diabetics had extreme elevations of femoral blood ketone bodies: 87.5, 20.4, and 17.4 mM/L. Measurement of ketone bodies in vitreous humour or pericardial fluid using clinical laboratory methodologies is recommended in unexplained deaths in chronic alcoholics as well as diabetics.

KEYWORDS: alcoholic ketoacidosis, autopsy, diagnosis, acetone, acetoacetate, β-hydroxybutyrate, forensic science, forensic toxicology, forensic pathology, death

Sudden death in a chronic alcoholic with a subsequent negative autopsy is a common problem. Such cases have only the stigmata of alcoholism, such as a fatty liver, and an inconsequential blood alcohol level. Speculations on the mechanism of these ''fatty liver deaths'' have been varied but unconvincing (1). Recently Thomsen et al. in Denmark offered the hypothesis that these deaths result from fatal alcoholic ketoacidosis (2,3) and provided supporting evidence of raised blood levels of ketone bodies (acetone, acetoacetate, and β-hydroxybutyrate). The clinical literature on alcoholic ketoacidosis (AKA) is scant, and probably belies the true frequency of the syndrome (4–16), but it suggests that AKA is a relatively benign condition and only fatal when associated with some other disease process. This makes the Thomsen hypothesis all the more challenging. Autopsy investigations are hampered by the fact that simple clinical laboratory methodologies for ketone bodies, particularly β-hydroxybutyrate (17), cannot be applied to autopsy blood due to hemolysis, and the alternative coupled enzymatic head-space gas chromatographic method (18) is complex and labor-intensive. We set out to test the Thomsen hypothesis by measuring ketone bodies in a consecutive autopsy series, including both alcoholics and non-alcoholics. We also measured ketone bodies in vitreous humour and pericardial fluid with a view to establishing whether or not these samples, which would be suitable for analysis by simpler instrumentation, had ketone body levels which mirrored blood.

Methods

Samples were obtained from cases submitted for routine medicolegal autopsy or external examination. Cases with severe trauma or advanced putrefaction were excluded. Cases were categorized as chronic alcoholic on the basis of amamnestic data from hospital records, medical practitioner records, and police reports, and as diabetic on the basis of medical history. Vitreous humour was obtained by the standard procedure using a 5 mL syringe and 19 G needle. A femoral venous blood sample was obtained in cases of external examination by exposure of the vessel, proximal cross clamping and needle puncture. In autopsy cases the external iliac vein was cross clamped and a distal sample obtained by needle and syringe. At autopsy pericardial fluid was aspirated using a clean syringe and blood samples obtained from both the inferior vena cava and superior vena cava by needle and syringe after cross clamping the vessels close to the right atrium. A blood sample from the ascending aorta was obtained by needle and syringe without prior cross clamping of the vessel. All samples were stored in plain glass vials with minimal head-space, immediately refrigerated at 4°C and transferred into head-space vials for analysis within 24 h.

The principle of the analytical method is the enzymatic conversion of β-hydroxybutyrate to acetoacetate followed by heating to convert acetoacetate to acetone. Quantitation of acetone then gives the molar equivalent of the total ketone bodies present. Omission of the enzymatic stage of the analysis allows quantitation of the molar equivalent of acetone and acetoacetate present, and subtraction of this value from the total ketone quantitation allows calculation of the β-hydroxybutyrate concentration. The method used is a modification of one previously published, in that it uses an internal rather than an external standard, and is suitable for forensic postmortem samples (2,3,18).

For acetone and acetoacetate the standard, or sample (500 μL), was added to a 20 mL PTFE faced septa head-space vial in which

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sodium chloride (0.5 g), 10 mM butan-l-ol (50 μL), and 0.2 M phosphate buffer (500 μL) had been added. The vial was sealed, incubated for 60 min at 100°C for decarboxylation and assayed for acetone using head-space gas chromatography.

For β-hydroxybutyrate the standard, or sample (500 μL), was added to a 20 mL PTFE faced septa head-space vial in which 0.2 M phosphate buffer (500 μL), 0.4 M pyruvate solution (50 μL), 30 mM NAD solution (50 μL), lactate dehydrogenase enzyme (10 μL), β-hydroxybutyrate dehydrogenase enzyme (10 μL), and 10 mM butan-l-ol (50 μL), solution had been added. The vial was sealed and incubated for 45 min at 37°C. The vial was then heated to 100°C for 60 min for decarboxylation and assayed for acetone using head-space gas chromatography.

Analysis was by head-space gas chromatography using a Perkin-Elmer 8500 series with a flame ionization detector attached to a Perkin-Elmer HS-40 XL autosampler and a Waters 746 integrator. Autosampler conditions were as follows: thermostating temperature 60°C, needle temperature 65°C, transfer temperature 60°C, thermostating time 12 min, and GC cycle time 13 min. Gas chromatograph conditions were as follows: column DB WAX100, oven temperature 60°C, FID 150°C, injector temperature 150°C, carrier gas helium, flow rate 14 mL/min, and analysis time 13 min. Butan-l-ol (10 mM, 50 μL) as internal standard had a retention time of 8.30 and acetone a retention time of 2.13.

All chemicals used were of analytical grade. Standard solutions were stored at 4°C and replaced every three weeks. All analyses were performed in duplicate together with the paired standards of acetone. Single standards of acetoacetate and of β-hydroxybutyrate were used to confirm that the enzymatic and heating steps had been successfully completed. Nine-point calibration curve correlation coefficients for acetone were greater than 0.99. Analytical precision was better for vitreous and pericardial fluid than for blood samples. At concentrations above 0.5 mM/L duplicates were within 10% of the mean and precision was best within the range of diagnostic interest (4 to 130 mM/L).

Results

Of the 105 total cases there were 71 non-alcoholics and non-diabetics, comprising 48 males and 23 females, mean age 62 years, median 67 years, range 18 to 96 years, Q_1 49 years, Q_3 73 years. Chronic alcoholics numbered 22, comprising 11 males and 11 females, mean age 61 years, median 62 years, range 36 to 83 years, Q_1 51 years, Q_3 72 years. Twelve diabetics are not included in the data analysis, except for four cases of interest (see Table 5), because of the small numbers.

For the 71 non-alcoholics the summary data for total ketone bodies in the six sample sites are shown in Table 1. For all sample sites there was a negatively skewed distribution. When contrasted with the four blood samples, the range and the interquartile range was noticeably narrower for vitreous and pericardial fluid, sites relatively protected from agonal and postmortem changes. For femoral vein total ketones there was no correlation with subject age ($n = 70$, Spearman's rank correlation $r_s = 0.192$, $t = 1.61$, $P = 0.1$). There was a moderately strong correlation between total ketones in femoral vein blood and vitreous ($r_s = 0.74$), pericardial fluid ($r_s = 0.78$), inferior vena cava blood ($r_s = 0.74$), superior vena cava blood ($r_s = 0.76$), and aortic blood ($r_s = 0.72$). Detailed case data on eleven outliers (15% of the 70 cases) identified visually from a histogram of total ketones in femoral vein blood (values greater than 2.5 times the median) are shown in Table 2. Separate summary data for acetoacetate with acetone and for β-hydroxybutyrate provided no additional useful information. Data for acetoacetate with acetone are given for specific cases of interest in Tables 2, 3, and 5. There was poor correlation between femoral venous blood β-hydroxybutyrate and acetoacetate/acetone ($r_s = 0.28$).

TABLE 1—*Total ketones (mM/L) in non-alcoholic population.*

Sample Site	*n**	Mean	Median	Range	Q_1†	Q_3†	r_s‡
Vitreous	67	0.79	0.49	0.19–3.35	0.33	0.97	0.74
Pericardial	46	0.40	0.35	0.02–1.54	0.22	0.50	0.78
Femoral v	70	1.52	1.00	0.23–8.08	0.60	1.85	...
Inferior vc	40	1.83	1.27	0.30–6.49	0.70	2.52	0.74
Superior vc	43	1.57	1.07	0.32–6.00	0.65	1.88	0.76
Aorta	47	1.67	0.90	0.25–9.96	0.63	1.68	0.72

* n = number of samples; femoral blood and vitreous only from external examinations; all samples from autopsies, with some sampling failures.
† Q_1, and Q_3 = quartiles.
‡ r_s = Spearman's rank correlation with femoral vein paired samples.

Among the 22 chronic alcoholics there were four extreme outliers, the case details of which are shown in Table 3. The summary data of the other 18 chronic alcoholics are shown in Table 4. There was a moderately strong correlation between femoral venous blood total ketones and vitreous total ketones both with ($r_s = 0.84$) and without ($r_s = 0.66$) the four outliers and similarly for pericardial fluid both with ($r_s = 0.89$) and without ($r_s = 0.85$) the four outliers. Comparing femoral venous blood total ketones in these 18 alcoholics with the non-alcoholics ($n = 70$) by the Mann-Whitney U test disclosed no significant ($P = 0.05$) difference between the two populations.

Among the 12 diabetics there were four clear outliers identified and their case details are shown in Table 5. For the remaining eight diabetics the femoral venous blood total ketones ranged from 0.71 to 4.0 mM/L, mean 1.82 mM/L.

Discussion

For convenience the term ''ketone bodies'' is used in clinical practice to include only acetone, acetoacetate and β-hydroxybutyrate, and it is in this sense that the term is used in this paper. The terminology is convenient because all three compounds are metabolically related but it is inaccurate because it excludes other biologically important ketones, e.g., pyruvate, but includes β-hydroxybutyrate, which does not have a ketone structure although it is part of ketone metabolism.

The ability of the brain to selectively utilize ketone bodies instead of glucose during fasting/starvation diminishes to one-fifth or one-fourth the otherwise obligatory rate of protein breakdown (4). In fasting ketosis, acetoacetate and β-hydroxybutyrate serve as fat-derived, water-soluble fuel capable of crossing the blood-brain barrier by facilitated diffusion. Extremely high free fatty acid levels in blood, ranging from 1800 to 3800 μEq/L have been a consistent finding in clinical cases of alcoholic ketoacidosis (5,6). Acetyl-CoA, which is generated from β-oxidation of fatty acids is the precursor of ketogenesis. Two critical enzymes in the pathway to acetoacetate production are found in liver mitochondria only (7). Consequently, the liver is the only appreciable site of ketone body production. Reversible conversion of acetoacetate to β-hydroxybutyrate is by a mitochondrial enzyme found in most tissues, including liver. Excess acetoacetate in liver is converted into β-hydroxybutyrate and extra-hepatic tissues can convert β-hydroxybutyrate back into acetoacetate and utilize both of these ketone bodies as respiratory substrates.

TABLE 2—*Non-alcoholic cases with raised femoral vein ketone bodies.*

Case	Total Ketones (mM/L)	Weight (kg) Height (cm)	Case Features
NA1	8.08	48, 152	46M, found dead, haemopericardium, ruptured myocardial infarction
NA2	5.37	74, 125	67M, witnessed sudden death, previous stroke, no autopsy
NA3	4.91	55, 171	69M, sudden death, pulmonary thromboembolism, 17 days post abdominal surgery, fatty liver
NA4	4.72	80, 161	69M, septicaemia, pneumonia, cor pulmonale, hepatomegaly (1840 g), in-hospital death
NA5	4.71	60, 155	68F, pulmonary thromboembolism, pneumonia, myocardial infarction, in-hospital death
NA6	4.11	59, 161	64F, pneumothorax, asthma, bronchopneumonia, in-hospital death
NA7	4.02	62, 160	49F, hepatomegaly (1845 g), cholestatic hepatocellular necrosis (presumed drug-induced)
NA8	3.30	54, 154	96F, smoke inhalation, survived 11 h
NA9	3.25	80, 164	74M, found dead at golf, two previous myocardial infarctions, no autopsy
NA10	3.16	92, 158	57M, found dead, coronary thrombosis, cardiomegaly (780 g) with fibrosis, nutmeg liver, raised liver enzymes in life
NA11	2.76	108, 190	57M, sudden death at squash, hypertensive, atherosclerotic coronary artery disease

TABLE 3—*Chronic alcoholics with markedly raised femoral vein ketone bodies.*

Case	Total Ketones (mM/L)	Acetoacetate + Acetone, (mM/L)	Weight (kg) Height (cm)	Case Features
A1	129.9	103.1	65, 165	55M, insulin dependant diabetic, hypothermia, no anatomical cause of death, femoral vs. glucose 64 mM/L (N = 3.3–5.8)
A2	39.4	21.5	55, 154	61F, ethanol-negative, found dead, no anatomical cause of death
A3	38.5	17.0	64, 163	51M, ethanol-negative, depression, suicidal hanging
A4	18.6	2.7	57, 169	75F, ethanol-negative, atherosclerotic heart disease with nutmeg liver, hypothermia

TABLE 4—*Total ketones (mM/L) in chronic alcoholic population.*

Sample Site	n*	Mean	Median	Range	Q_1*	Q_3*
Vitreous	14	0.96	0.76	0.28–3.05	0.40	1.23
Pericardial	18	1.01	0.87	0.26–2.62	0.45	1.41
Femoral v	18	1.80	1.29	0.40–6.80	0.66	2.20
Inferior vc	15	2.13	1.59	0.39–6.21	0.77	3.12
Superior vc	16	1.76	1.57	0.16–4.90	0.91	2.23
Aorta	16	2.14	1.72	0.39–10.7	0.85	2.30

NOTE: Excluded from this data set are four extreme outliers (see Table 3).

* n = number of samples; Q_1 and Q_3 = quartiles.

The combination of starvation and alcohol abuse together appears to play a critical role in precipitating ketoacidosis (5). The syndrome of alcoholic ketoacidosis (AKA) is characterized by a metabolic acidosis, malnutrition and binge drinking superimposed upon chronic alcohol abuse (8). The typical clinical picture is that of an alcohol debauch terminated by anorexia with cessation of both food and alcohol intake, and finally, a variable period of hyperemesis. By the time AKA develops there is no measurable blood alcohol. The common symptoms of nausea, vomiting and abdominal pain are accompanied by few objective physical findings (8). Mental status is usually normal or only slightly impaired but severe obtundation or coma occasionally occurs (9).

Although the pathophysiology of AKA is complex, it seems that the pivotal variable is probably a relative deficiency of insulin. This results from starvation with consequent hepatic glycogen depletion, the inhibition of gluconeogenesis by an increased NADH/NAD ratio resulting from alcohol metabolism, and extracellular fluid volume depletion with α-adrenergic inhibition of insulin secretion (10). Individuals with higher insulin levels would probably present with the syndrome of alcohol-induced hypoglycemia without ketoacidosis. Possibly the major factor separating AKA from alcohol-induced hypoglycemia is the dehydration and the starvation-induced α-adrenergic inhibition of insulin secretion in the former (9).

Morbidity and mortality associated with AKA in a clinical setting is rarely due to the acid-base disturbance but rather to concurrent disorders. Treatment of AKA with the intravenous administration of glucose and large amounts of fluid is rapidly effective (5). The glucose infusion increases insulin levels which inhibit ketone body production by the liver so that ketone body levels fall to zero in a few hours. Concomitant volume repletion is necessary because the existing volume depletion can inhibit insulin release via circulating catecholamines and adrenergic nerve endings in the islets of Langerhans (11).

Blood ketone body levels reflect hepatic production and peripheral disposition. The latter comprises the two processes of renal excretion and oxidation by peripheral tissues (1). Utilization of ketone bodies by peripheral tissues is insulin dependent (12) and consequently the low insulin levels found in AKA may add peripheral underutilization of ketone bodies to hepatic overproduction, thus contributing to elevated blood levels (11,13).

The biochemical hallmark of AKA is ketoacidosis without marked hyperglycemia (9). By contrast, diabetic ketoacidosis may be defined by the triad of hyperglycemia, acidosis and ketosis. In AKA the ratio of serum acetoacetate to hydroxybutyrate, which is normally 1:1, is characteristically increased to between 2:1 and 9:1 (14). The ratio of β-hydroxybutyrate to acetoacetate tends to be higher in AKA, averaging about 6:1, than in diabetic ketoacidosis where the ratio averages about 3:1 (6,12,15). Clinical diagnosis is hampered because the nitroprusside test (Acetest) for ketonuria is sensitive to acetoacetate but not to β-hydroxybutyrate (6). Acetone is thought to be the product of a non-enzymatic decarboxylation of acetoacetate. Acetone production is therefore a function of the level of acetoacetate and the duration of its elevation, so that the presence of acetone is indicative of a sustained severe

TABLE 5—*Diabetic cases with raised femoral vein ketone bodies.*

Case	Total Ketones, (mM/L)	Acetoacetate + Acetone, (mM/L)	Weight (kg) Height (cm)	Case Features
D1	87.5*	83.8	55, 156	28M, IDD†, found dead, femoral blood glucose 71.5 mM/L, fatty liver
D2	20.4	6.4	71, 175	68M, NIDD†, found dead, established myocardial infarction
D3	17.4	7.6	59, 165	73F, NIDD, sudden witnessed collapse, no autopsy

* Analysis performed after storage at −20°C for 2 months.
† IDD = insulin-dependent diabetic; NIDD = non-insulin-dependent diabetic.

ketoacidosis (11). However, the extent, if any, of postmortem conversion of acetoacetate to acetone is not known and it is advisable and convenient to make a combined analysis of these two ketones in autopsy samples (3).

Reported blood or plasma levels of acetoacetate in fasting subjects have ranged up to 0.23 mM/L, and of β-hydroxybutyrate up to 0.65 mM/L (3). The non-alcoholic population in the present study shows higher levels (Table 1) and a skewed distribution with a tail of significantly high levels, reflecting premortem chronic disease or a prolonged agonal period (Table 2). The finding is not surprising since it can hardly be expected that a forensic autopsy population would have levels comparable to fasting healthy individuals. The data do provide another basis for comparison with the alcoholic autopsy cases. Reported blood or plasma levels of acetoacetate in AKA have ranged up to 7.5 mM/L and β-hydroxybutyrate up to 20.5 mM/L (3). In one clinical study of 14 episodes of AKA the mean β-hydroxybutyrate concentration was 8.08 mM/L with a range of 1.19 to 16.6 mM/L (16). The four clearly possible cases of AKA in this study (Table 3) have very high levels of total ketones, ranging from 18.6 to 129.9 mM/L. In the other 18 alcoholics levels ranged up to 6.8 mM/L (in femoral blood), which include cases with abnormally high values judged by clinical criteria but not significantly different from the general autopsy population.

The highest ketone levels were seen in a case of combined chronic alcoholism and insulin-dependent diabetes (Table 3, case A1) in which a history typical of AKA was combined with a history of failure to take insulin. The high peripheral blood glucose level and the comparatively low β-hydroxybutyrate level are more in keeping with a diabetic ketoacidosis. Two other cases (A2 and A3) have similar ketone levels of 39.4 and 38.5 mM/L but provide an interesting contrast. The one was a negative autopsy (no apparent cause of death) in a chronic alcoholic and a prime candidate for the diagnosis of fatal AKA. The other was a suicidal hanging in which the precise details leave little doubt that the man was mentally alert, although depressed. In the fourth case (A4) there was coronary artery disease and autopsy evidence of hypothermia as well as AKA. All of which suggests that AKA may be a potential cause or contributory factor in a death but is not necessarily lethal. This is in keeping with the clinical concensus that AKA is fatal only when associated with some other illness. Even so, the diagnosis of AKA at autopsy would identify a potentially significant contributory factor in a death. In the present state of knowledge it is uncertain whether AKA alone is sufficient to account for death, but it seems to be present in about 10% of chronic alcoholics coming to medicolegal autopsy. To resolve this issue requires the collection of a considerable body of data on AKA in chronic alcoholic deaths, whose circumstances are well documented.

Future studies can make use of vitreous humour (or pericardial fluid) as an alternative specimen to blood. Data from this study (Table 1, Table 4) show that there is a strong correlation between blood and vitreous ketone body levels. Furthermore, median values in vitreous and pericardial fluid are lower than in blood and ranges are narrower, with less marked skewing of the distribution of values. This suggests that both vitreous and pericardial fluid may be less affected by any agonal or postmortem rises in ketone body levels. The ability to use vitreous or pericardial fluid means that simpler and less expensive analytical techniques for ketone bodies can be applied. Currently available clinical laboratory methodologies are not suitable for autopsy blood because it is partly hemolyzed (17) and consequently the laborious coupled enzymatic headspace GC method (2,3,18) must be used. We do not recommend this GC method but rather suggest exploring the use of innovative clinical technologies, such as biosensor electrodes, applied to vitreous or pericardial fluid.

In summary, alcoholic ketoacidosis can be diagnosed at autopsy by measurement of total ketone bodies (acetone, acetoacetate, and β-hydroxybutyrate) in vitreous humour or pericardial fluid, as alternatives to blood. Very high levels (above 10 mM/L in femoral blood and 5 mM/L in vitreous), indicative of profound AKA, can be expected in about 10% of all alcoholics coming to medicolegal autopsy. Other alcoholics will have abnormal but less markedly raised levels (up to about 8 mM/L in blood, and 4 mM/L in vitreous) comparable to the general autopsy population. AKA is associated with a typical history of an alcoholic binge followed by a day or more of anorexia, and consequently an insignificant blood alcohol level. The presence of AKA represents a potentially significant contributory factor in a death when associated with other illness. It may be an explanation for sudden deaths in alcoholics in whom the autopsy is negative (so-called ''fatty liver deaths''), but further studies are required before such deaths can be confidently attributed to AKA alone. The mechanism of these deaths is obscure but could be related to a critical fall in blood pH to around 7.0, precipitating vascular collapse. Because AKA is not currently viewed as a lethal condition, the autopsy diagnosis must be interpreted in the context of the complete case investigation.

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