Journal Pre-proof

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PII: S1262-3636(20)30089-6

DOI: https://doi.org/doi:10.1016/j.diabet.2020.05.011

Reference: DIABET 101170

To appear in: *Diabetes & Metabolism*

Received Date: 21 March 2020

Please cite this article as: Boudou P, Djibré M, Ibrahim F, Fellahi S, Gilon P, Andreelli F, Ferré P, Boissan M, Massive lactic acidosis and ketoacidosis with glucagon deficiency in a chronic alcoholic patient, *Diabetes and Metabolism* (2020), doi: https://doi.org/10.1016/j.diabet.2020.05.011

Massive lactic acidosis and ketoacidosis with glucagon deficiency in a chronic alcoholic patient

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Received 21 March 2020; Accepted 25 May 2020

Abbreviations:

BMI: body mass index

GH: growth hormone

IGF-1: insulin-like growth factor-1

NAD: nicotinamide adenine dinucleotide

SHBG: sex hormone-binding globulin

A non-diabetic chronic alcoholic and undernourished male patient [body mass index (BMI): 16.6 kg/m^2] was admitted to our hospital emergency department. He had fasted for the previous 3 days. His blood lactate and ketone body concentrations were massively elevated (18 mmol/L and 14 mmol/L, respectively). Ethanolaemia was negative. Massive metabolic acidosis was noted with a pH of 7.04. Renal function remained normal, but there was mild hepatocellular deficiency and no acute pancreatitis. The patient was hypoglycaemic at admission with a blood glucose level of 3.0 mmol/L, and low concentrations of insulin, C-peptide and insulin-like growth factor (IGF)-1, as well as very low glucagon concentrations (5.2 ng/L; normal range: 8–74 ng/L) despite the prevailing glycaemia. In contrast, cortisol, sex hormone-binding globulin (SHBG) and growth hormone (GH) concentrations were elevated.

While in the intensive care unit (ICU), the patient received a saline solution of dextrose, thiamine, pyridoxine, folic acid and nicotinamide. Progressive normalization of his blood glucose was associated with increases in insulin and C-peptide, and decreases in urinary cortisol, circulating GH and SHBG, but no change in plasma glucagon. His biological markers normalized by day 2 and he left the hospital on day 5.

The patient was reexamined in hospital 7 months later for his thiamine status, and a liquid meal test was performed (Delical® HP-HC Lactalis, 4 mL/kg) to determine his glucagon secretion response. His total thiamine concentration before the meal was 118 nmol/L, indicating a deficiency. Basal blood glucose was 6.5 mmol/L, and increased modestly during the meal together with normal insulin secretion. However, basal glucagon remained very low (7.4 ng/mL) and was raised to only 15.8 ng/mL 2 h after the meal. These data are summarized in Table I.

Alcohol metabolism in the liver induces massive formation of nicotinamide adenine dinucleotide + hydrogen (NADH, H^+) and acetyl-CoA, which leads to lactate and ketone body overflow. However, no alcohol was detected in the patient's blood, and severe lactic acidosis is uncommon in alcoholic patients [1] as is also the association of lactic acidosis and ketoacidosis [1,2].

Liver failure may account for unusually high lactate concentrations, as the liver normally takes up blood lactate for gluconeogenesis. However, in this case, there was no major hepatocellular deficiency, as proteinaemia, prothrombin time and activated partial thromboplastin time (APTT) were normal. Yet, the patient's blood glucose was lower than that seen in either undernourished patients with low BMI scores [3] or starving human subjects [4], suggesting that a reduced capacity for glucose synthesis may have contributed to the elevated lactate concentration. In addition, thiamine (vitamin B1) deficiency due to chronic malnutrition may also have been a contributing factor. Thiamine pyrophosphate is an obligatory cofactor for a number of enzymes, and a lack of thiamine has major metabolic consequences because: (*i*) pyruvate then cannot be used as an energy substrate by the liver or any other oxidative tissues, yielding lactate instead; and (*ii*) acetyl-CoA coming from fatty acids is then preferentially orientated in the liver towards ketone body synthesis instead of the Krebs cycle.

The ketone body levels seen in our patient were higher than those observed after long-term starvation in humans [3]. One important factor in this case was marked hypoglycaemia, which may have contributed to the low insulin level and favouring, with cortisol and GH, the observed massive lipolysis of adipose tissue and high concentrations of plasma fatty acids. Thus, in this case, acute starvation and chronic malnutrition were certainly crucial aetiological factors.

However, the puzzling feature of this patient's low basal plasma glucagon concentration persisted even 7 months after recovery. Such low glucagon can contribute to hypoglycaemia and high lactate concentrations by reducing gluconeogenic capacity. Interestingly, despite the low glucagon concentrations, ketone body levels were very high, thereby suggesting that, in humans, while glucagon is necessary for maintaining glucose homoeostasis, it is not required for ketone body synthesis in conditions of low insulin [5]. Nevertheless, the reasons for this patient's glucagon deficiency are still unclear. There was no sign of acute or chronic pancreatitis. However, an inherent defect of glucagon synthesis, maturation or secretion in this patient cannot be dismissed.

In conclusion, while it has not been possible to be definitive due to a lack of further investigations, we can propose that the extreme metabolic situation of our patient was a consequence of alcohol abuse inducing mild liver dysfunction, malnutrition and starvation associated with a defect of glucagon production.

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INFORMED CONSENT

Informed consent regarding this report was obtained from the patient.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest in relation with this work.

ACKNOWLEDGMENTS

The authors thank Dr Sylvia Sanquer for measurement of free fatty acids, and Dr Guillaume Lefèvre and Professor Muriel Fartoukh for their critical comments about this letter. The authors also thank Dr Carol Featherstone of Plume Scientific Communication Services SAS for the professional editing.

FUNDING

This research did not receive any specific grant from funding agencies in the public, commercial or not-for-profit sectors.

Figure Caption

Table I

Patient's laboratory and test meal results

Blood parameters		**Patient's values**	**Reference values**
pH		7.04	7.35–7.45
$PaCO_2$	(mmHg)	10	35–45
PaO_2	(mmHg)	138	> 80
SaO_2	(%)	97.4	95–99
Bicarbonate	(mmol/L)	3	23–31
Lactate	(mmol/L)	18	0.4–1.5
Ketone bodies	(mmol/L)	14	< 0.6
Fasting glycaemia	(mmol/L)	3.0	4.1–5.9
Urea	(mmol/L)	5.5	3–7
Creatinine	(mmol/L)	90	45–97
AST	(U/L)	208	< 35
ALT	(U/L)	87	< 43
γ-GT	(U/L)	491	< 45
Alkaline phosphatases	(U/L)	144	< 115
Total bilirubin	(μmol/L)	24	< 17
Lipase	(U/L)	21	4–30
Protein	(g/L)	76	60–84
Prothrombin time	(%)	77	> 70
APTT	(patient/control)	0.92	0.80–1.20
Ethanolaemia	(g/L)	< 0.10	< 0.10
Salicylate	(mg/L)	Undetectable	Negative
Methanol	(g/L)	Undetectable	Negative
Ethylene glycol	(g/L)	Undetectable	Negative

Time in emergency (h)		**0**	**3**	**8**	**10**	**24**	**48**	**72**	
Blood parameters									**Reference values**
Lactate	(mmol/L)	18	10.2	2.8	ND	2.2	ND	1.2	0.4–1.5
Glucose	(mmol/L)	3.0	4.47	12.55	14.15	8.27	5.3	7.17	4.1–5.9
Insulin	(mUI/L)	0.77	2.67	ND	8.21	12	3.71	5.88	2.7–23.5
C-peptide	(nmol/L)	0.2	0.398	1.12	1.62	1.24	0.56	0.76	0.36–1.25
Cortisol	(nmol/L)	1679	1653	955	660	401	339	339	145–475
Growth hormone	(ng/mL)	2.8	1.93	1.37	0.73	0.55	1.13	0.57	< 6.6
IGF-1	(ng/mL)	29	27.8	30.3	31.4	36.4	31.2	37.6	46.5–192
Glucagon	(ng/L)	5.2	5.2	5.2	5.2	5.2	5.2	5.2	8–74
SHBG	(nmol/L)	107	88.7	81.8	79.2	69	66.9	70.9	11.75–47.05
Free fatty acids	(mmol/L)	2.76	1.90	0.89	0.62	1.21	0.78	0.90	1.2–3.3 (24-h fasting)

Test meal (min)	**0**	**15**	**30**	**60**	**90**	**120**
Blood parameters						
Glucose (mmol/L)	6.15	8.05	7.7	6.27	6.44	5.36
Insulin (mIU/L)	4.48	40.6	51.9	38.5	31.7	24.9
C-peptide (nmol/L)	0.62	1.57	2.13	2.80	3.00	2.43
Glucagon (ng/L)	7.4	9.6	10.9	11.4	9.0	15.8

Thiamine (nmol/L):		**Reference**
Not phosphorylated	0	0–8
Diphosphorylated	117	120–230
Triphosphorylated	1	0–20
Total	118	126–250

$PaCO_2/PaO_2$: partial pressure of carbon dioxide/oxygen; SaO_2: oxygen saturation; AST/ALT: aspartate/alanine aminotransferase; γ-GT: gamma-glutamyltransferase; APTT: activated partial thromboplastin time; ND: not determined; IGF-1: insulin-like growth factor-1; SHBG: sex hormone-binding globulin