



HAL
open science

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

Philippe Boudou, Michel Djibré, Fidaa Ibrahim, Soraya Fellahi, Patrick Gilon, Fabrizio Andreelli, Pascal Ferré, Mathieu Boissan

► **To cite this version:**

Philippe Boudou, Michel Djibré, Fidaa Ibrahim, Soraya Fellahi, Patrick Gilon, et al.. Massive lactic- and keto- acidosis with glucagon deficiency in a chronic alcoholic patient. *Diabetes & Metabolism*, In press, pp.S1262-3636(20)30089-6. 10.1016/j.diabet.2020.05.011 . inserm-02886101

HAL Id: inserm-02886101

<https://inserm.hal.science/inserm-02886101>

Submitted on 1 Jul 2020

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

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

Philippe Boudou^{a*}, Michel Djibré^{b*}, Fidaa Ibrahim^a, Soraya Fellahi^{c,d}, Patrick Gilon^e, Fabrizio Andreelli^f, Pascal Ferré^{g,h*} and Mathieu Boissan^{c,d*}

^aBiochemistry and Hormonology Unit, Saint-Louis Hospital, Department of Biochemistry and Molecular Biology, Groupe Hospitalier Saint-Louis/Lariboisière, Paris, France

^bAssistance Publique–Hôpitaux de Paris, Hôpital Tenon, Service de Médecine Intensive Réanimation, Paris, France

^cINSERM UMR_S 938, Saint-Antoine Research Center, Sorbonne Université, Paris, France

^dAssistance Publique–Hôpitaux de Paris, Service de Biochimie et Hormonologie, Hôpital Tenon, Paris, France

^ePole of endocrinology, diabetes and nutrition, Experimental and Clinical Research Institute, Université catholique de Louvain, Brussels, Belgium

^fSorbonne Université, Assistance Publique–Hôpitaux de Paris, Diabetes Department, Hospital Pitié-Salpêtrière, Paris, France

^g Centre de Recherche des Cordeliers, INSERM, Sorbonne Université, Université de Paris, F-75006 Paris, France

^hDepartment of Oncology and Endocrine Biochemistry, Pitié Salpêtrière–Charles Foix University Hospital, Assistance Publique–Hôpitaux de Paris, Paris, France

* Philippe Boudou and Michel Djibré contributed equally to this work

* Pascal Ferré and Mathieu Boissan contributed equally to this work

Correspondence to Pr Pascal Ferré, Centre de Recherches des Cordeliers, 15 rue de l'école de médecine, 750006 Paris, France

pascal.ferre@crc.jussieu.fr, Tel : + 33 1 44 27 24 32

Abbreviations:

BMI: Body mass index

GH: Growth hormone

IGF1: Insulin-like growth factor-1

NAD: Nicotinamide dinucleotide

SHBG: Sex hormone-binding globulin

A non-diabetic, chronic alcoholic and undernourished patient (BMI= 16.6 kg/m²) was admitted to the emergency department of the hospital. He had fasted for the previous three days. His blood lactate and ketone body concentrations were massively elevated (respectively, 18 mmol/L and 14 mmol/L). Ethanoemia was negative. Massive metabolic acidosis was noted with a pH of 7.04. Renal function remained normal. There was mild hepatocellular deficiency but no acute pancreatitis. The patient was hypoglycemic at admission with a blood glucose level of 3.0 mmol/L and low insulin, C-peptide, and insulin-like growth factor-1 (IGF1) concentrations, as well as a very low glucagon concentrations (5.2 ng/L, N: 8-74 ng/L) for the prevailing glycemia. By contrast, cortisol, sex hormone-binding globulin (SHBG), and growth hormone (GH) concentrations were elevated. In the intensive care unit, he received a saline solution of dextrose, thiamine, pyridoxine, folic acid and nicotinamide. Progressive normalization of blood glucose was associated with increases in insulin and C-peptide and a decrease of urinary cortisol, circulating GH and SHBG but no change of plasma glucagon. His biological markers normalized by day 2 and he left the hospital on day 5. The patient was re-examined in hospital 7 months later for his thiamine status and a liquid meal test was performed (Delical HP-HC Lactalis, 4 mL/kg) for the 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 a normal insulin secretion. Basal glucagon remained very low (7.4 ng/mL) and raised to only 15.8 ng/mL 2 hours after the meal. These data are summarized in Table 1.

Alcohol metabolism in the liver induces massive formation of NADH, H⁺ and acetyl-CoA leading to lactate and ketone body overflow. However, no alcohol was detected in the blood and severe lactic acidosis is uncommon in alcoholic patients [1] as well as the association of lactic acidosis and ketoacidosis [1,2].

A liver failure could have accounted for the unusually high lactate concentrations since the liver normally takes up blood lactate for gluconeogenesis. However, there was no major hepatocellular deficiency since proteinemia, prothrombin time, and activated partial thromboplastin time (APTT) were normal. Nevertheless, his blood glucose was lower than that seen in undernourished patients with a low BMI [3] or in starved human subjects [4], suggesting a reduced capacity for glucose synthesis which might have contributed to the elevated lactate concentration. Finally, thiamine (vitamin B1) deficiency due to chronic malnutrition might be also a contributing factor. Thiamine pyrophosphate is an obligatory cofactor of a number of enzymes and the lack of thiamine has major metabolic consequences since (i) pyruvate cannot be used as an energy substrate by the liver or by other oxidative tissues and can yield lactate and (ii) acetyl-CoA coming from fatty acids will be preferentially oriented in the liver towards ketone body synthesis rather than to the Krebs cycle.

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

A puzzling feature is the low basal plasma glucagon concentration (even 7 months after recovery). This low glucagon by reducing the gluconeogenic capacity can contribute to the hypoglycemia and to the high lactate concentration. Interestingly, despite the low glucagon concentration, ketone body levels were very high suggesting that, in humans, if glucagon is necessary to maintain glucose homeostasis, it is not required for ketone body synthesis in conditions of low insulin [5]. The reasons for the glucagon deficiency in this patient are

unclear. There was no sign of acute or chronic pancreatitis. An inherent defect in glucagon synthesis, maturation or secretion in this patient cannot be dismissed.

In conclusion, the extreme metabolic situation of this patient was a consequence of alcohol abuse inducing mild liver dysfunction, malnutrition, starvation and thiamine deficiency associated to a defect in glucagon production.

REFERENCES

1. Fulop M. Alcoholism, ketoacidosis, and lactic acidosis. *Diabetes Metab Rev.* 1989;5(4):365-
2. Cusi K, Consoli A. alcoholic ketoacidosis and lactic acidosis. *Diabetes Rev.* 1994;2:195-208.
3. Nogueira JP, Maraninchi M, Lorec AM, Corroller AB, Nicolay A, Gaudart J, Portugal H, Barone R, Vialettes B, Valero R. Specific adipocytokines profiles in patients with hyperactive and/or binge/purge form of anorexia nervosa. *Eur J Clin Nutr.* 2010;64(8):840-844.
4. Owen OE, Felig P, Morgan AP, Wahren J, Cahill GF, Jr. Liver and kidney metabolism during prolonged starvation. *J Clin Invest.* 1969;48(3):574-583.
5. Sonnenberg GE, Stauffacher W, Keller U. Failure of glucagon to stimulate ketone body production during acute insulin deficiency or insulin replacement in man. *Diabetologia.* 1982;23(2):94-100.

INFORMED CONSENT

An informed consent was obtained from the patient.

ACKNOWLEDGMENTS

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

CONFLICT OF INTEREST

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

FUNDING

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

Table 1. Laboratory results and test meal

Blood parameters		Patient value							Reference values
pH		7.04							7.35-7.45
PaCO ₂	(mmHg)	10							35-45
PaO ₂	(mmHg)	138							> 80
SatO 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 glycemia	(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
γGT	(U/L)	491							< 45
Alkaline phosphatases	(U/L)	144							< 115
Total bilirubin	(□mol/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
Ethanolemia	(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	(hours)	0	3	8	10	24	48	72	Reference values
Blood parameters									
Lactate	(mmol/L)	18	10.2	2.8	n.d.	2.2	n.d.	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	n.d.	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
GH	(ng/ml)	2.8	1.93	1.37	0.73	0.55	1.13	0.57	< 6.6
IGF1	(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 (minutes)		0	15	30	60	90	120		
Blood parameters									
Glucose (mmol/L)		6.15	8.05	7.7	6.27	6.44	5.36		
Insulin (mUI/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		
Cortisol (nmol/L)		453	n.d.	n.d.	n.d.	n.d.	n.d.		
Glucagon (ng/L)		7.4	9.6	10.9	11.4	9.0	15.8		
Thiamine (nmol/L)		References							
- Not phosphorylated	0	0-8							
- Di-phosphorylated	117	120-230							
- Tri-phosphorylated	1	0-20							
- Total	118	126-250							