XXIV Riunione Scientifica Regionale SID - AMD

DIABETES EVOLUTION:
DALLA PREVENZIONE ALL'INNOVAZIONE

Acidosi lattica
Eziopatogenesi e classificazione

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Il dr. Andrea Angioi dichiara di **non aver ricevuto** negli ultimi due anni compensi o finanziamenti da Aziende Farmaceutiche e/o Diagnostiche

Dichiara altresì il proprio impegno ad astenersi, nell'ambito dell'evento, dal nominare, in qualsivoglia modo o forma, aziende farmaceutiche e/o denominazione commerciale e di non fare pubblicità di qualsiasi tipo relativamente a specifici prodotti di interesse sanitario (farmaci, strumenti, dispositivi medico-chirurgici, ecc.)

Acidosi lattica: eziopatogenesi e classificazione

- **Acido lattico: definizione e ruolo metabolico**
- **Acidosi lattica: definizione e classificazione**
- **Acidosi lattica associata a metformina**

Lactic acid

Background

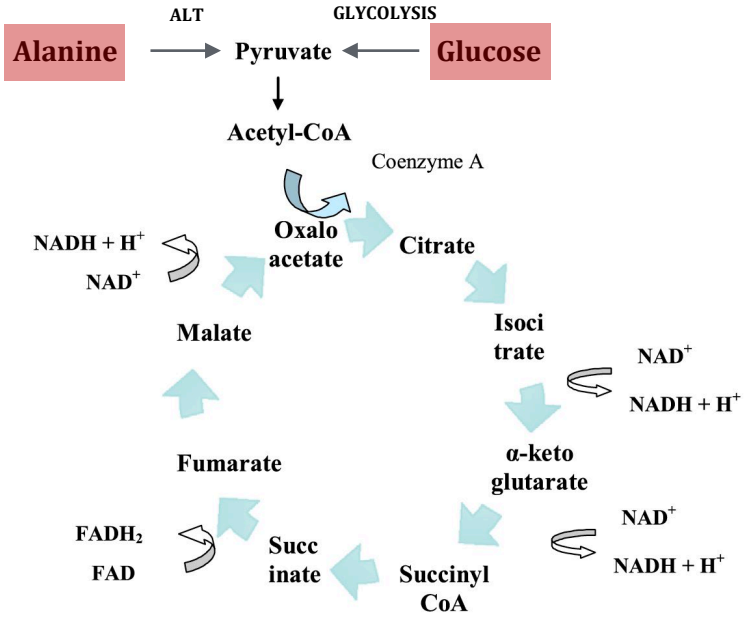
- Lactic acid is an endogenous substrate for **glycolysis**, constantly produced by muscle and other tissues.
- Lactic acid is **not** a toxin, but it is **a moderate acid**
- The lactate concentration results from a balance between its **production and its elimination.**
- Useful marker of **ischemia,** but also a crucial element in **discriminating** metabolic disorders, even in the absence of an overt disease

L-Lactate – Metabolism

Glycolysis and Krebs' Cycle: how metabolism handles glucose

Cytosol

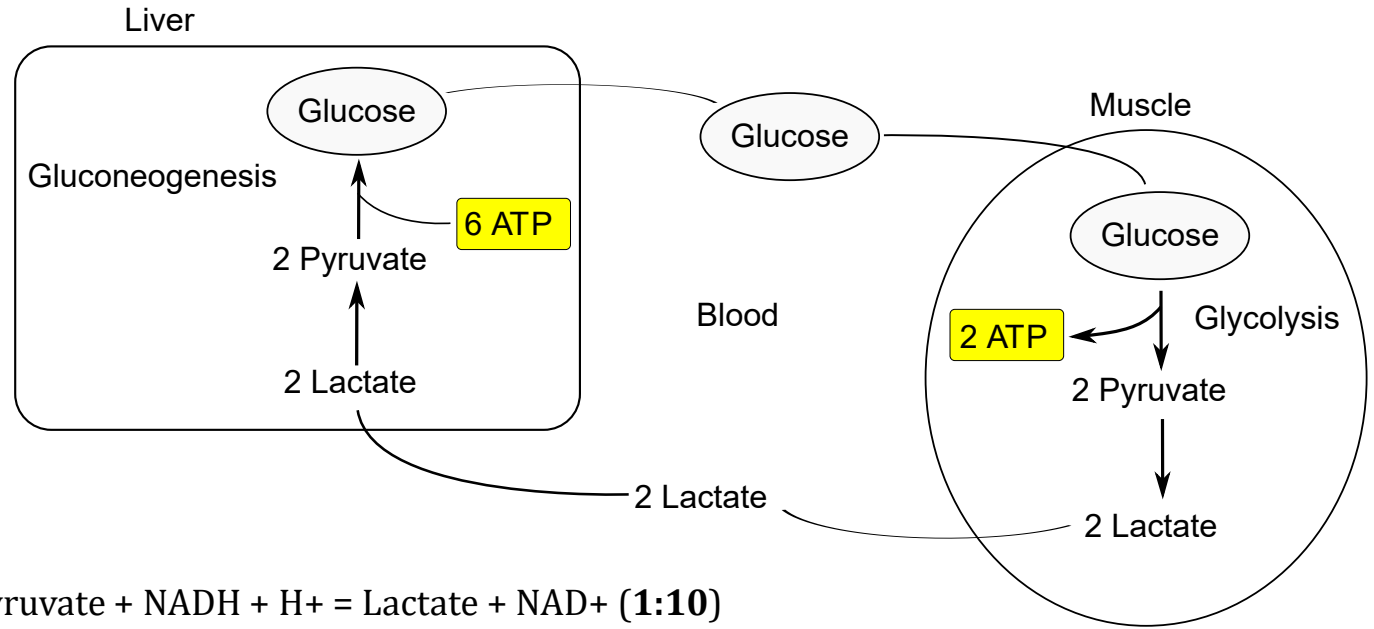
Mitochondrion



Adeva-Andany M. et al. - Mitochondrion 2014

Lactic acid

Cori's Cycle: how metabolism handles glucose and its costs



Pyruvate + NADH + H+ = Lactate + NAD+ (**1:10**)

Adeva-Andany M. et al. - Mitochondrion 2014

Lactic acidosis

Clinical definition

- Lactate concentrations >5 mmol/L [0-4.9 mmol/L]
- Metabolic acidosis

	pH	**H+** (mEq/L)	**pCO2** (mmHg)	**HCO3-** (mEq/L)
Normal values	7.36-7.42	40	36-42	24-28
Respiratory acidosis	↓	↑	↑↑	↑
Respiratory alkalosis	↑	↓	↓↓	↓
Metabolic acidosis	↓	↑	↓	↓↓
Metabolic alkalosis	↑	↓	↑	↑↑

Lactic acidosis

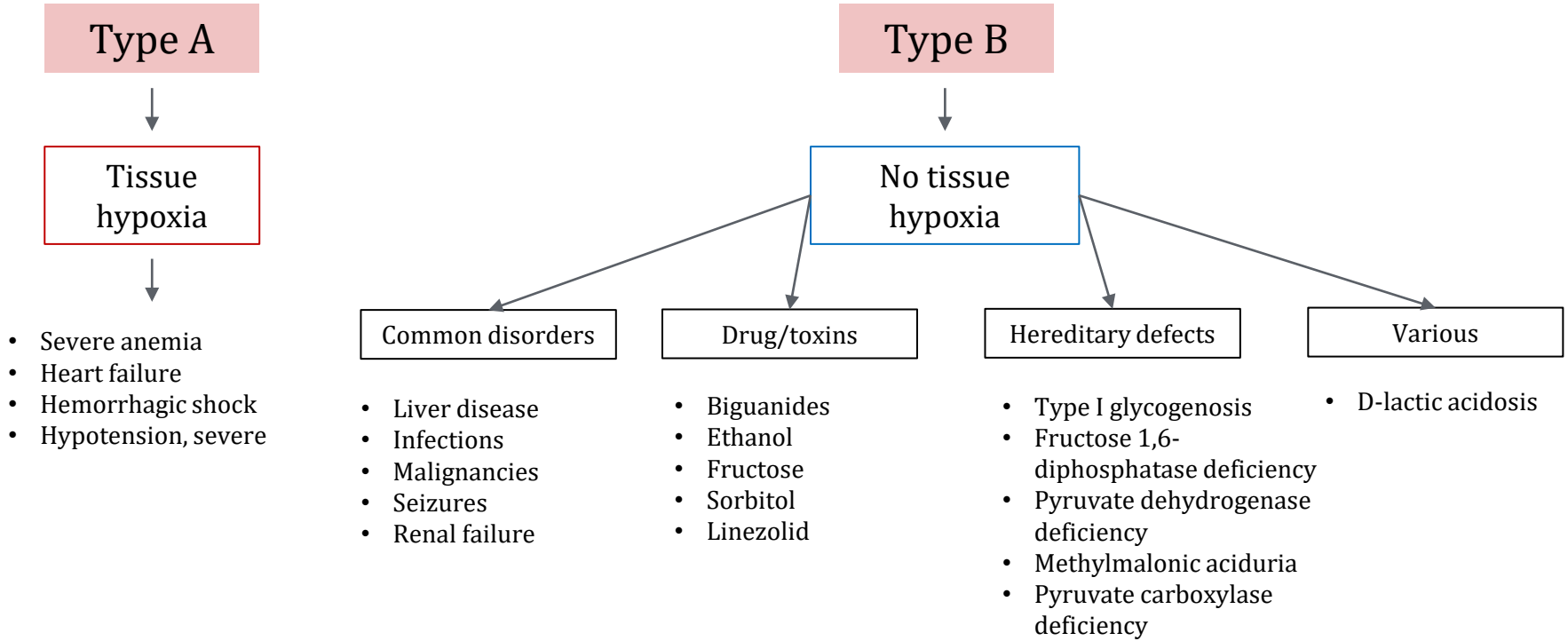
Differences between similar metabolic patterns - Some examples

Table 1. Mild Lactic Acidosis Superimposed on Metabolic Acidosis

Acid-Base Parameters	*Normal*	*5-mEq/L Lactic Acidosis*	*Diarrheal Acidosis*	*5-mEq/L Lactic Plus Diarrheal Acidosis*
Anion gap (mEq/L)	12	17	12	17
$[HCO_3^-]$ (mEq/L)	25	20	10	5
pCO_2 (mm Hg)	40	35	21	16
pH	7.40	7.38	7.30	7.11
$[H^+]$ (nm/L)	40	42	50	77

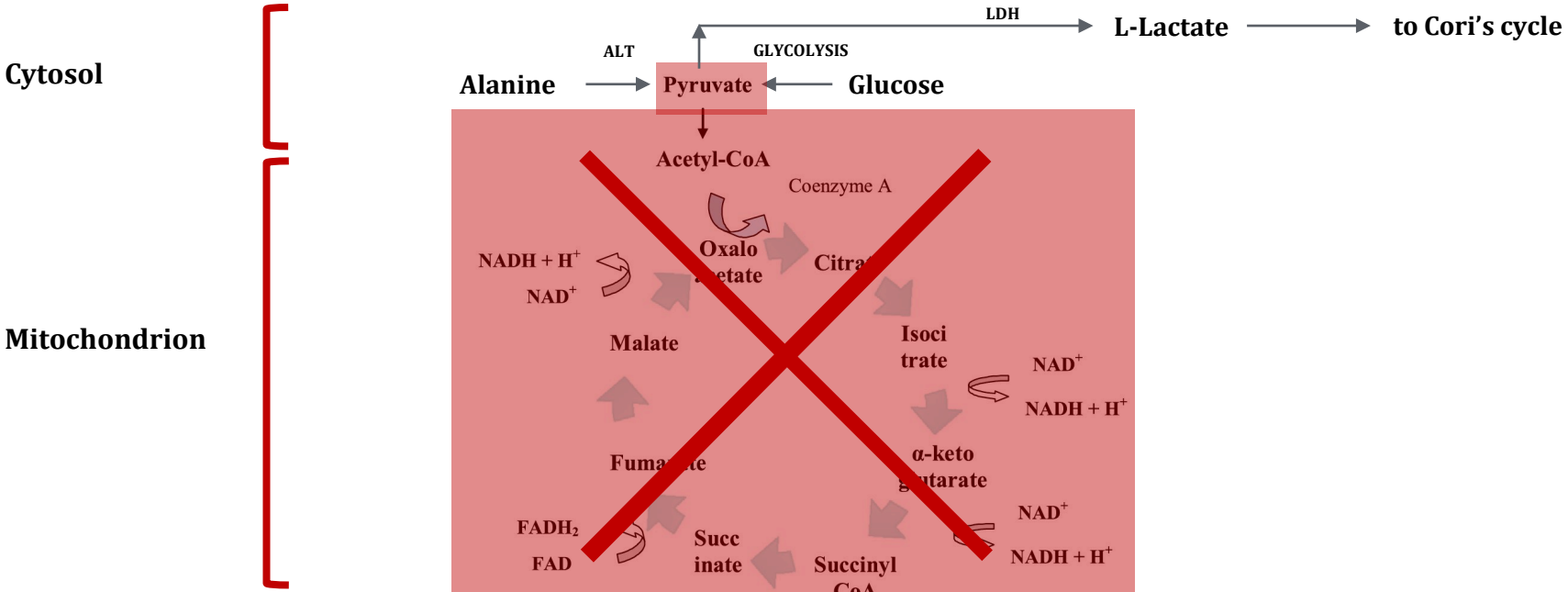
Lactic acidosis

Clinical Classification (by Cohen and Woods)



Lactic acidosis – Type A

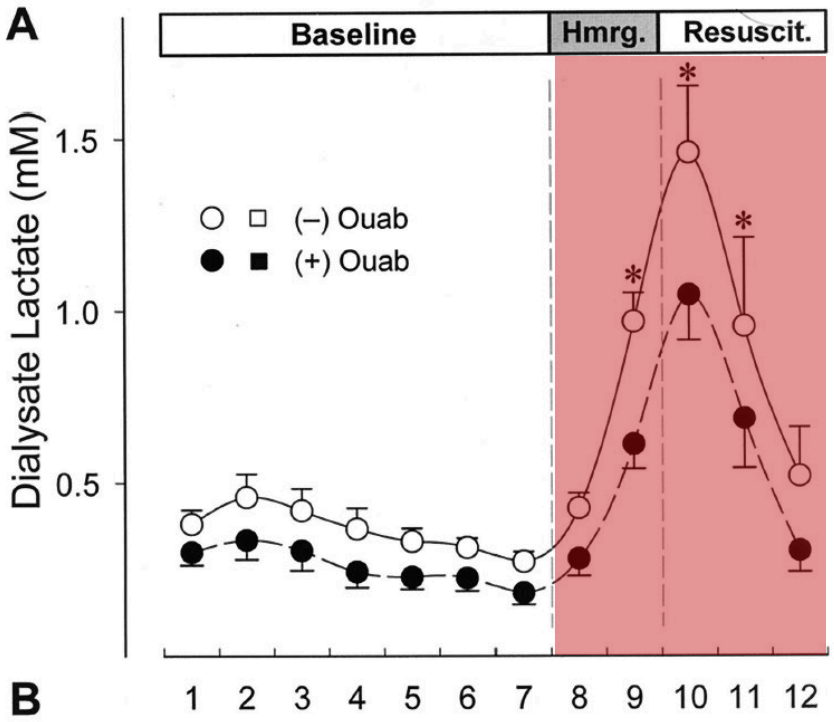
Hypoxia – Type A lactic acidosis



M. Adeva-Andany et al. / Mitochondrion 17 (2014)

Lactic acidosis – Type B

Epinephrine



Increased glycolysis has been associated with increased stimulation of the sarcolemmal Na-K ATPase.

Lactic acidosis is not only associated with hypoxia but every stress that induces elevated epinephrine concentrations

Epinephrine stimulates lactate production in well-oxygenated skeletal muscle by increasing the activity of the Na-K ATPase

Lindinger MI et alii - Am J Physiol. 1992

Lactic acidosis – Type B

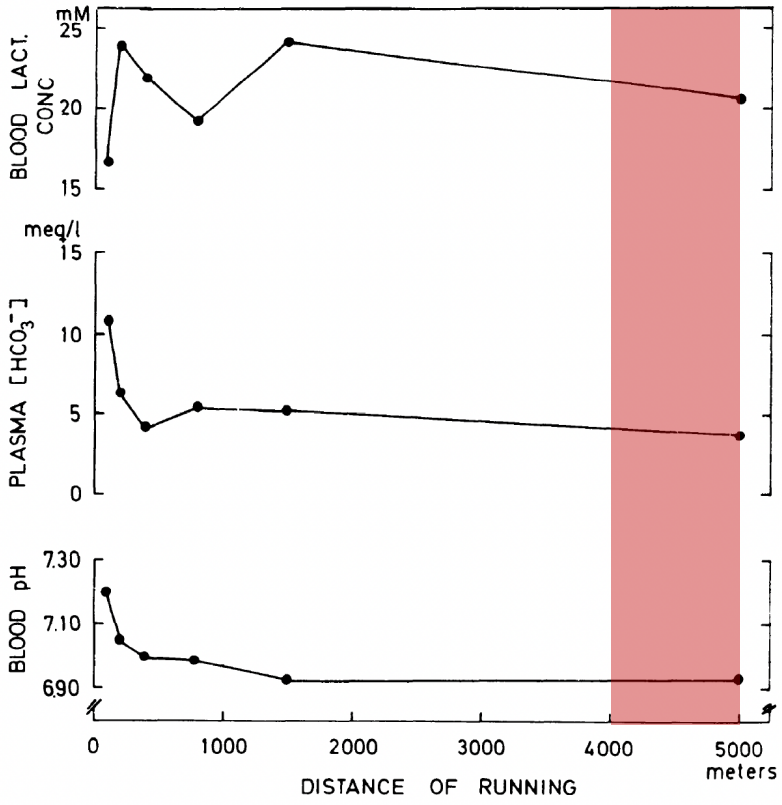
Seizures – a model of lactate overload

	0–4 MIN	15 MIN	30 MIN	60 MIN
pH	7.14±0.06 (6.86–7.36)	7.24±0.05 (7.08–7.47)	7.31±0.04‡ (7.17–7.48)	7.38±0.04§ (7.20–7.52)
P_{CO_2} (mm Hg)	45±4.6 (31–65)	39±2.7 (31–55)	38±2.4 (30–51)	39±3.0 (31–58)
P_{O_2} (mm Hg)	87±4.9	88±5.5	86±3.4	88±3.7
Na (meq/liter)	140±1.2 (136–145)	138±0.7 (134–140)	137±0.4¶ (136–139)	137±0.6¶ (135–139)
K (meq/liter)	3.8±0.2 (3.0–4.9)	3.8±0.2 (2.7–4.5)	3.9±0.3 (2.8–4.8)	3.9±0.3 (3.0–5.2)
Cl (meq/liter)	99±2	98±2	98±2	98±2
CO_2 content (mmol/liter)	17.1±1.1 (13–23)	17.5±1.3 (11–24)	20.0±1.4§ (14–25)	23.6±1.1§ (21–30)
BUN (mg/dl)	8±1	8±1	7±1	8±1
Glucose (mg/dl)	156±20	152±24	162±27‖	155±18‖
Lactate (meq/liter)	12.7±1.0 (8.9–16.0)	8.9±1.0** (6.8–13.2)	9.5±1.0** (6.2–12.7)	6.6±0.7§ (4.2–10.7)
Pyruvate (meq/liter)	0.32±0.03 (0.20–0.42)	0.31±0.03 (0.16–0.43)	0.35±0.02 (0.27–0.43)	0.31±0.03 (0.19–0.44)
Beta-hydroxybutyrate (meq/liter)	0.06±0.03‖	0.07±0.04‖	0.06±0.03‖	0.06±0.03‖
Anion gap (meq/liter)†	25±1.8 (19–32)	22±1.9 (17–32)	18±1.9** (12–27)	14±2.3§ (7–26)

Orringer C.E. et alii - NEJM 1972

Lactic acidosis – Type B

Intense physical activity – Lactate overload



Osnes J.B. and Hermansen L. – J. Appl. Physiol 1972

Lactic acidosis – Type B

Some examples – Lactate overload – Intense physical activity

	Rest	Exercise Bouts				Recovery, min					
		1	*2*	*3*	*4*	5	15	25	40	60	90
					Whole blood						
$[Lac^-]_a$	0.7±0.1	7.4±1.0*	12.9±1.5*	14.3±1.3*	15.3±1.4*	14.4±1.6*	10.5±1.7*	7.7±1.2*	4.7±0.8*	2.5±0.4*	1.5±0.3*
$[Lac^-]_{fv}$	0.8±0.1	8.9±0.7*†	15.2±2.0*†	16.4±1.6*†	16.7±1.6*†	15.1±1.5*†	11.8±1.8*†	8.0±1.4*	4.7±0.8*	2.6±0.5*	1.4±0.2*

Lindinger MI et alii - Am J Physiol. 1992

Lactic acidosis – Type B

Asthma, severe

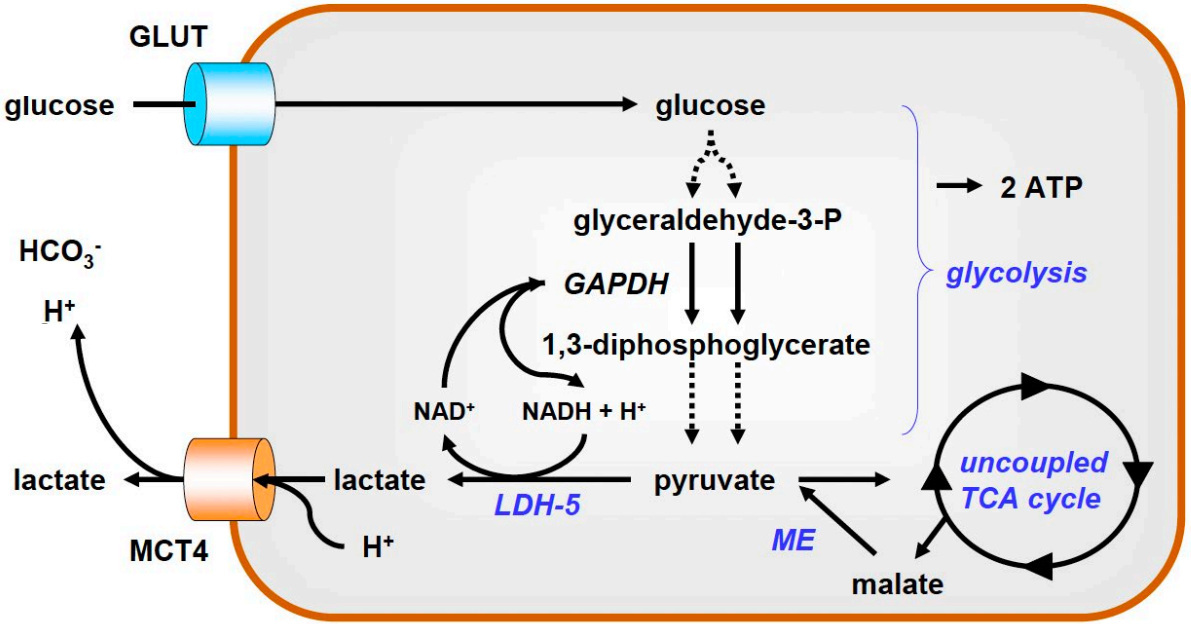
Patient	pH	PCO_2 (torr) (kPa)	HCO_3 (mmol/L)	Base Excess (mmol/L)	Anion Gap (mmol/L)	Blood Gas Lactate (mmol/L)	Plasma Lactate (mmol/L)	Serum Pyruvate (mmol/L)	Lactate/ Pyruvate Ratio
1	7.36	31 (4.1)	17	−7	8	5.3	4.6	0.482	9.5
2	7.36	25 (3.3)	14	−9.7	23	6.0	6.4	0.662	9.6
3	7.37	26 (3.5)	15	−8.7	9	7.7	2.9	0.296	9.7
4	7.32	31 (4.1)	16	−9	5	7.9	6.8	0.638	10.6
5	7.34	36 (4.8)	19	−6.1	13	5.9	5.5	0.466	11.8
6	7.37	29 (3.9)	17	−7.2	—	5.8	5.7	0.512	11.1
7	7.25	34 (4.5)	14	−11.5	7	8.1	7.4	0.594	12.4
8	7.34	32 (4.3)	17	−8	6	7.4	3.8	0.301	12.6
9	7.27	37 (4.9)	16	−9.4	4	7.5	4.7	0.372	12.6
10	7.32	34 (4.5)	17	−7.7	12	8.7	4.3	0.300	14.3
11	7.39	32 (4.3)	19	−4.4	4	6.7	8.3	0.512	16.2
12	7.28	41 (5.5)	19	−7.4	8	8.7	9.0	0.540	16.6
13	7.28	44 (5.9)	20	−6	—	5.5	5.8	0.292	19.8
14	7.34	24 (3.2)	12	−11.6	12	6.8	8.0	0.338	23.6
15	7.33	36 (4.8)	18	−6.5	7	6.3	5.1	0.178	28.6
16	7.08	65 (8.7)	18	−12.4	2	5.3	<0.5	0.243	—

Dashes represent missing data.

Lindinger MI et alii - Am J Physiol. 1992

Lactic acidosis – Type B

Neoplasms and ischaemic cells



Ischaemic cancer cells are adapted toward the use of glycolysis while Kreb's cycle is poorly active due to low O2 tension in the extracellular space.

Lactic dehydrogenase helps to recycle lactate to pyruvate in order to oxidate NADH+, allowing glycolytic activity

Dhup S et alii. Curr Pharm Des 2012

Lactic acidosis – Type B

Some examples – Other drugs

Drug	Key features
NRTIs (zidovudine, lamivudine, didanosine, stavudine)	Mitochondrial cytopathy
Metformin	Mitochondrial cytopathy
Epinephrine	Tissue hypoxia
β_2 agonists	Increased pyruvate generation
Isoniazid	Hepatocyte toxicity
Tetracycline	Mitochondrial cytopathy
Propofol	Mitochondrial cytopathy associated with rhabdomyolysis and multiorgan failure
Propylene glycol (solvent for drugs like nitroglycerin, lorazepam, etomidate, phenytoin)	Accumulation of lactate from metabolism of propylene glycol
Linezolid	Mitochondrial cytopathy

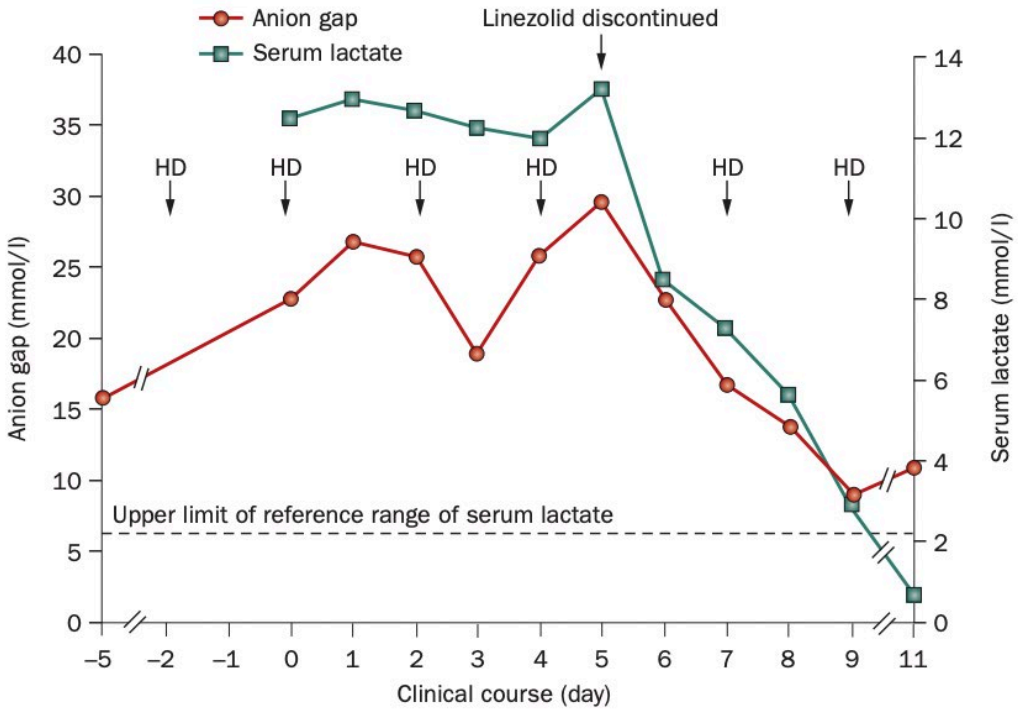
Velez, J. C. Q. & Janech, M. G. Nat. Rev. Nephrol 2010

Lactic acidosis – Type B

Some examples – Linezolid and septic shock

The mechanism of action of linezolid seems to involve the prevention of peptide bonds in ribosomes (bacteria).

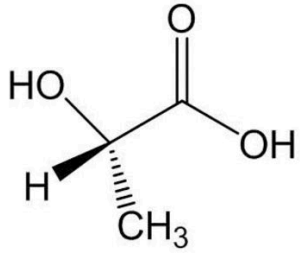
Nucleotide similarities between domain V of the bacterial 23S ribosomal RNA and human mitochondrial 16S ribosomal RNA enable, to some extent, linezolid to bind to this mitochondrial subunit



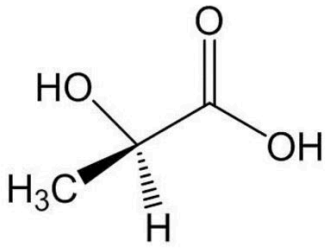
Velez, J. C. Q. & Janech, M. G. Nat. Rev. Nephrol 2010

Lactic acid

Lactate may exist in the human body as two stereoisomers: L-lactate and D-lactate



L-lactic acid



D-lactic acid

D-Lactate

Relevant sources

Dietary intake:

- sour milk, yogurt, molasses, apples, tomatoes, pickles, beer, and wines

Not sufficient alone

Bacterial fermentation:

- Undigested carbohydrates in the gastrointestinal tract

e.g. short bowel syndrome

Exogenous infusions:

- Sodium lactate and lactated ringer solution

Heavy resuscitation volumes with Ringer

Thiamine deficiency (beriberi)

- lactic acidosis, peripheral edema, and muscle swelling in the absence of cardiac failure due to vasodilatation, neurological alterations

Alcohol

- degradation of ethanol, methanol, ethylene glycol, and propylene glycol is catalyzed by the enzyme alcohol dehydrogenase and transformed into aldehydes

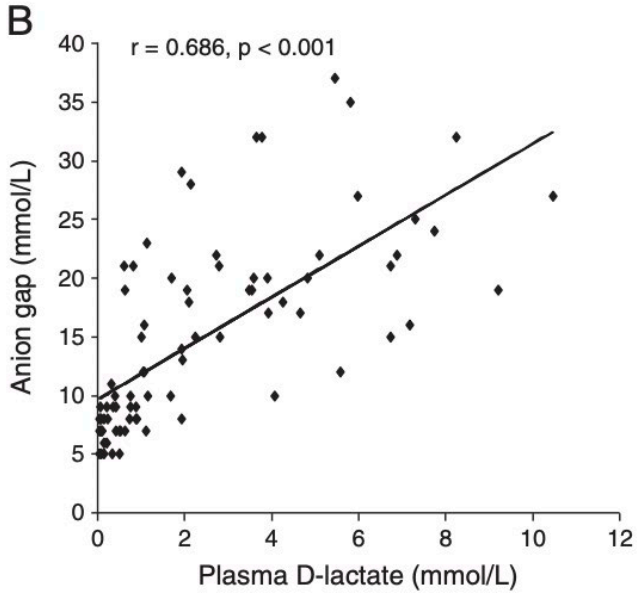
Not sufficient alone

D-Lactate

Relevant sources – Diabetic ketoacidosis

Diabetic ketoacidosis appears with elevated anion gap, which according to this experience is influenced by D-lactate

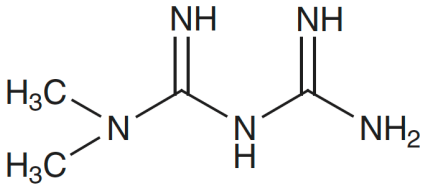
D-lactate cannot be dosed by blood gas analyses and should be inferred by an elevated anion gap in absence of other causes



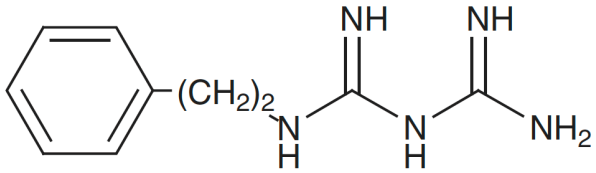
Lu J et alii. Clin Chim Acta 2011

METFORMIN-ASSOCIATED LACTIC ACIDOSIS

Biguanides



Metformin



Phenformin

Metformin - Kynetics

VARIABLE	COMMENT
Bioavailability	50–60 percent; absorbed mainly from the small intestine; estimated absorption half-life, 0.9 to 2.6 hours
Plasma concentration	Maximal, 1 to 2 μg per milliliter (approximately 10^{-5} M) 1 to 2 hours after an oral dose of 500 to 1000 mg; negligible binding to plasma proteins
Plasma half-life	Estimated at 1.5 to 4.9 hours
Metabolism	Not measurably metabolized
Elimination	About 90 percent is eliminated in urine in 12 hours; multiexponential pattern involving glomerular filtration and tubular secretion
Tissue distribution	Distributed in most tissues at concentrations similar to those in peripheral plasma; higher concentrations in liver and kidney; highest concentrations in salivary glands and intestinal wall

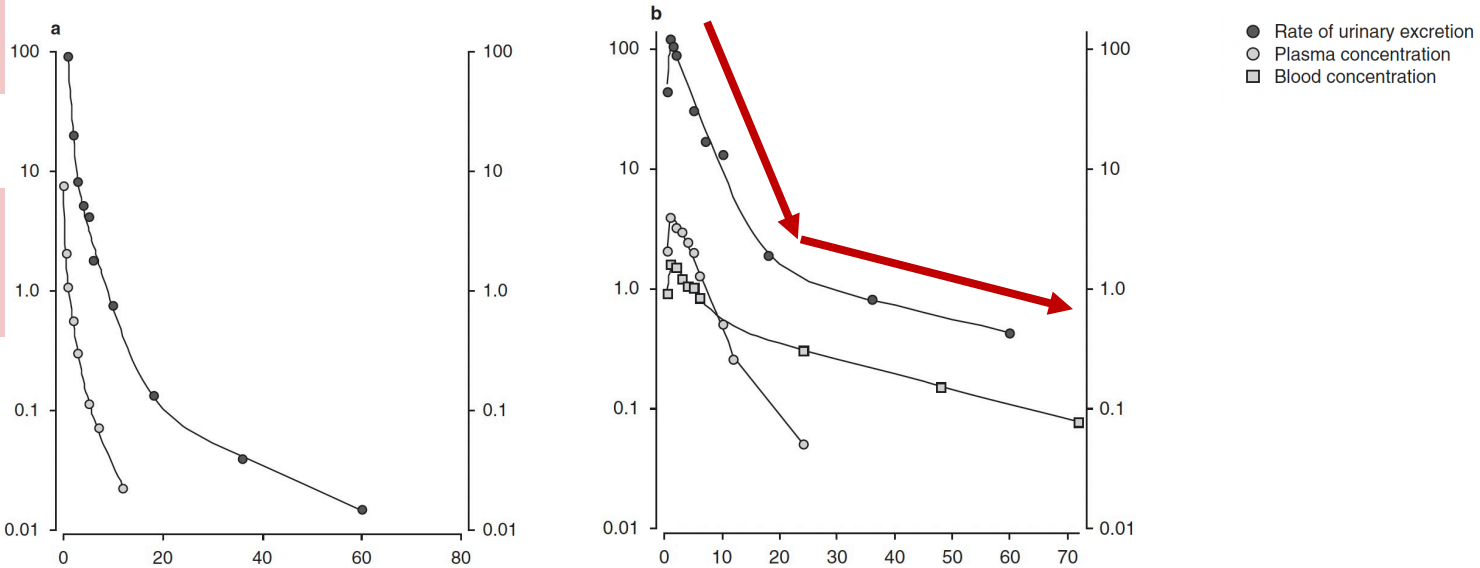
Bailey CJ et alii. N Engl J Med. 1996.

Metformin excretion

a) Time course of mean plasma concentrations and mean rate of urinary excretion of metformin following a short infusion (0.25 g over 15 min). (b) Time course of concentrations of metformin in plasma and in blood, and rate of urinary excretion of metformin in a healthy subject following an oral dose of 1.5 g. The prolonged elimination half-life from blood is due to the slow uptake and loss from erythrocytes.

Peak is achieved in 3 hours, but its elimination (renal) is slow

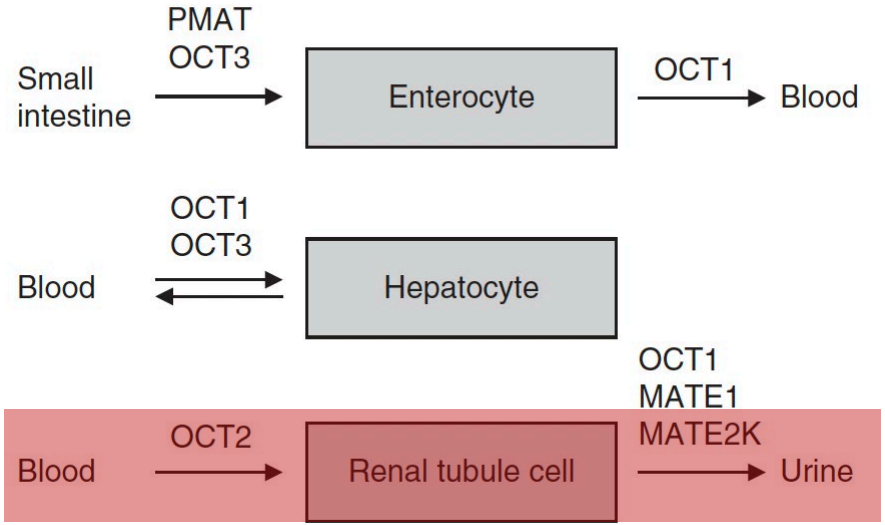
Plasmatic clearance is influenced by a steady, slow release of drug from erythrocytes

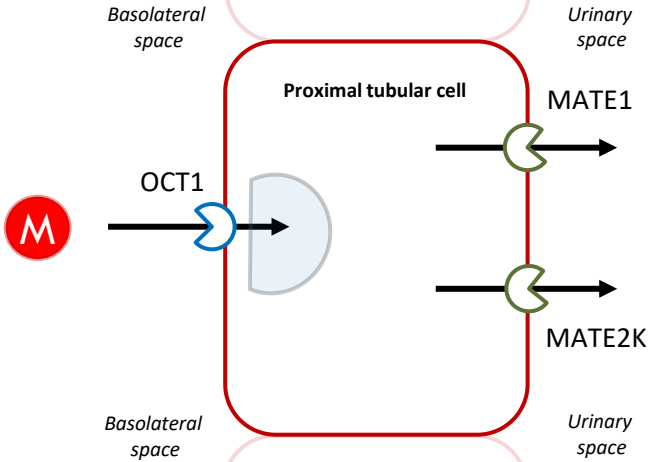


Graham G. G. et alii – Clin. Pharmacokinet. 2011

Metformin transporters

Major known transporters involved in the absorption, hepatic uptake and urinary excretion of metformin. MATE= multidrug and toxin extrusion transporter; OCT= organic cation transporter; PMAT= plasma membrane
monoamine transporter.

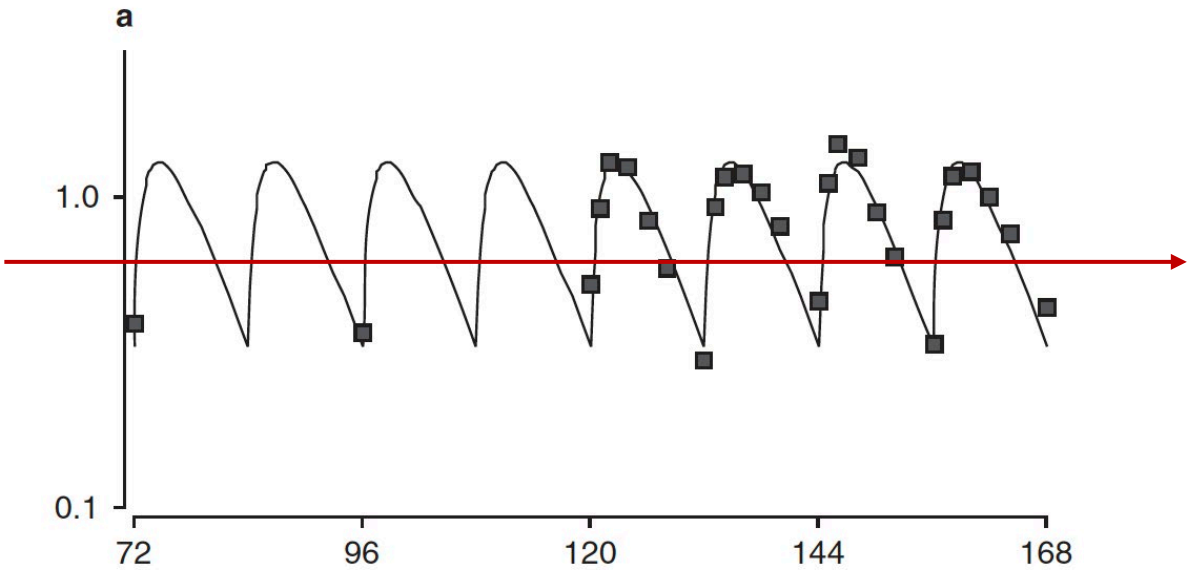




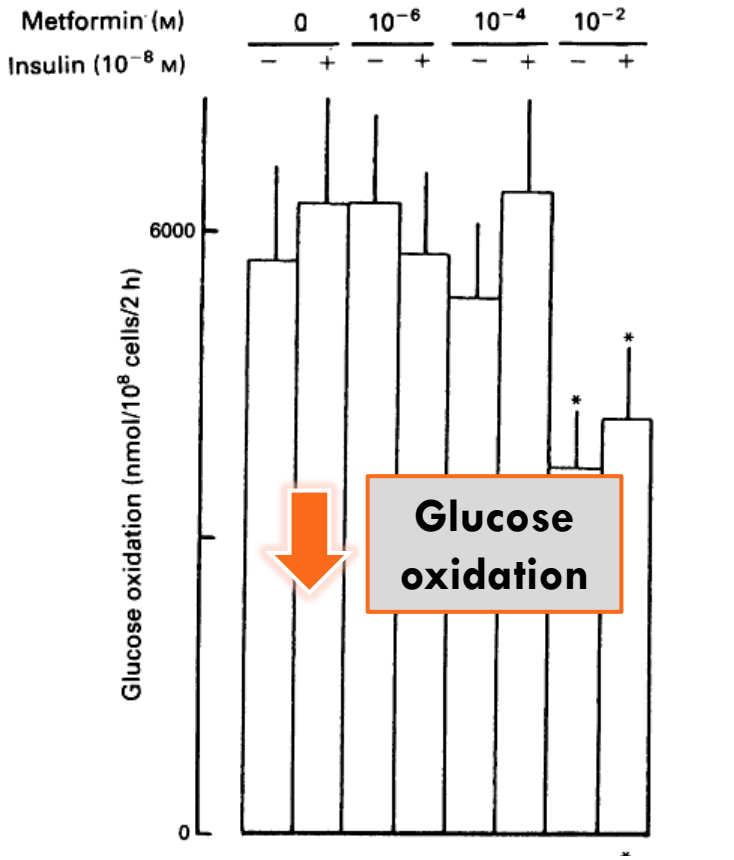
Graham G. G. et alii – Clin. Pharmacokinet. 2011

Metformin

Steady state in normal individuals



Graham G. G. et alii – Clin. Pharmacokinet. 2011



Br. J. Pharmacol. (1992), **105**, 1009–1013

Effect of metformin on glucose metabolism in the splanchnic bed

[1]C.J. Bailey, Carol Wilcock & Caroline Day

Department of Pharmaceutical Sciences, Aston University, Birmingham B4 7ET

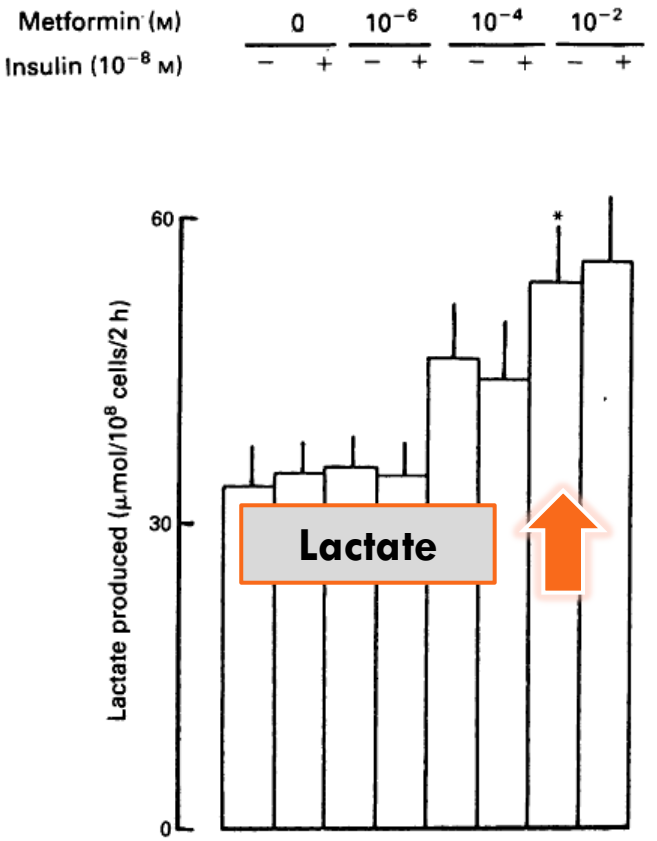


Figure 4 Glucose oxidation to CO_2 and lactate production by rat hepatocytes incubated for 1 h with metformin (10^{-6}–10^{-2} mol l^{-1}) in the absence and presence of insulin (10^{-8} mol l^{-1}). Values are mean with s.e.mean shown by vertical lines, $n = 8$. *$P < 0.05$ versus control receiving same amount of insulin (Student's t test).

Metformin associated lactic acidosis

Definition

Metformin associated lactic acidosis is defined by a lactic acidosis which is associated with a documented, recent, intake of metformin

Terms like »metformin-induced lactic acidosis» are not consistent in our clinical practice and can be used only in patients without comorbidities that intorduced pathologic doses of metformin (suicide or dose errors)

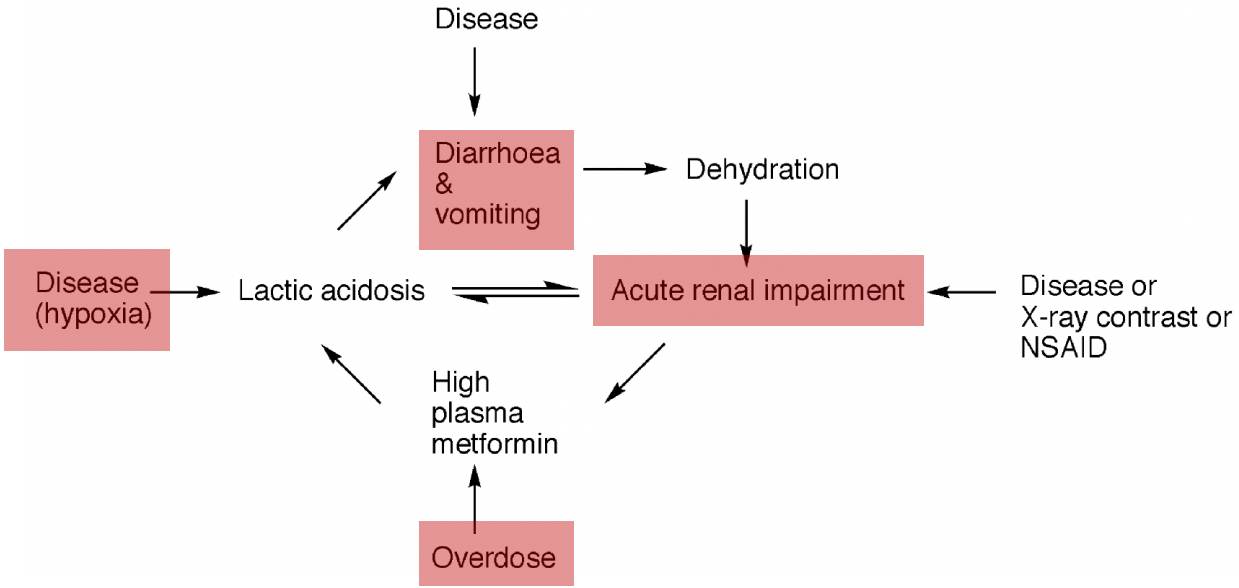
23.4 casi/100.000 pazienti in trattamento (2000-2016)
70.1 casi/100.000 pazienti in trattamento (2016-2021)

Mortalità del 21.4% (2000-2016)
Mortalità del 17% (2016-2021)

Angioi A. et alii – J Nephrol 2018

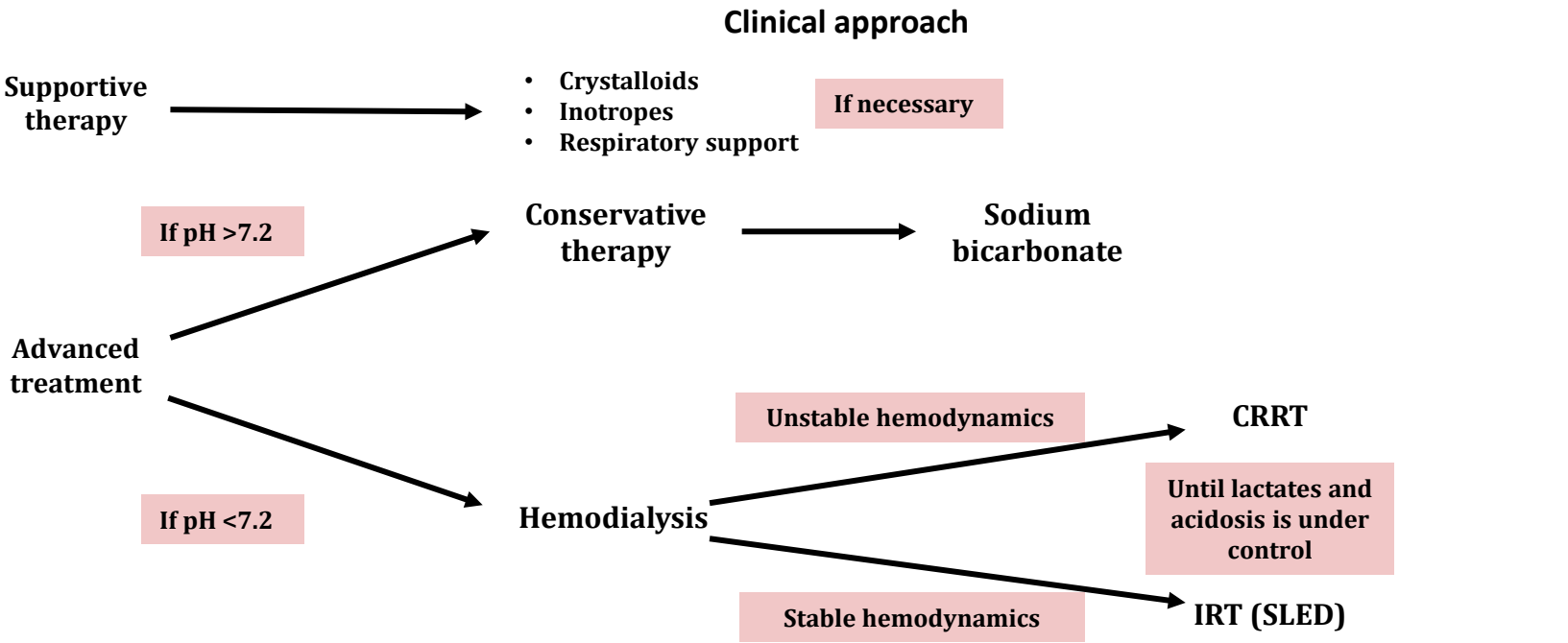
Metformin associated lactic acidosis

Mechanism of disease



Graham G. G. et alii – Clin. Pharmacokinet. 2011

Metformin associated lactic acidosis



Conclusioni

- L'acidosi lattica si associa ad un'**incrementata produzione** di acido lattico, ad una **ridotta clearance**, o **entrambi;**
- L'acidosi lattica può essere distinta in forme **ipossiche** e **non**, ma non mancano forme **spurie;**
- L'acidosi lattica è una spia di un meccanismo patologico talvolta **occulto;**
- L'acidosi lattica indotta da metformina è molto rara, mentre **le forme associate sono più frequenti,** sensibilmente più di quanto osservato nei trial clinici e descritto nelle metanalisi
- In caso di MALA e MILA, il trattamento emodialitico (SLEDD e CRRT) è **risolutivo** in poche sedute e segue la cinetica del farmaco


Grazie per l’attenzione

Metformin

Our experience, ARNAS Brotzu, S.C.D.U. Nefrologia, Dialisi e Trapianto

Table 1 Descriptive statistics of selected patients at admission. M:F (male/female ratio); SD (standard deviation); CKD (chronic kidney disease)

Demographics and baseline characteristics	
Demographics	
N° of patients	28
M:F	1.5: 1
Mean age ± SD	66.7 ± 9
% of ≥ 65 years	60.7
% of ≥ 80 years	3.5
Status on admission	
N° days with symptoms ± SD before the admission	6.04 ± 5
Days of admission	10.6 ± 6.7
Systolic Pressure (mmHg)	125 ± 32.3
Diastolic Pressure (mmHg)	64.6 ± 16
Body temperature (°C)	36.9 ± 0.8
% Oliguria	71.4
Renal function	
Mean sCr (mg/dl) before the admission	1.16 ± 0.48
Mean eGFR CKD EPI (ml/min/1.73 m2) before the admission	71.9 ± 26.5
AKI stage (%)	Stage I – 0% Stage II – 3.6% Stage III – 96.4
CKD stage n (%) before the AKI	Stage I - 14 (50) Stage II - 7 (25) Stage III - 7 (25) Stage IV - 0 (0) Stage V - 0 (0)
Comorbidities	
% Heart Failure	14.2
% Iodinated contrast agent	3.5
% Moderate to severe anemia	35.7
% Vascular disease	21.4
% Non-acute pulmonary disease	7.1
% SIRS	57.1
% Sepsis	14.2
Treatment	
% Hemodialysis post-admission	100
Number of hemodialysis sessions	2.26 ± 2

Angioi A. et alii – J Nephrol 2018

Metformin

Our experience, ARNAS Brotzu, S.C.D.U. Nefrologia, Dialisi e Trapianto

Table 2 Laboratory parameters at time 0 (admission) and at 36 h, intended as means and standard deviation (SD); EB (excess of bases), pCO_2 (CO_2 partial blood pressure)

Laboratory parameters at time 0 (admission) and at 36 h, intended as means and standard deviation (SD)

Variable (mean ± SD)	*Time 0*	*Time 1 (36 h)*	*Sig.*
Serum Creatinine (mg/dl)	8.1 ± 3.1	5.3 ± 2.8	$p < 0.05$
Blood Urea Nitrogen (mg/dl)	96.8 ± 47.4	54.6 ± 27.4	$p < 0.05$
Hemoglobin (g/dl)	10.7 ± 1.6	11.2 ± 1.8	*p NS*
Potassium (mEq/L)	5.93 ± 1.4	4.03 ± 0.8	$p < 0.05$
Glycemia (mg/dl)	178.8 ± 123	160.1 ± 24	*p NS*
C-reactive protein (mg/dl)	8.6 ± 8.9	4.3 ± 2.3	$p < 0.05$
pH, serum	7.01 ± 0.22	7.35 ± 0.7	$p < 0.05$
HCO_3 -(mmol/L)	7.72 ± 4.4	22.7 ± 6.4	$p < 0.05$
EB (mmol/L)	−19.3 ± 11.7	−1.92 ± 5.6	$p < 0.05$
Lactate (mmol/L)	13.7 ± 6	2.6 ± 2.6	$p < 0.05$
Anion gap (mmol/L)	36.2 ± 8.2	13.2 ± 4.1	$p < 0.05$
$VpCO_2$ (mEq/L)	25.7 ± 9.5	39.1 ± 4.4	$p < 0.05$
VpO_2 (mEq/L)	65.4 ± 10.5	42.4 ± 9.9	$p < 0.05$

Angioi A. et alii – J Nephrol 2018

Metformin associated lactic acidosis

Esperienza monocentro - ARNAS Brotzu

Dati demografici e caratteristiche di base			
Demografia			
	Dal 2000 al 2014	Dal 2016 al 2021	Significatività
N° dei pazienti	28	30	
M:F	1,5 : 1	1,3 :1 (F:M)	*pNS*
Età media ± SD	66,7 ± 9,0	72,9 ± 8,4	*p < 0,05*
% ≥ 65 anni	60,7	86,7	*pNS*
% ≥ 80 anni	3,5	23,3	*p < 0,05*
Incidenza	23,4 / 100.000	70,1 / 100.000	
Condizioni al ricovero			
N° giorni con sintomi ± SD prima dell'ingresso in reparto	6,4 ± 5,0	4,0 ± 3,17	*P < 0,05*
Giorni di ricovero	10,6 ± 6,7	11,83 ± 10,18	*pNS*

Unpublished data

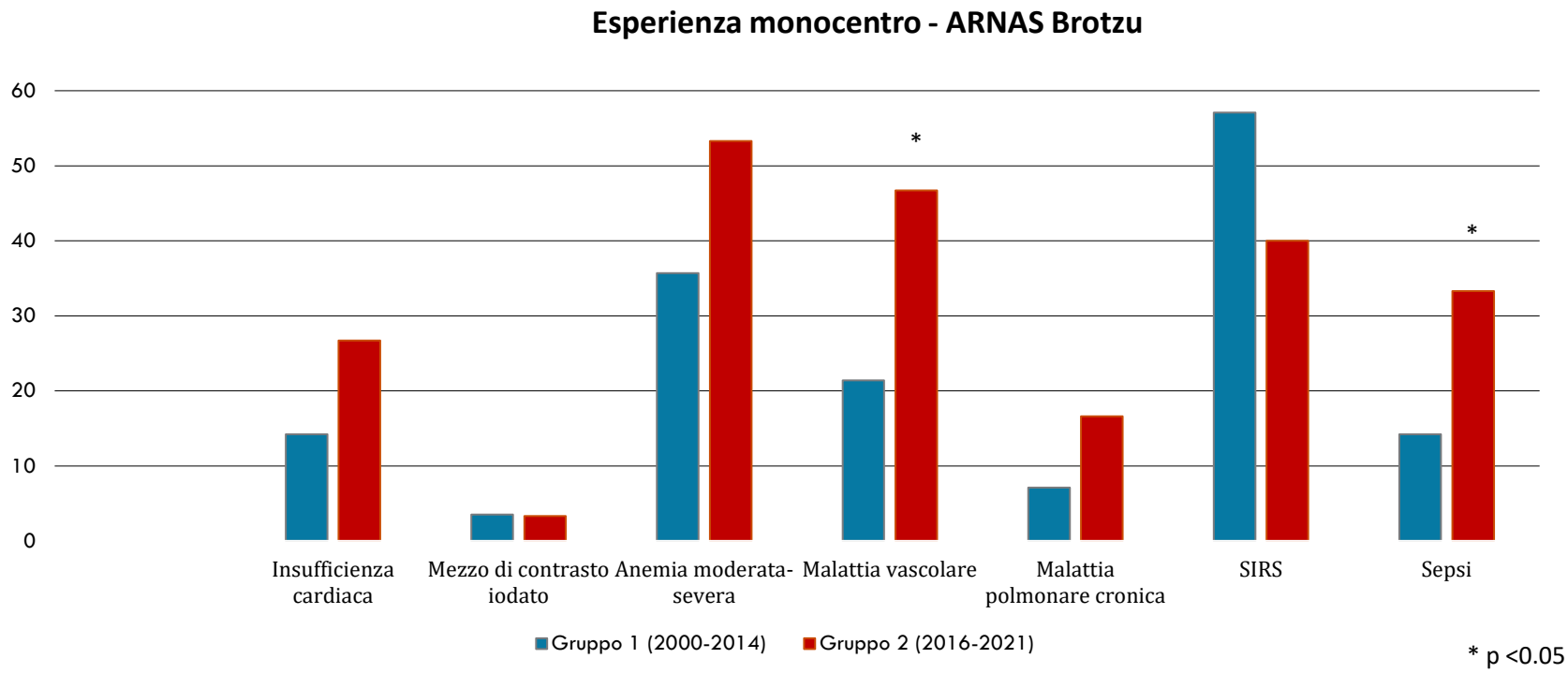
Metformin associated lactic acidosis

Esperienza monocentro - ARNAS Brotzu

Dati demografici e caratteristiche di base			
Funzionalità renale			
	Dal 2000 al 2014	Dal 2016 al 2021	Significatività
Media sCr (mg/dl) prima dell'ingresso in reparto	1,16 ± 0,48	1,48 ± 0,31	pNS
Media eGFR CKD EPI (ml/min/ 1,73 m^2) prima del ricovero	71,9 ± 26,5	46,5 ± 12,43	**p < 0,05**
AKI stadio (%)	Stadio I – 0% Stadio II – 3,6% Stadio III – 96,4%	Stadio I – 40% Stadio II – 3,3% Stadio III – 56,7%	
CKD stadio n (%) prima dell'AKI	Stadio I – 14 (50) Stadio II – 7 (25) Stadio III – 7 (25) Stadio IV – 0 (0) Stadio V – 0 (0)	Stadio I – 4 (14) Stadio II – 6 (20) Stadio III – 20 (66) Stadio IV – (0) Stadio V – 0 (0)	

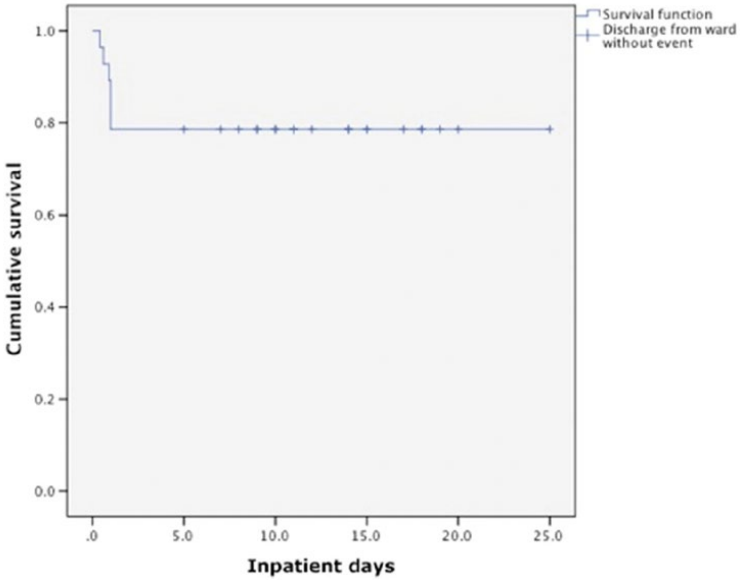
Unpublished data

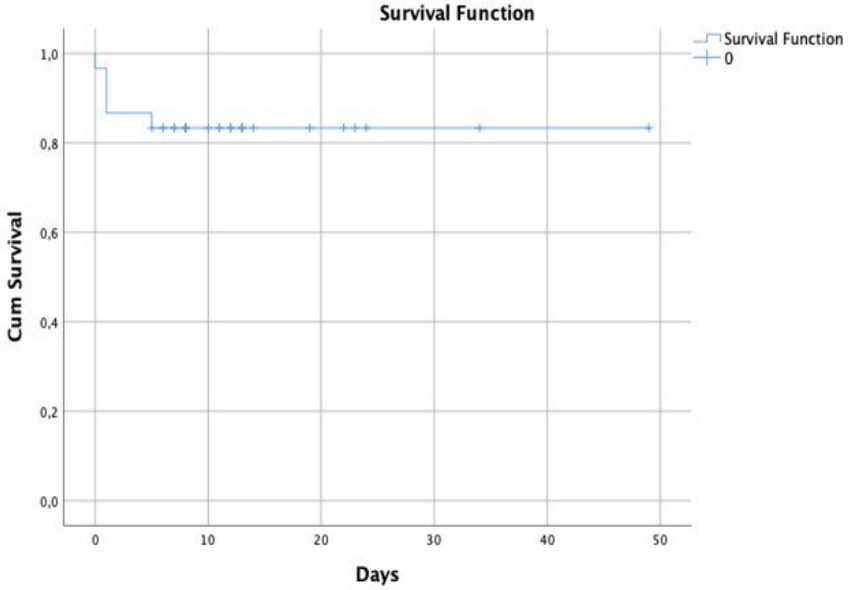
Metformin associated lactic acidosis



Metformin associated lactic acidosis

Esperienza monocentro - ARNAS Brotzu





Mortality rate: **21.4%**

Mortality rate: **17%**

Unpublished data