Kroppens reaktion ved faste og stress metabolisme
DSKE temadag 23. Marts 2015

- Hvorfor vigtigt?
- Metabolisme
  - dødsårsager ved faste og stress-metabolisme
- Proteinbehov
  - anabol resistens
  - aminosyre-behov

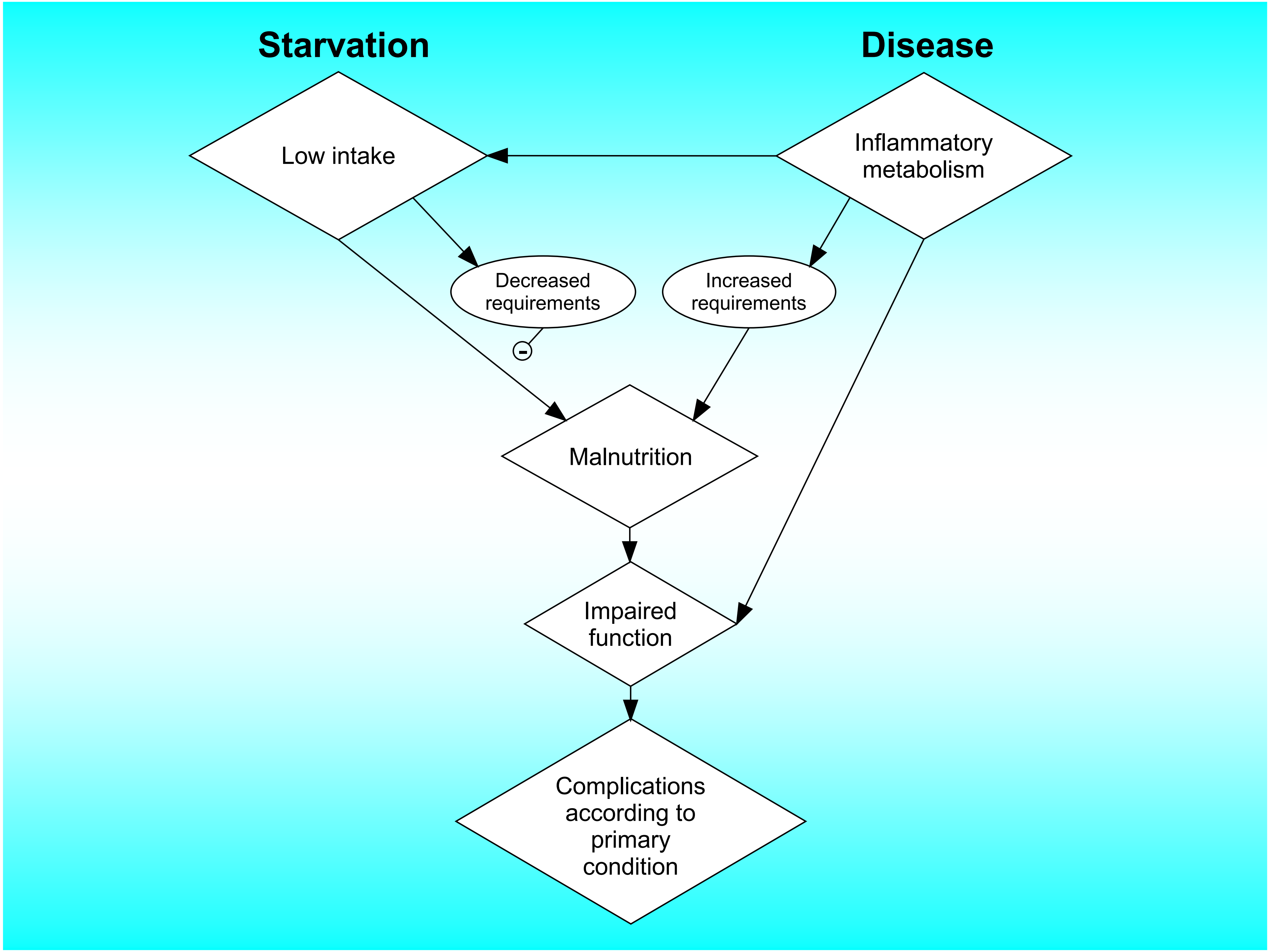
Jens Kondrup. Overlæge, Ernæringsenheden, Rigshospitalet

Ernæringsterapi hos den stress-metabole patient

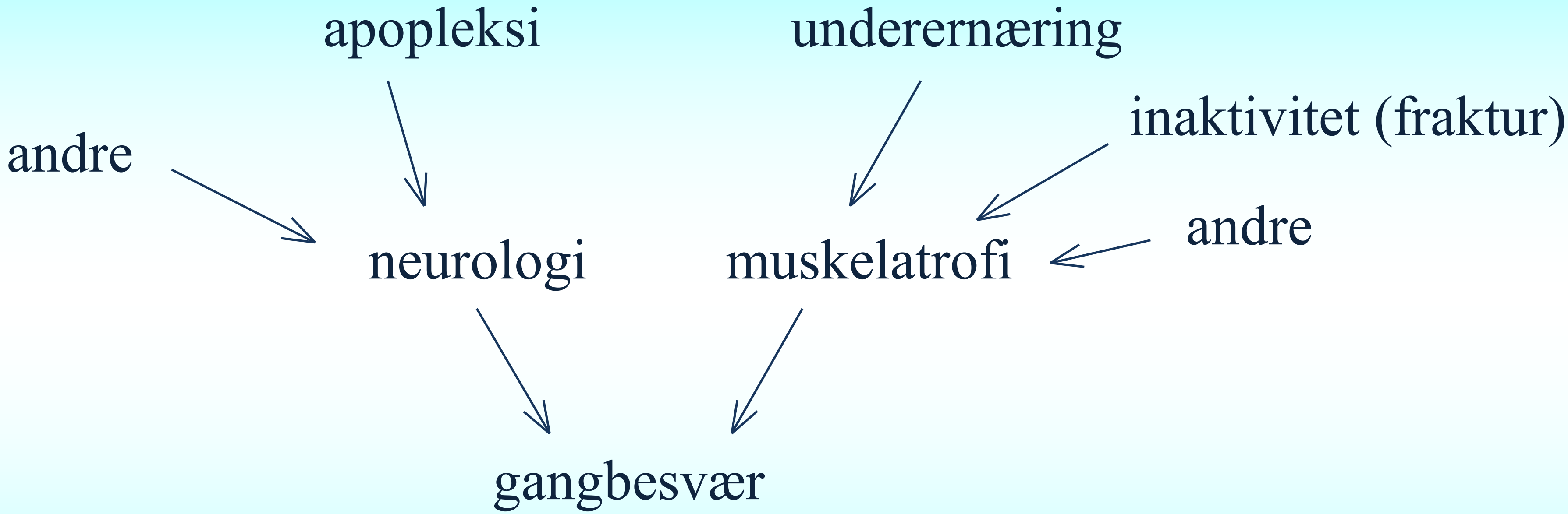
- **Hungersnød** → underernæring; ernæringsterapi er kausal behandling

- **Sygdomme** → dårlig almentilstand; komplikationer; dårlig livskvalitet.
  - Underernæring er én af komplikationerne (stress-metabolisme → nedsat appetit, øgede behov)
    - Immobilisering
    - Infektioner
    - Dårlig sårheling
    - etc
  - Alle disse konsekvenser af underernæring kan have andre årsager
  - Ernæringsterapi hjælper, hvis underernæring er en væsentlig (med-) årsag til tilstanden.

Stress-metabolisme ≈ katabolisme ≈ kachexi ≈ metaboliske forstyrrelser ved inflammatoriske tilstande.

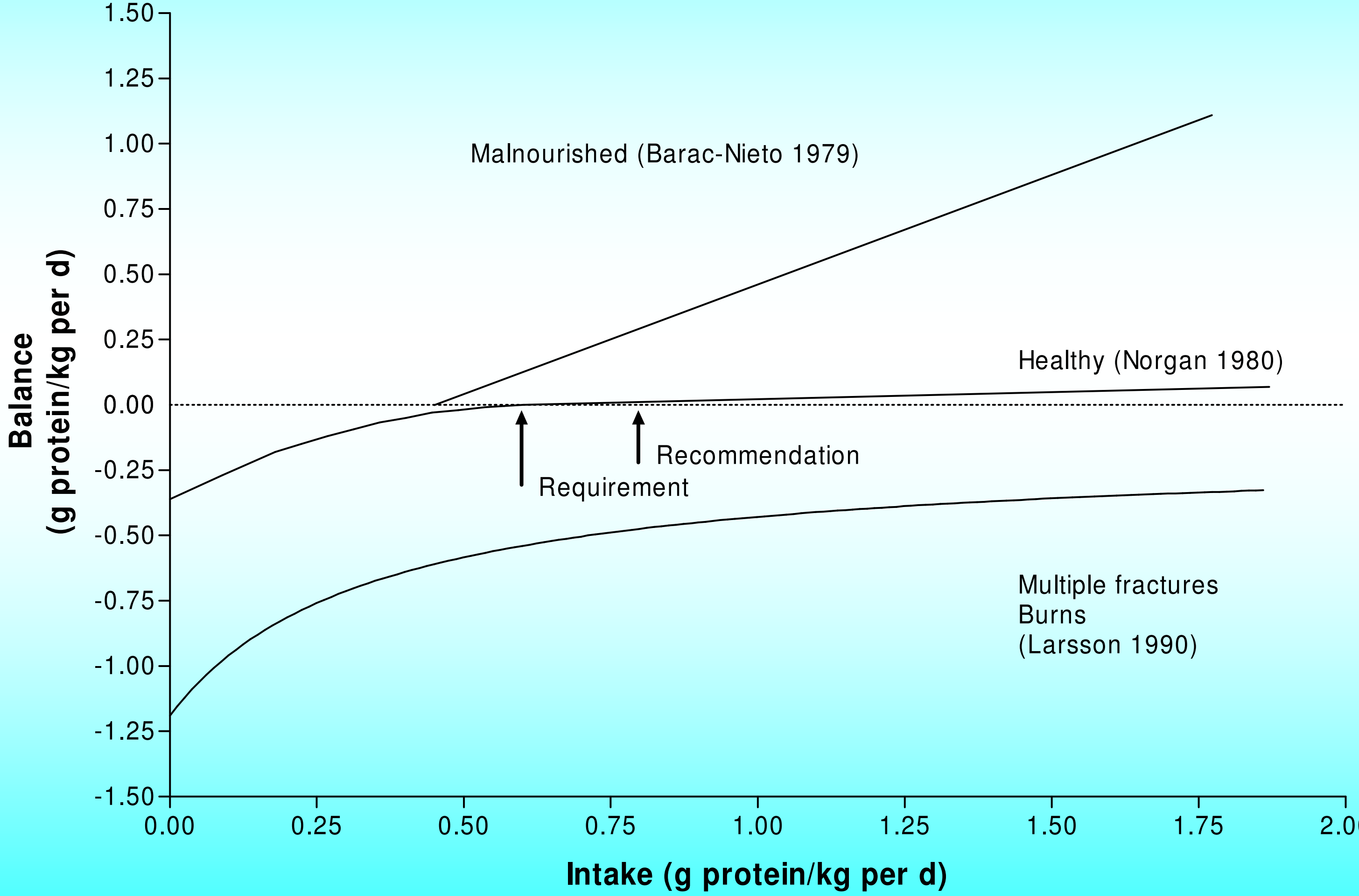

Starvation
Disease
Low intake
Inflammatory metabolism
Decreased requirements
Increased requirements
Malnutrition
Impaired function
Complications according to primary condition

Konkurrerende årsager?



Ernæringsterapi vil virke på gangbesvær, hvis underernæring er en dominerende årsag til gangbesværet, men i mindre grad hvis underernæringen er en mindre del af de samlede årsager til gangbesværet.

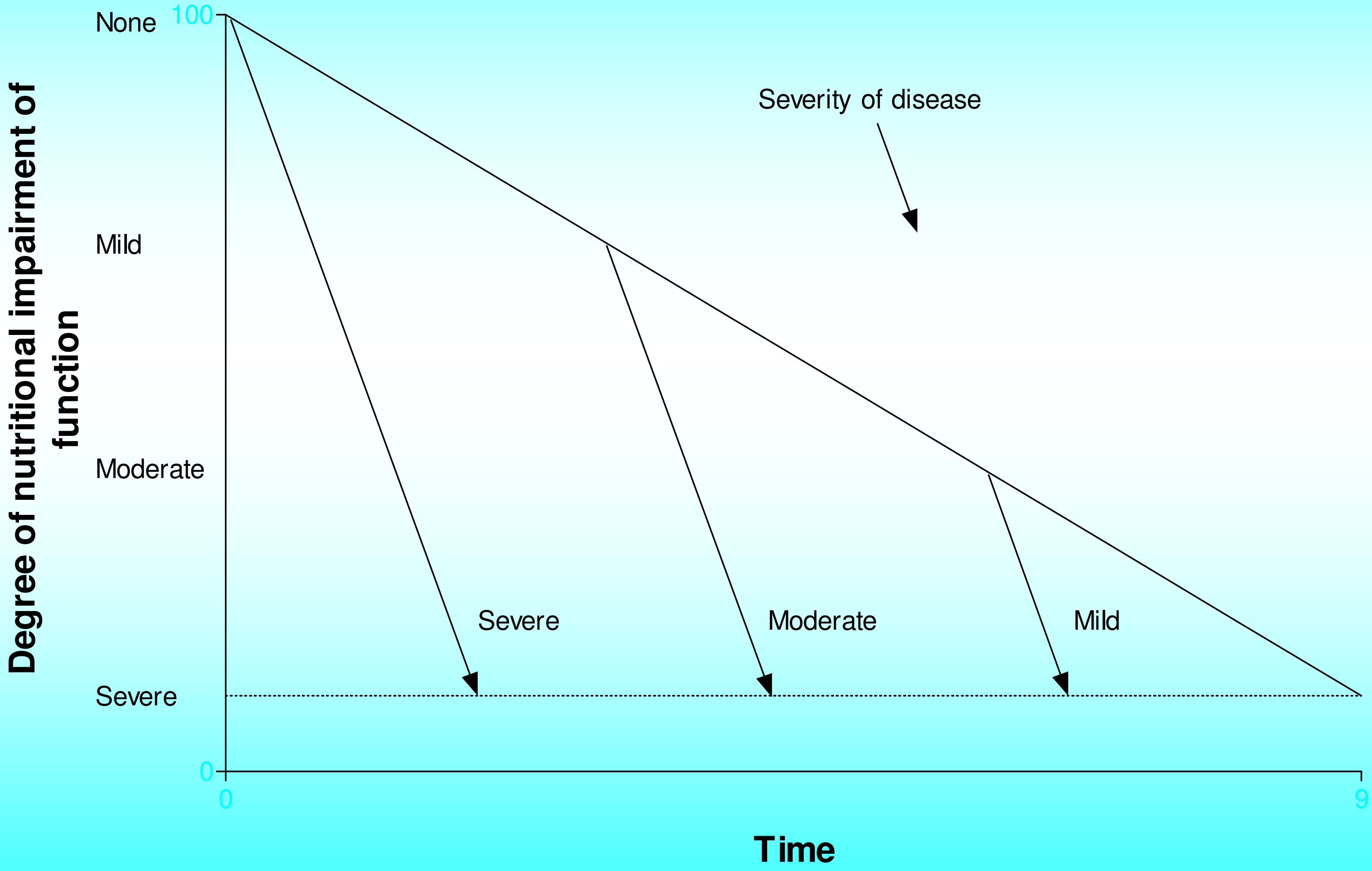
Protein requirement and utilization



Kondrup J, Nielsen K. Z Gastroenterol 1996;34:26-31.

In the hospital:

malnutrition & clinical condition, i.e. nutritional status and severity of disease (i.e. nutritional requirements/stress-metabolism)



Nutritional risk = risk of complications due to nutritional impairment

Energidepoter
ved 1800 Kcal per dag

Kilde	Væv	Kg	Kcal	Varighed
Fedt	Fedtvæv	15	141.000	78
Protein	Muskel	6[1)]	24.000	13
Glykogen	Muskel	0,15	600	0,3
	Lever	0,075	300	0,15
I alt			165.900	92

[1)] Kun ca. ½ af total 12 kg er mobiliserbar

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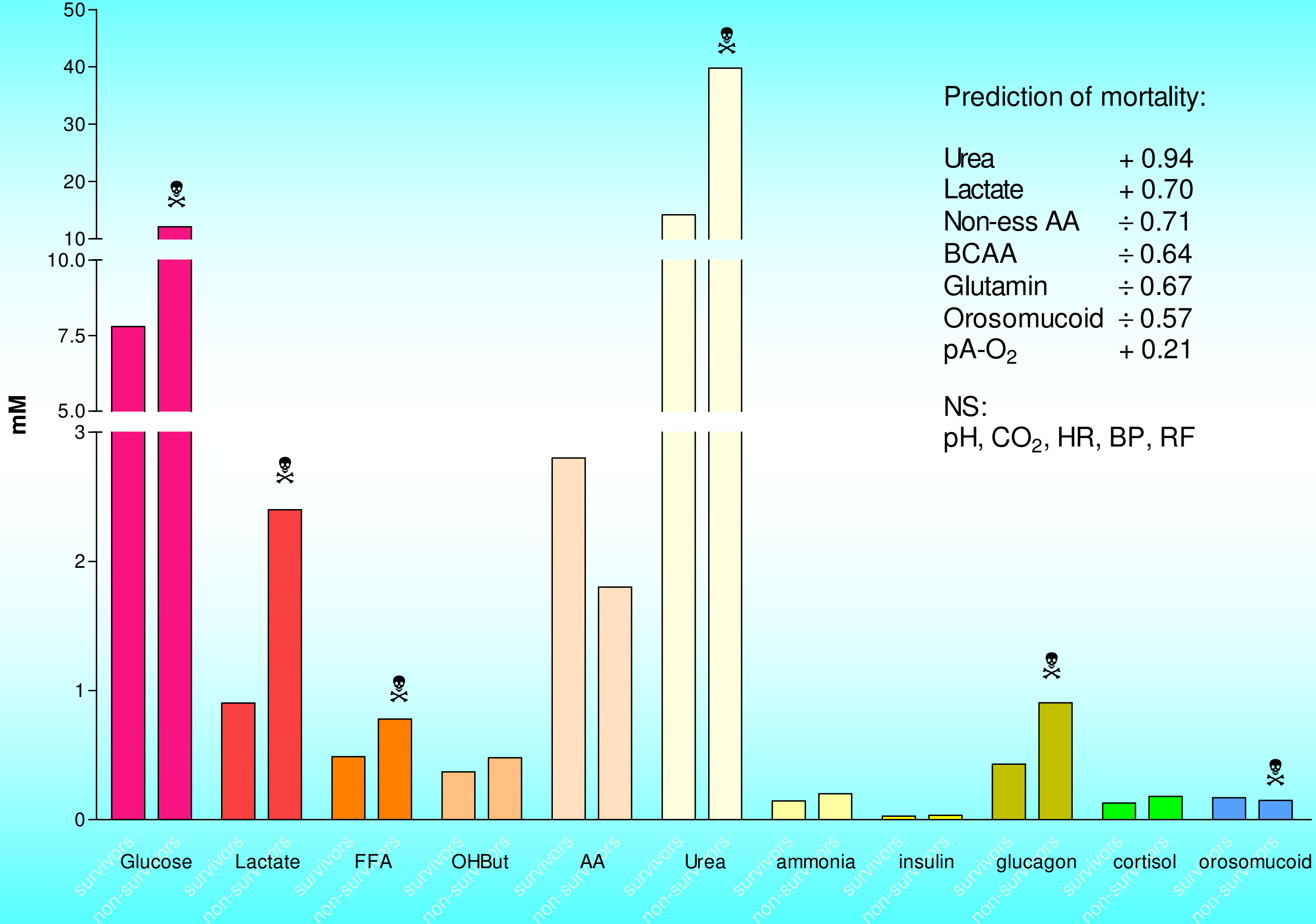
Death predictors in sepsis in 25 ICU patients
Moyer et al. 1981; J Trauma 21: 862-869



Splanchnic metabolism in non-sepsis SIRS, sepsis and multiorgan failure

Wilmore et al. Ann Surg 1980; 192: 491-504

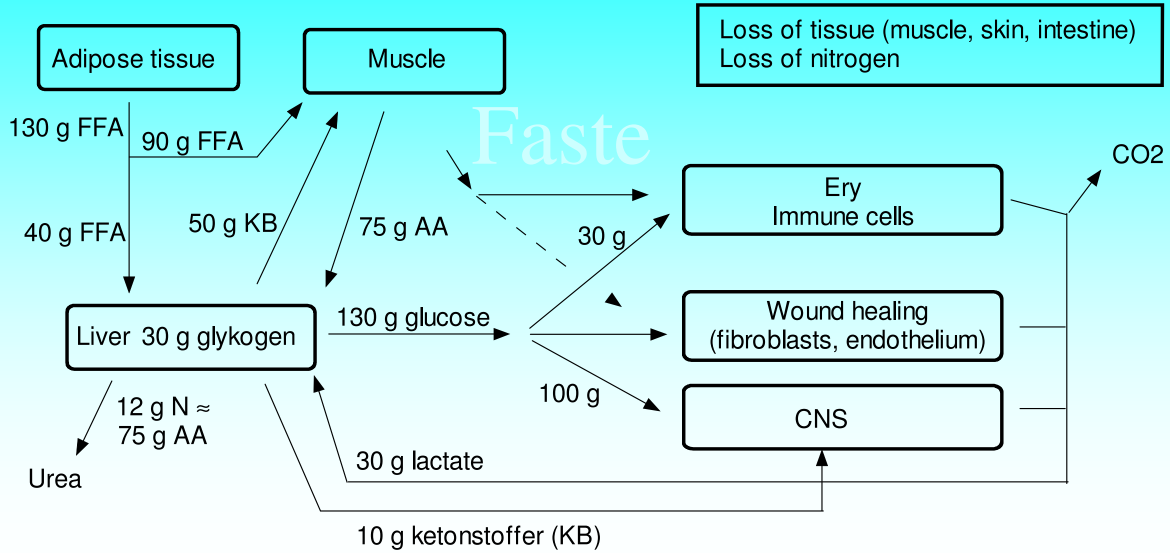
	Ctr	SIRS	Sepsis	MOF
% burn		58	62	65
Cardiac index, l/min per m^2	3.4	8.2	8.8	7.7
O_2 uptake, ml/min per m^2	126	228	238	244
Glucose, mM	4.2	5.6	7.1	6.3
Spl O_2 uptake, ml/min per m^2	37	68	66	73
Spl glucose output, mmol/min per m^2	0.4	0.64	0.84	0.36
P-lactate, mM	0.6	1.02	1.44	1.53
spl lactate uptake, mmol/min per m^2	0.15	0.38	0.43	0.27
P-alanine, mM	0.32	0.35	0.38	0.17
spl alanine uptake, mmol/min per m^2	0.04	0.12	0.21	0.04
P-C reactive protein, mg/dl	<1	25	27	14

Metabolism of wound

Wilmore et al. Ann Surg 1977; 186: 444-458

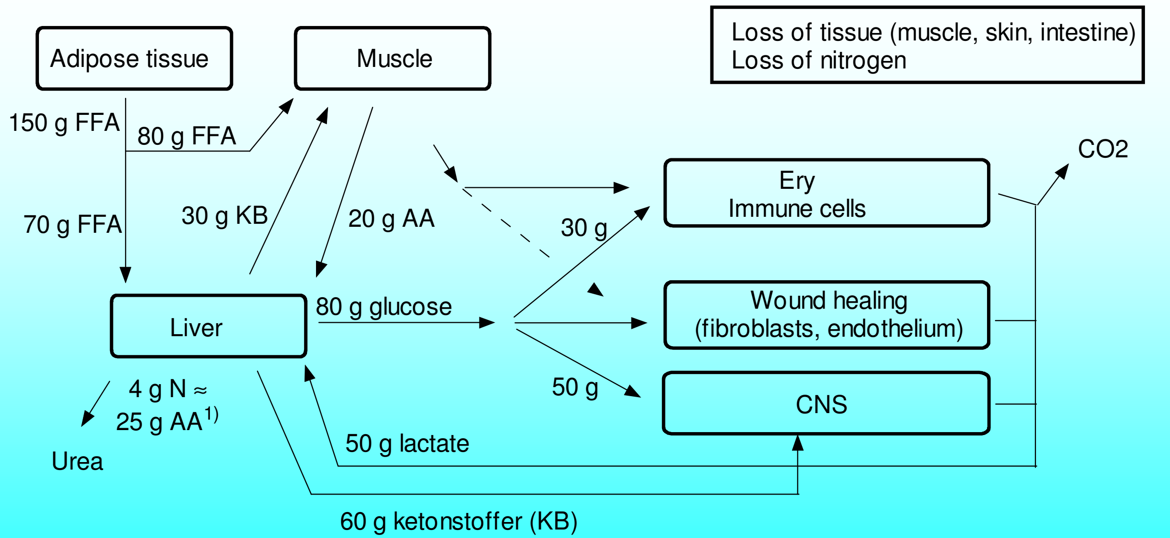
	Ctr	small	large
% burn		41	42
% leg burn		10	58
Glucoce mM	4.2	4.9	4.5
Cardiac index, l/min per m^2	3.4	7.8	7.5
O_2 uptake, ml/min per m^2	126	204	241
Leg blood flow, ml/min per 100 ml	2.6	4.2	8.0
Leg O_2 uptake, ml/min per m^2	0.12	0.19	0.24
Leg glucose uptake, mg/min per 100 ml	0.11	0.04	0.34
Leg lactate release, mg/min per 100 ml	0.02	0.06	0.30
Leg venous O_2, ml/100 ml	13.4	10.7	12.2

24 t faste
1800 kcal/day



Bursztein et al 1991; Cahill et al 1970 10.03.04

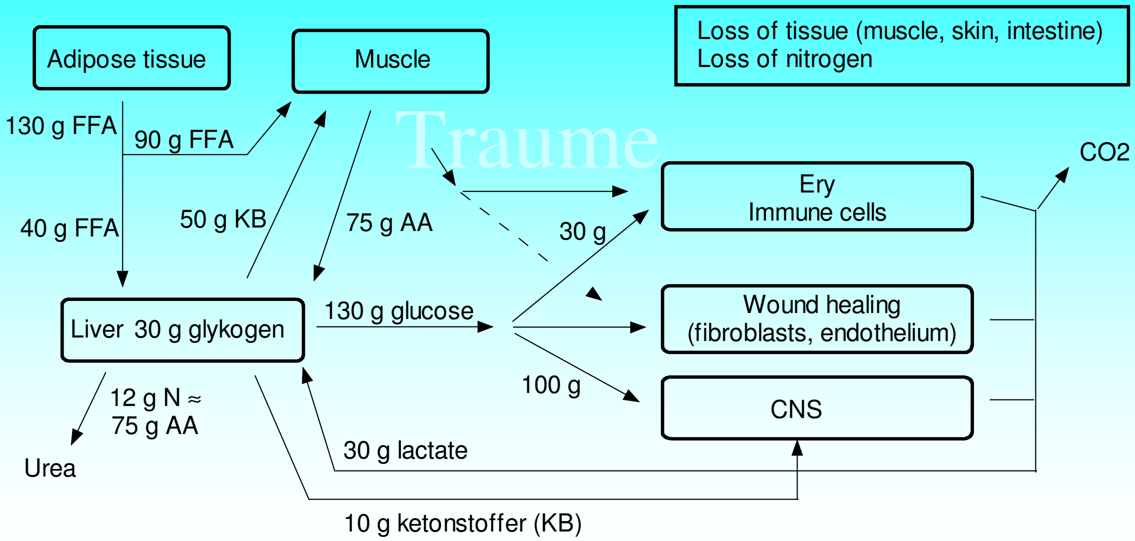
5-6 weeks' starvation
1450 kcal/day



1) less without acidosis

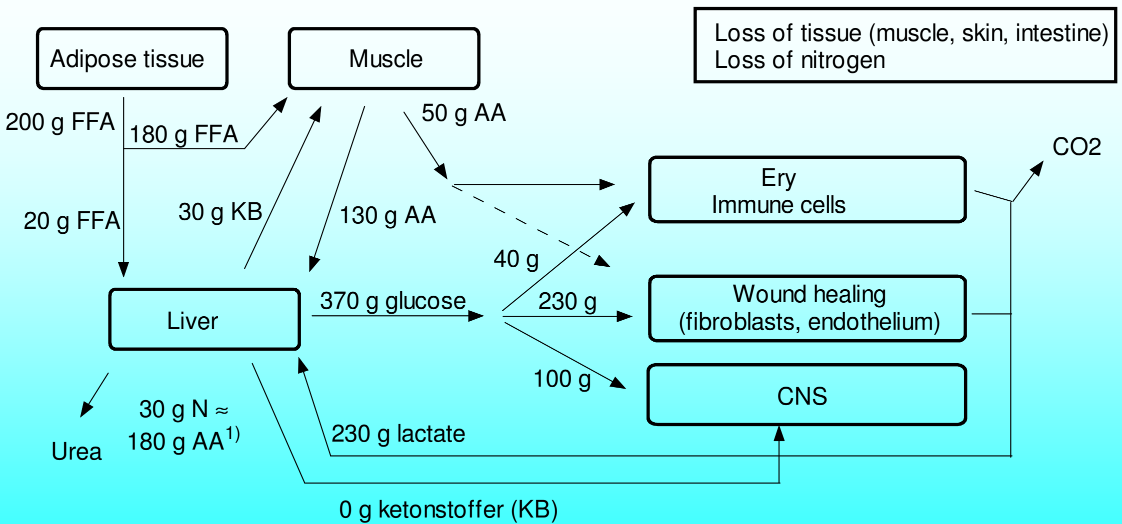
Bursztein et al 1991; Cahill et al 1970 10.03.04

24 t faste
1800 kcal/day



Bursztein et al 1991; Cahill et al 1970 10.03.04

24 t faste + traume (brandsår)
2700 kcal/day



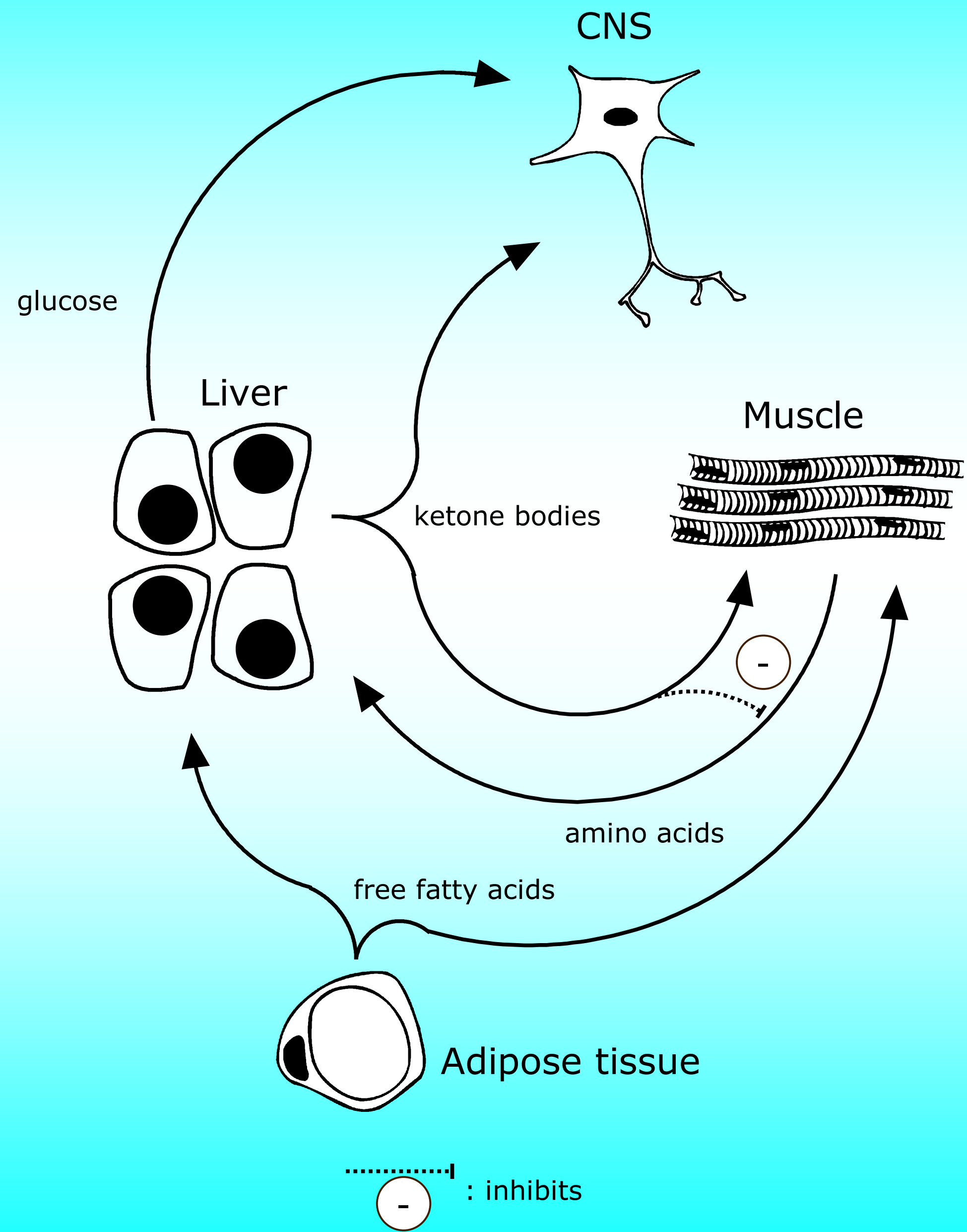
[1)] more with acidosis

Bursztein et al 1991; Cahill et al 1970 10.03.04

Starvation (S) *versus* Stress-metabolism (SM)

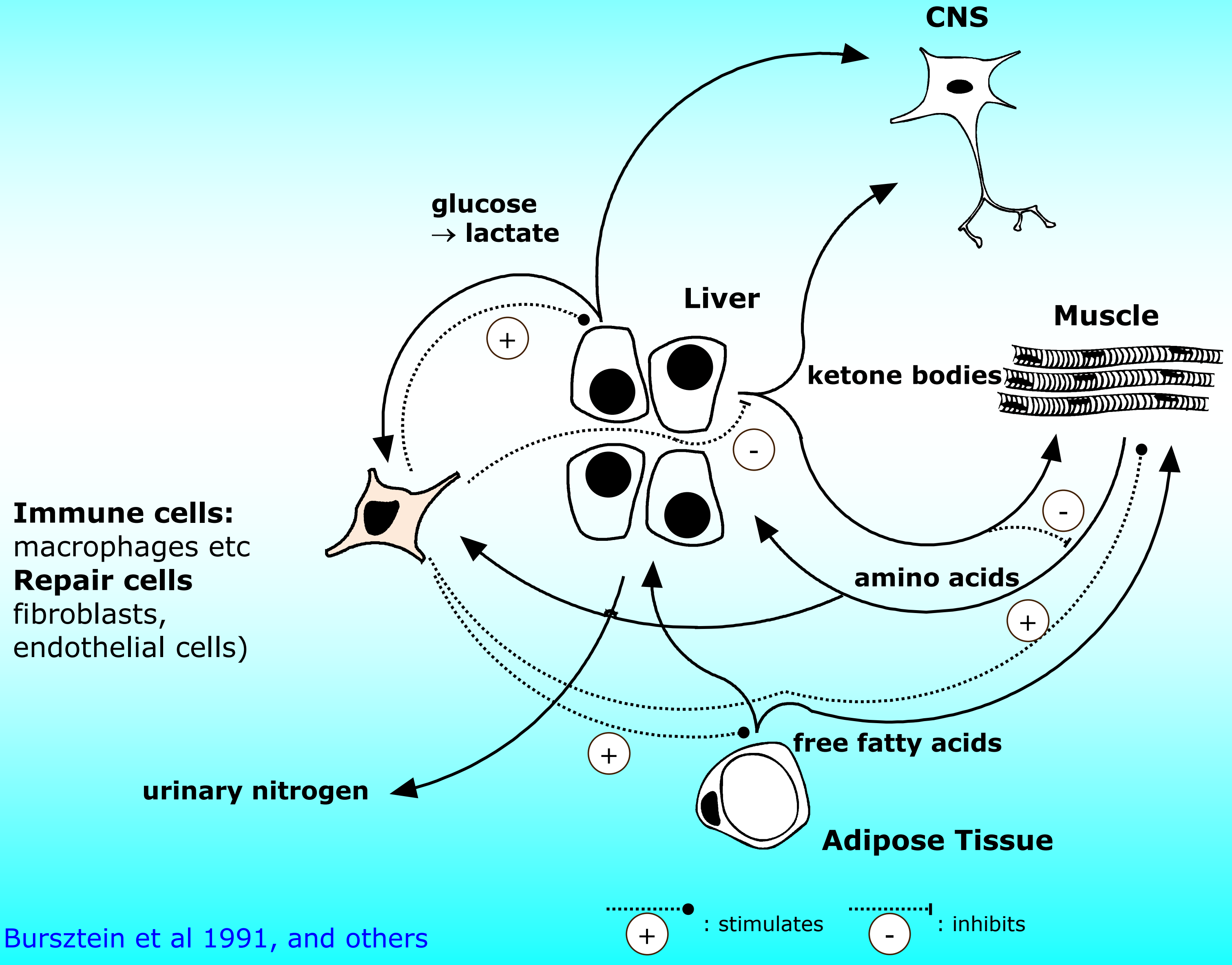
	S	SM	Cancer
24 h urinary nitrogen (LBM loss)	↓	↑↑	↔↑
REE	↓	↑	↔↑
P-glucose	↓	↑	↑
P-lactate	↑	↑↑	↑
P-FFA	↑	↑	↑
P-Ketone bodies	↑↑	↔↑	↑
P-Insulin	↓	↑	↔↑
Insulin resistance	↑	↑↑	↑
Glucose intolerance	↑	↑↑	↑
P-Catecholamines	↑	↑↑	?
P-Glucagon	↑	↑↑	?
P-Cortisol	↑	↑↑	?
P-TNF-α, Il-1, Il-6	↔	↑	↔↑
Afferent nerves (pain)	↔	↑	↔↑

Starvation



CNS
glucose
Liver
ketone bodies
Muscle
-
amino acids
free fatty acids
Adipose tissue
-
: inhibits

Macronutrient regulation in stress metabolism (burns)



After Bursztein et al 1991, and others

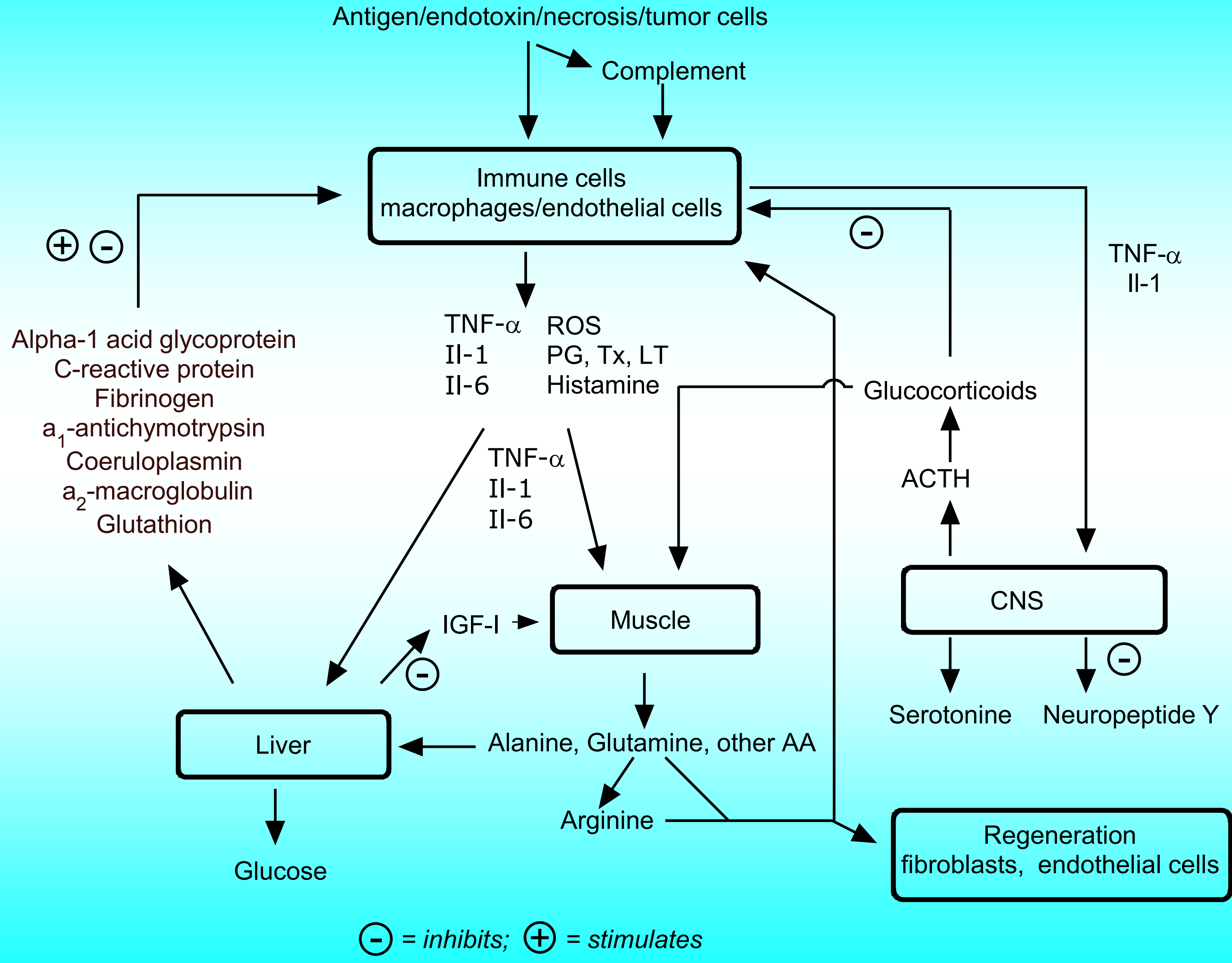
Katabole hormoner

Hormon	Årsag	Effekt
Katekolaminer	Sympatikus (smerter)	Feber, REE ↑ glykogenolyse glukoneogenese insulin-insensitivitet glukagon ↑ laktatproduktion (Na^+/K^+ ATPase ↑) lipolyse
Glukagon	Katekolaminer	glykogenolyse glukoneogenese ketogenese hepatisk AA optag ↑, ureagenese,
Cortisol	Sympatikus (smerter) Katekolaminer TNF-α	glukoneogenese insulin-insensitivitet lipolyse proteolyse

Stress metabolisme: Cytokiner

Cytokin	Årsag	Effekt
TNF-α, Il-1	Aktivering af makrofag/monocyt	PG → Feber, REE ↑, Neuropeptid Y ↓ → appetit ↓ ACTH → cortisol proteolyse (direkte?) hepatisk AA optag ↑ GH receptor ↓ → IGF-1 ↓ lipolyse ↑ ketogenese ↓
Il-6	Aktivering af makrofag/monocyt	hepatisk AA optag ↑ proteolyse glukoneogenese ketogenese ↓ akut fase proteiner GH receptor ↓ → IGF-1 ↓

Metabolism to recover



Hunger: Død ved tab af:

IRA fanger:
ca. 40% vægt
ca. 50% protein
ca. 85% fedt

øvrigt:
ca. 50% LBM eller protein
BMI <11-13

Dødsårsager:
respirationsstop
pneumoni
hudinfektioner
diaré (dehydrering)

Leiter et al. 1982 JAMA 248:2306-2307

Varighed af faste

	Faste		Stress
	24 t	5-6 uger	Brandsår
REE, Kcal	1800	1450	2700
Fedt, g/d	130	150	200
Protein, g/d	75	20	180
Død ved tab af:			
85% fedt (af 15 kg), dage	98	85	64
50% prot (af 12 kg), dage	80	300	33

Sepsis: dødelighed relateret til

- Granulocyt:
  - fagocytose ↓, O_2^- ↓, TNF-α induceret adhærence ↓
- Monocyt:
  - HLA-DR ↓, TNF-α receptor ↓, TNF-α induceret cytokin produktion ↓, LPS induceret Il-1 produktion ↓ Anergi (CD_4 Th1 celle: TNF-α ↓)
- Lavt akut fase protein response
- Autopsi:
  - Tab af CD_4 T celler fra milt, tab af lymfocytter og epitelceller fra tarm (apoptose, ikke nekrose). Mitokondrie dysfunktion og apoptose i monocytter
- Andre us.: Høj plasma TNF-α, Il-1, Il-6, Il-10

- men ingen større histologisk påvirkning af svigtende organer (ingen nekrose) – celler "holder bare op": stunning

Hotchkiss et al N Eng J Med 2003; 348: 138-150. Adrie et al 2001; Am J Respir Crit care Med 164; 389-395. Adrie Int Care Med 2000; 26: 364-375. Calvano et al. Arch Surg 1998; 133:1347-1350

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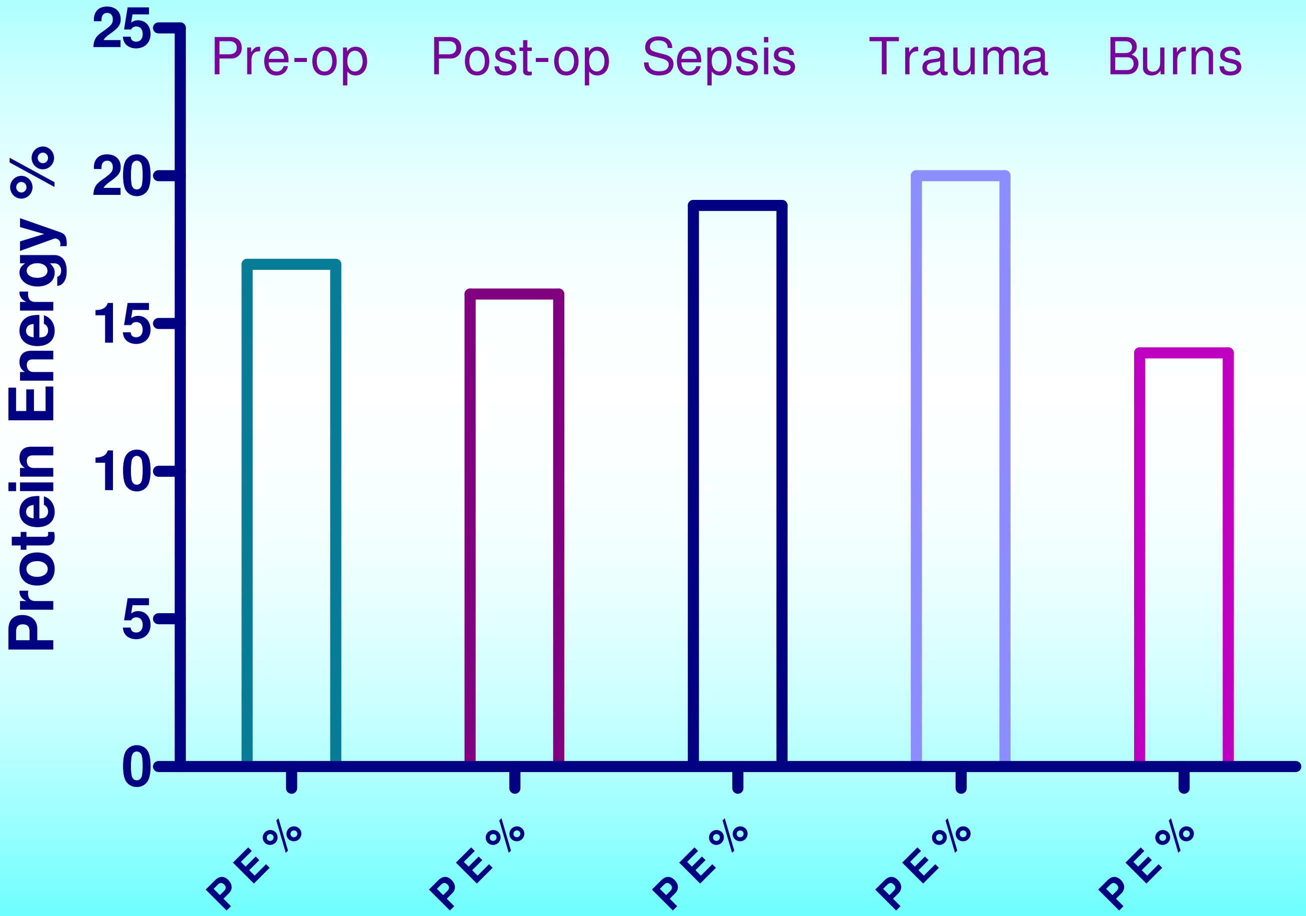
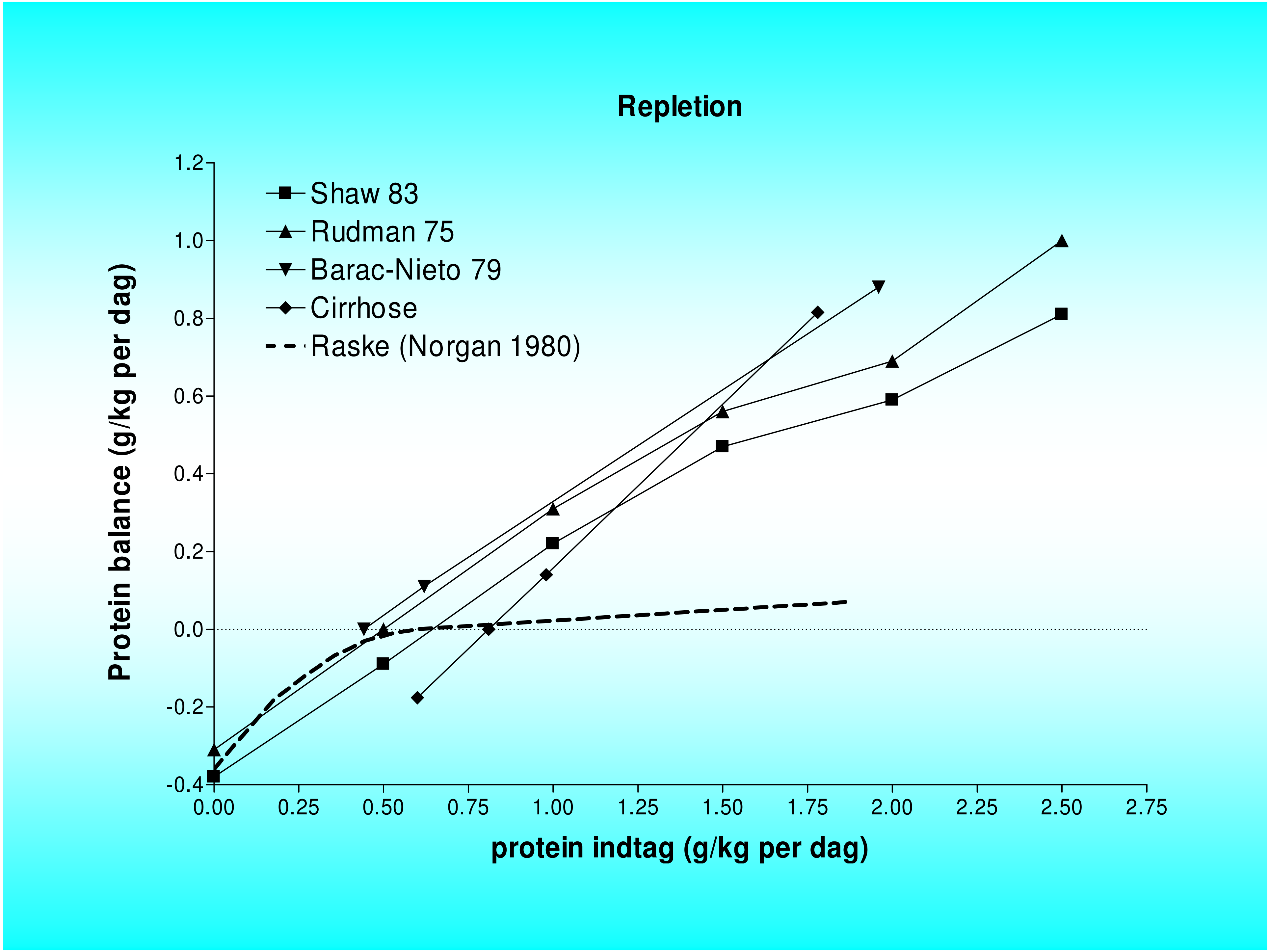
Duke et al. Surgery 1970; 68: 168-174

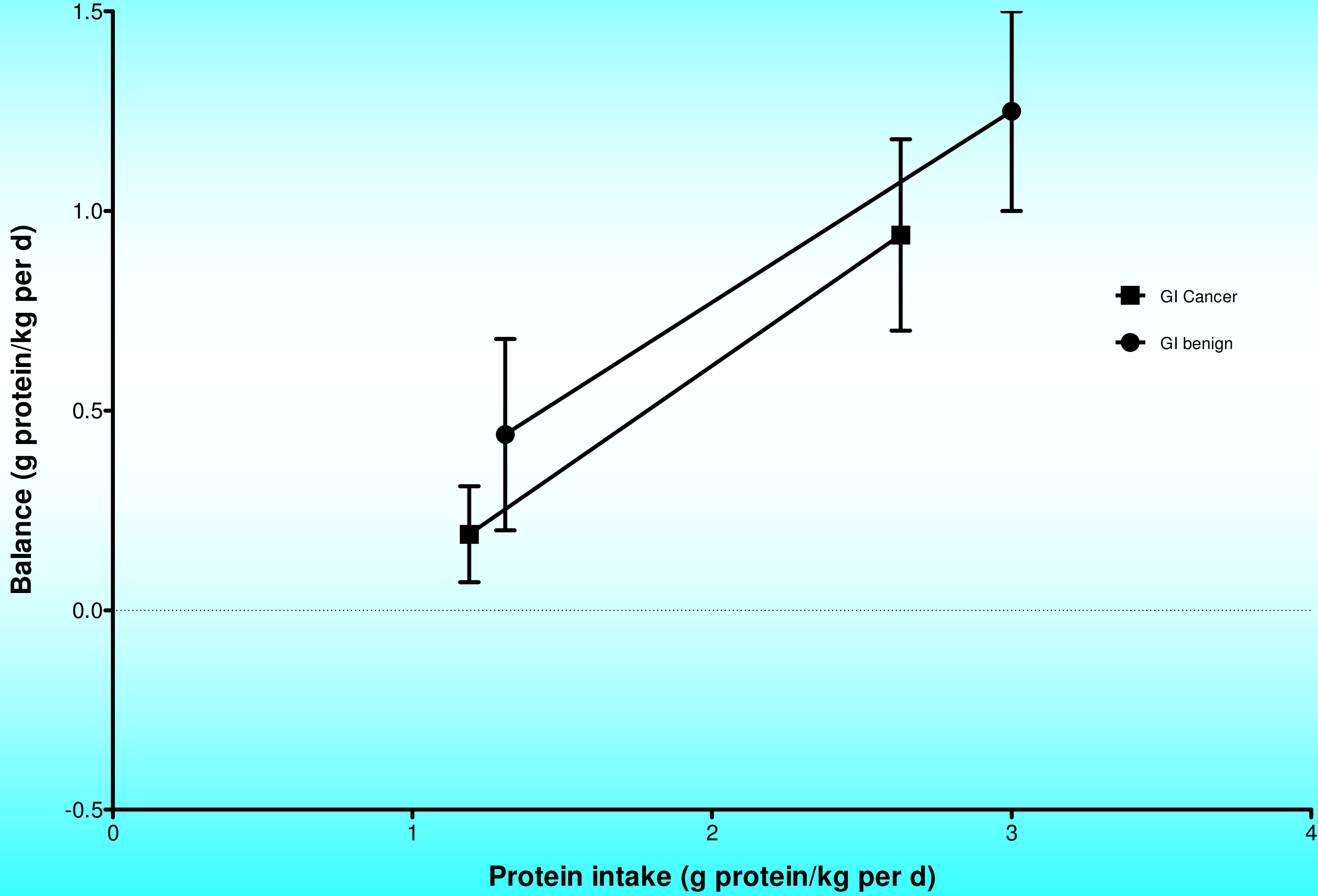


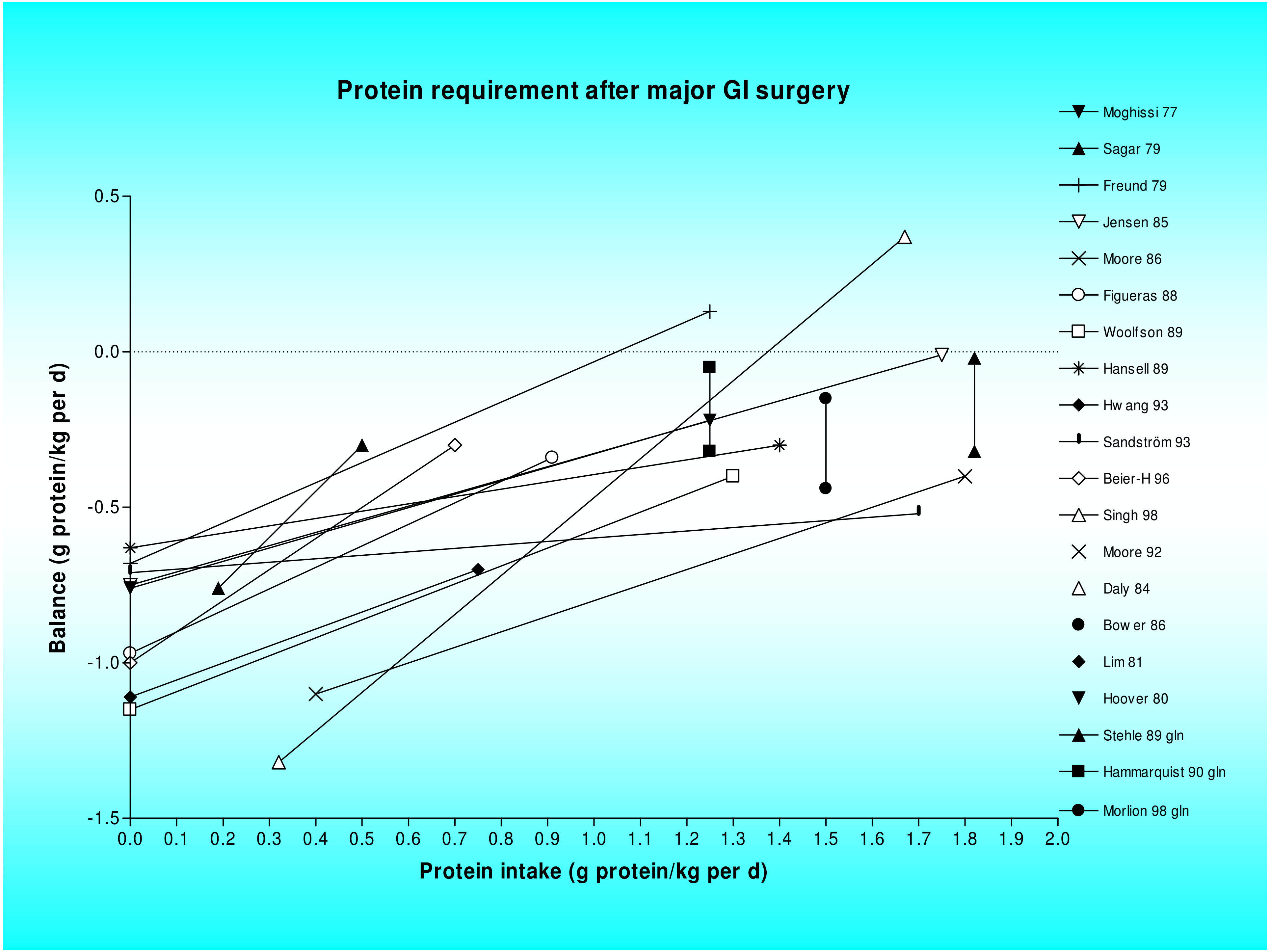
Hvis 25-30 kcal/kg → 18 E%= 1.1-1.3 g/kg per dag


Repletion
Shaw 83
Rudman 75
Barac-Nieto 79
Cirrhose
Raske (Norgan 1980)
Protein balance (g/kg per dag)
protein indtag (g/kg per dag)
1.2
1.0
0.8
0.6
0.4
0.2
0.0
-0.2
-0.4
0.00
0.25
0.50
0.75
1.00
1.25
1.50
1.75
2.00
2.25
2.50
2.75

Protein utilization in cancer patients

Bennegard et al 1983. Gastroenterology 85: 92-9.



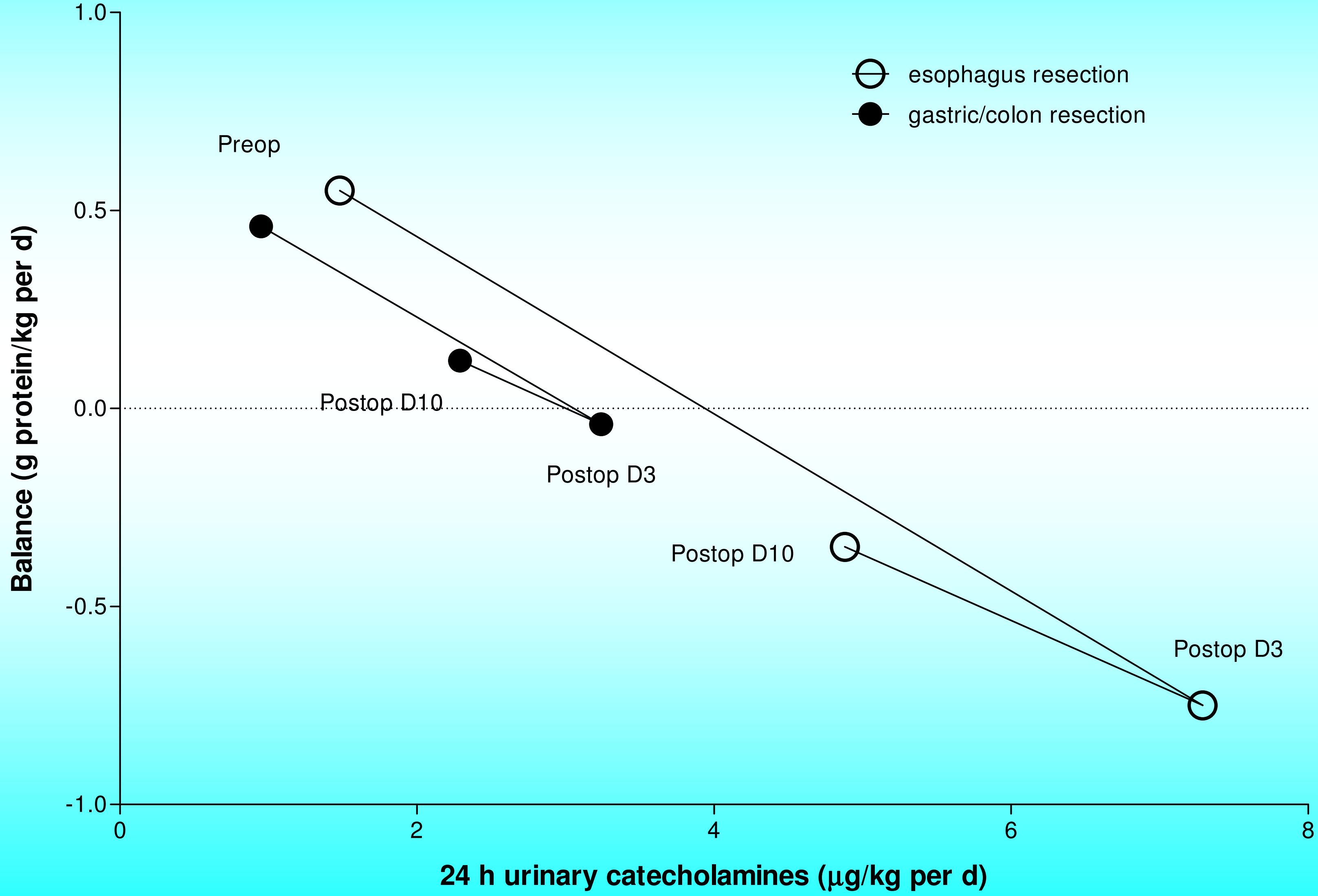


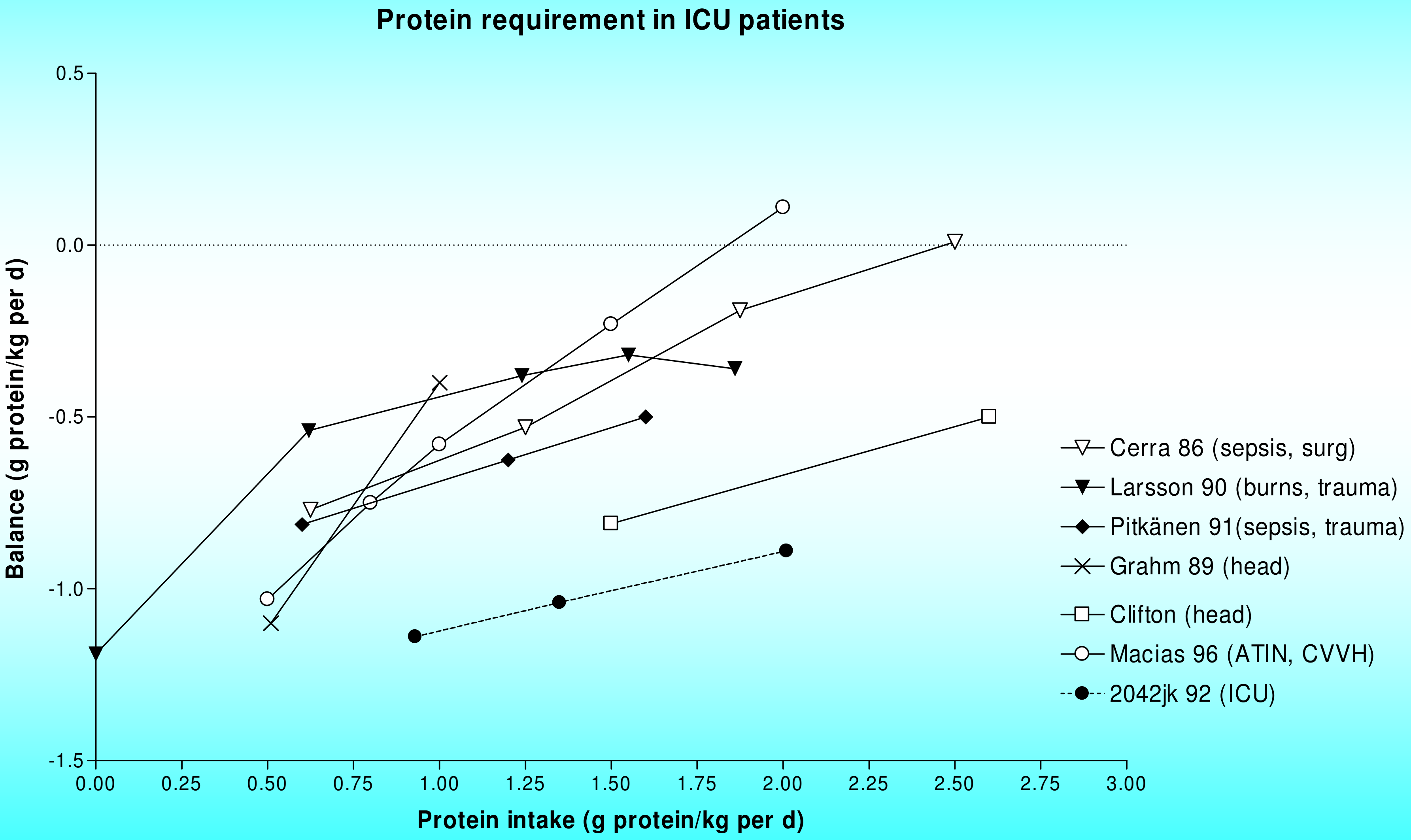
Protein requirement after major GI surgery
Balance (g protein/kg per d)
0.5
0.0
-0.5
-1.0
-1.5
Protein intake (g protein/kg per d)
0.0 0.1 0.2 0.3 0.4 0.5 0.6 0.7 0.8 0.9 1.0 1.1 1.2 1.3 1.4 1.5 1.6 1.7 1.8 1.9 2.0
Moghissi 77
Sagar 79
Freund 79
Jensen 85
Moore 86
Figueras 88
Woolfson 89
Hansell 89
Hw ang 93
Sandström 93
Beier-H 96
Singh 98
Moore 92
Daly 84
Bow er 86
Lim 81
Hoover 80
Stehle 89 gln
Hammarquist 90 gln
Morlion 98 gln

Protein requirement after major GI surgery

All ptt received 1.5 g protein/kg per day PN

Tashiro et al. Nutrition 1996;12:763-5.




Protein requirement in ICU patients
Balance (g protein/kg per d)
0.5
0.0
-0.5
-1.0
-1.5
0.00
0.25
0.50
0.75
1.00
1.25
1.50
1.75
2.00
2.25
2.50
2.75
3.00
Protein intake (g protein/kg per d)
Cerra 86 (sepsis, surg)
Larsson 90 (burns, trauma)
Pitkänen 91(sepsis, trauma)
Grahm 89 (head)
Clifton (head)
Macias 96 (ATIN, CVVH)
2042jk 92 (ICU)

E/N ratio Kreymann et al. Clin Nutr 2012, 31: 168-175

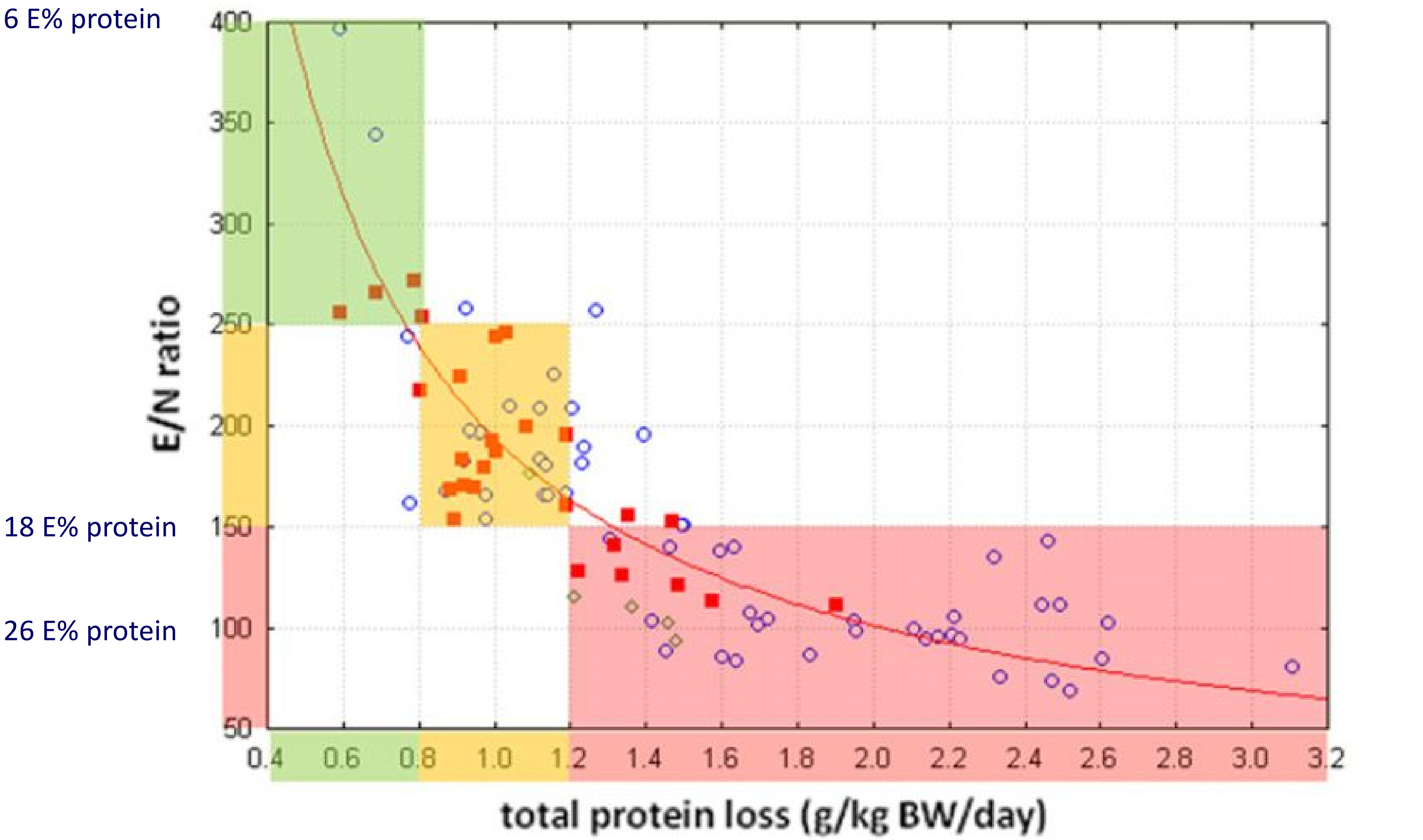


Fig. 6. Non-linear regression between total protein loss and E/N measured in all 91 cohorts. Blue circles depict cohorts of fed subjects, filled red squares depict cohorts of fasting subjects, and green diamonds cohorts of an undefined state. The figure shows 3 ranges of protein loss that can be discerned: A range of high protein losses (1.2–3.1 g/kg/day), moderate protein losses (0.8–<1.2 g/kg/day), and the range of mostly healthy volunteers (<0.8 g/kg/day).

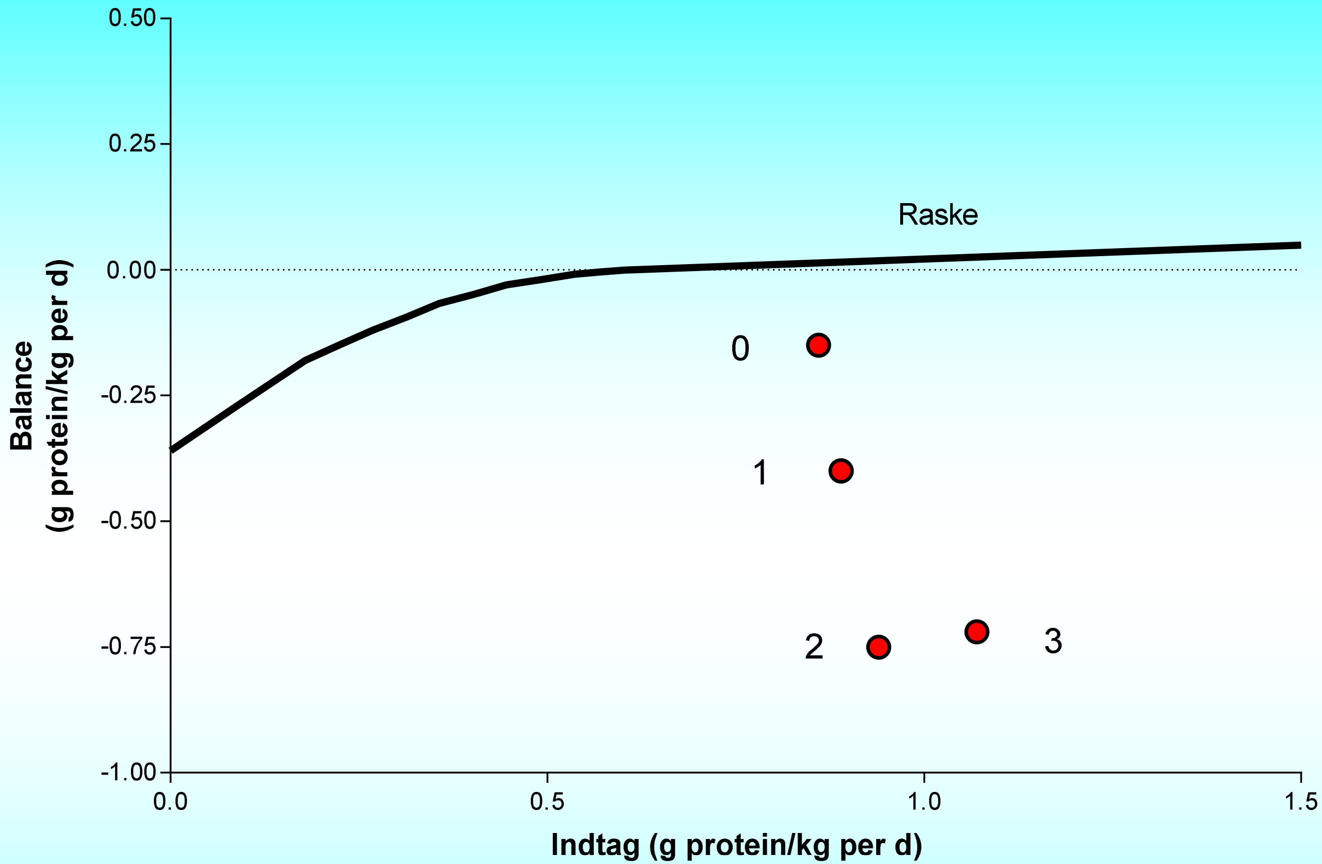
E% protein = 2560/(E/N ratio)

Protein intake, N excretion and N balance at given intakes

Based on Kreymann et al. Clin Nutr 2012, 31: 168-175

		g protein/kg per day		
Severity of Disease	Diagnosis	P intake	P excretion	P balance
0 (N=28)	Healthy Malnourished Alcoholics Obese Post-obese	0.86	1.01	-0.15
1 (N=14)	HIV infection Crohn's Colitis Femoral fracture Emphysema Cancer Spinal injury	0.89	1.28	-0.40
2 (N=12)	Sepsis GI Surgery Stroke	0.94	1.69	-0.75
3 (=32)	Critically ill Trauma Head injury Burns	1.07	1.79	-0.72

Proteinindtag og balance
Sværhedsgrad af sygdom, Score 0-3



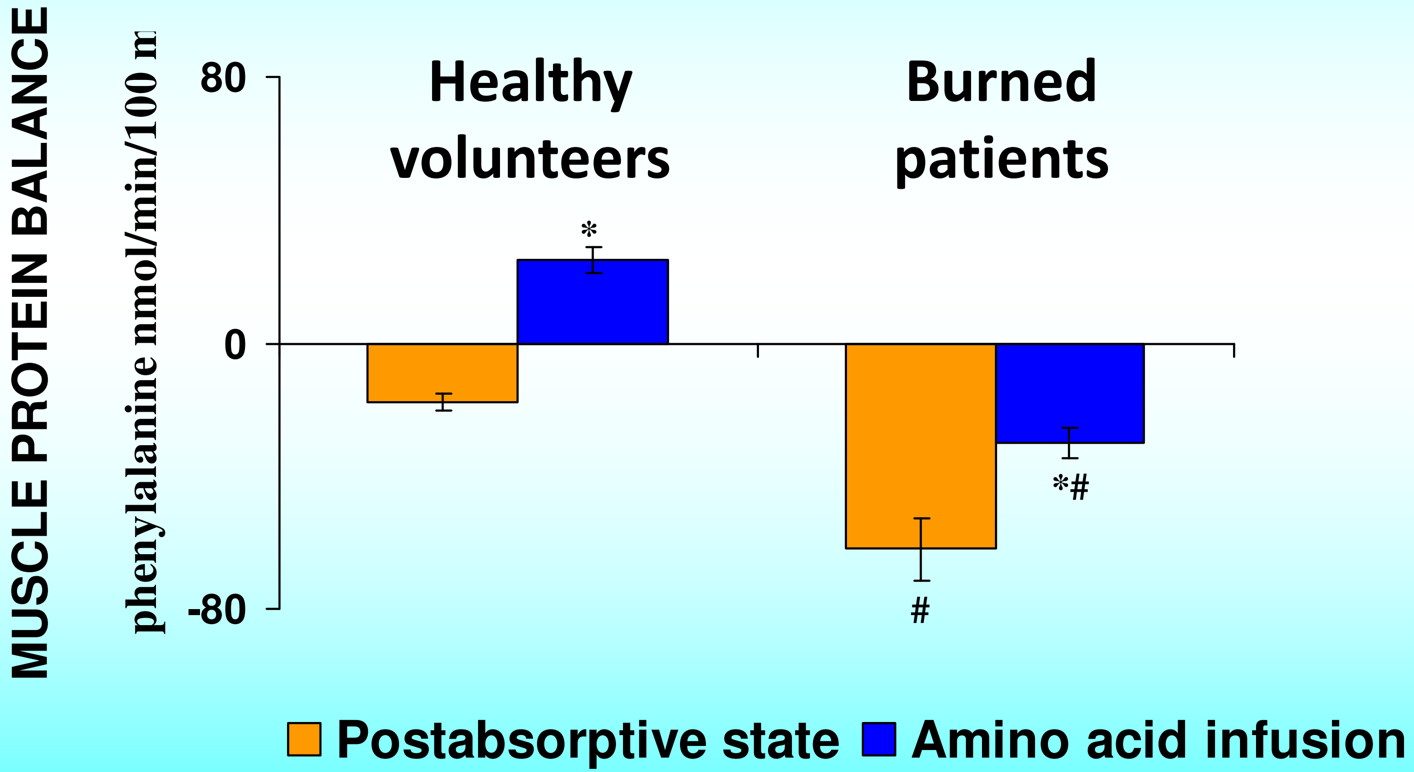
Ved indtag = ca. 1 g/kg er patienter med sværhedsgrad i sygdom score 1-2-3 i mere negativ balance end de raske og ikke-syge med score = 0.

Proteinbehovet kan skønnes at være indtaget + den negative balance, d.v.s. ca. 1,3 g/kg for score = 1 og ca. 1,7 g/kg for score = 2.

Patienter med score = 3 fik lidt mere protein, men var næsten i samme negative balance som patienter med score = 2, d.v.s. endnu højere behov. For disse patienter skal det dog dokumenteres, at de kan udnytte en højere proteinindgift, f.eks. ved måling af dU-carbamid.

EFFECTS OF AMINO ACID INFUSION ON SKELETAL MUSCLE PROTEIN BALANCE IN SEVERELY BURNED PATIENTS

Biolo & Wolfe, Clinical Nutrition (abstract) 2001



*, P<0.05 vs. postabsorptive state   #, P<0.05 vs. healthy volunteers

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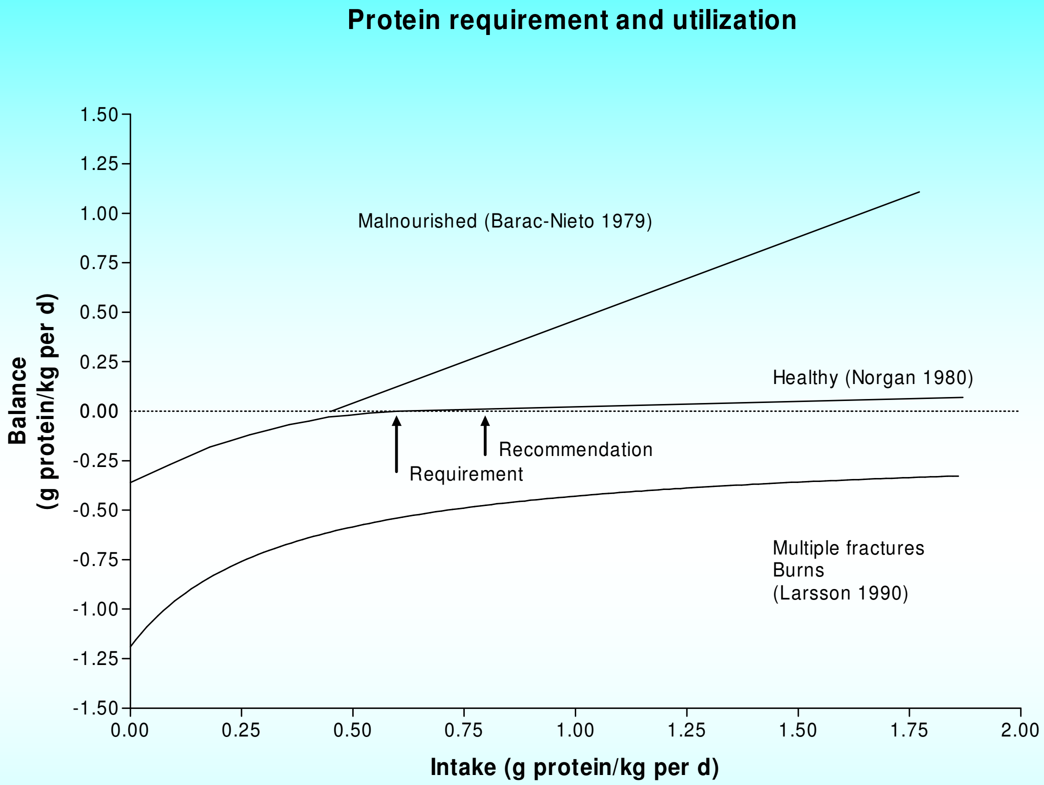
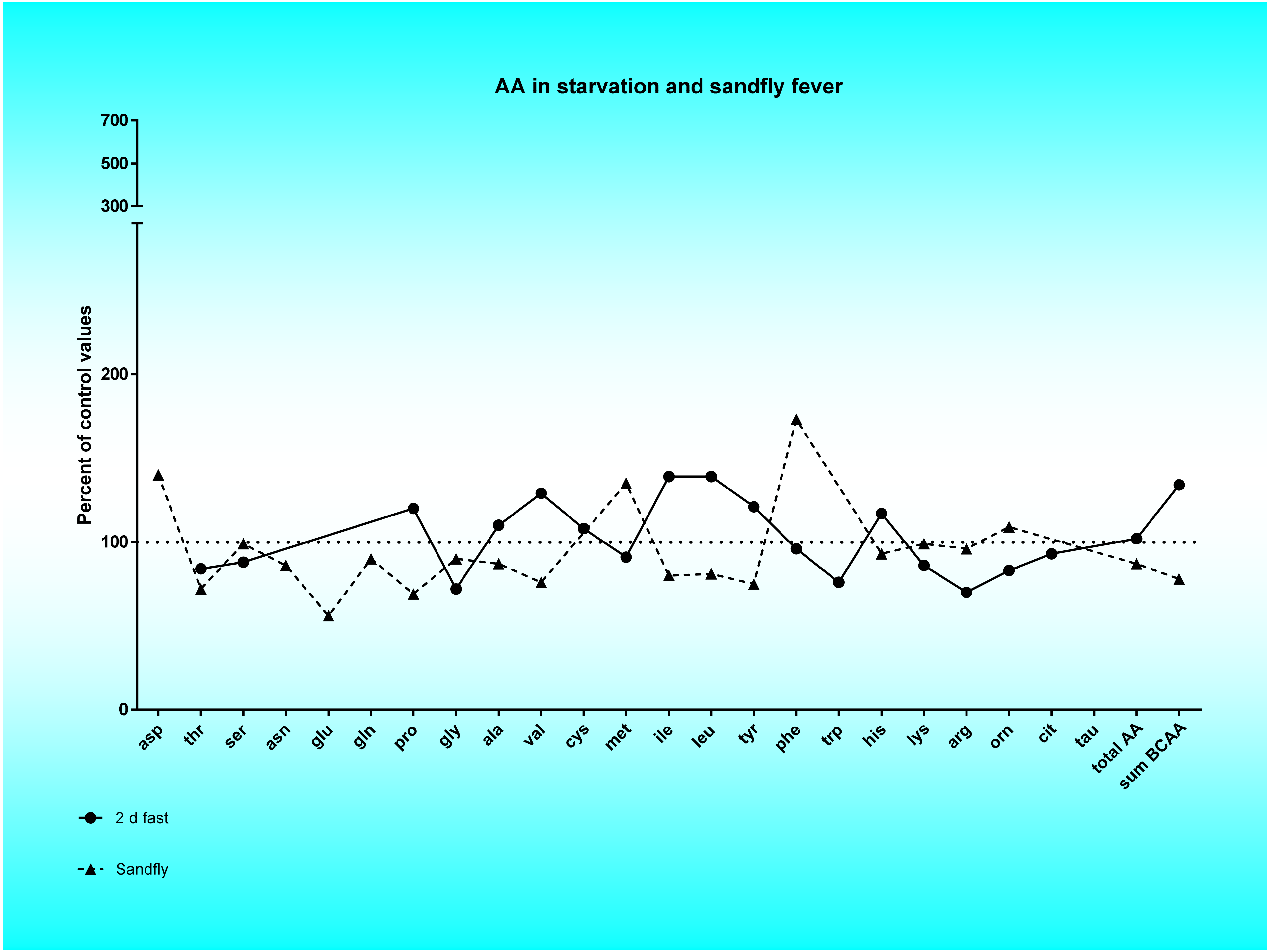
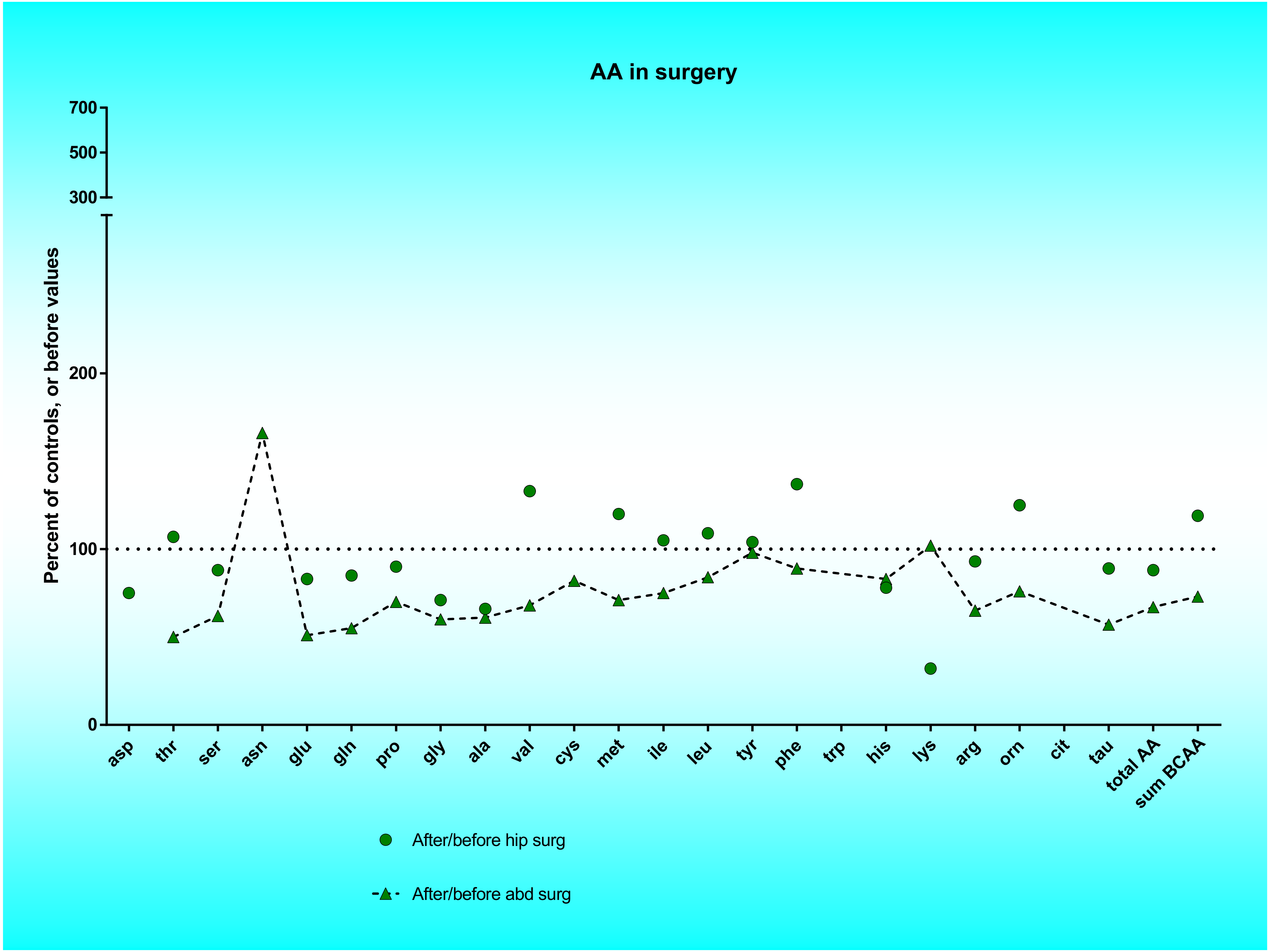


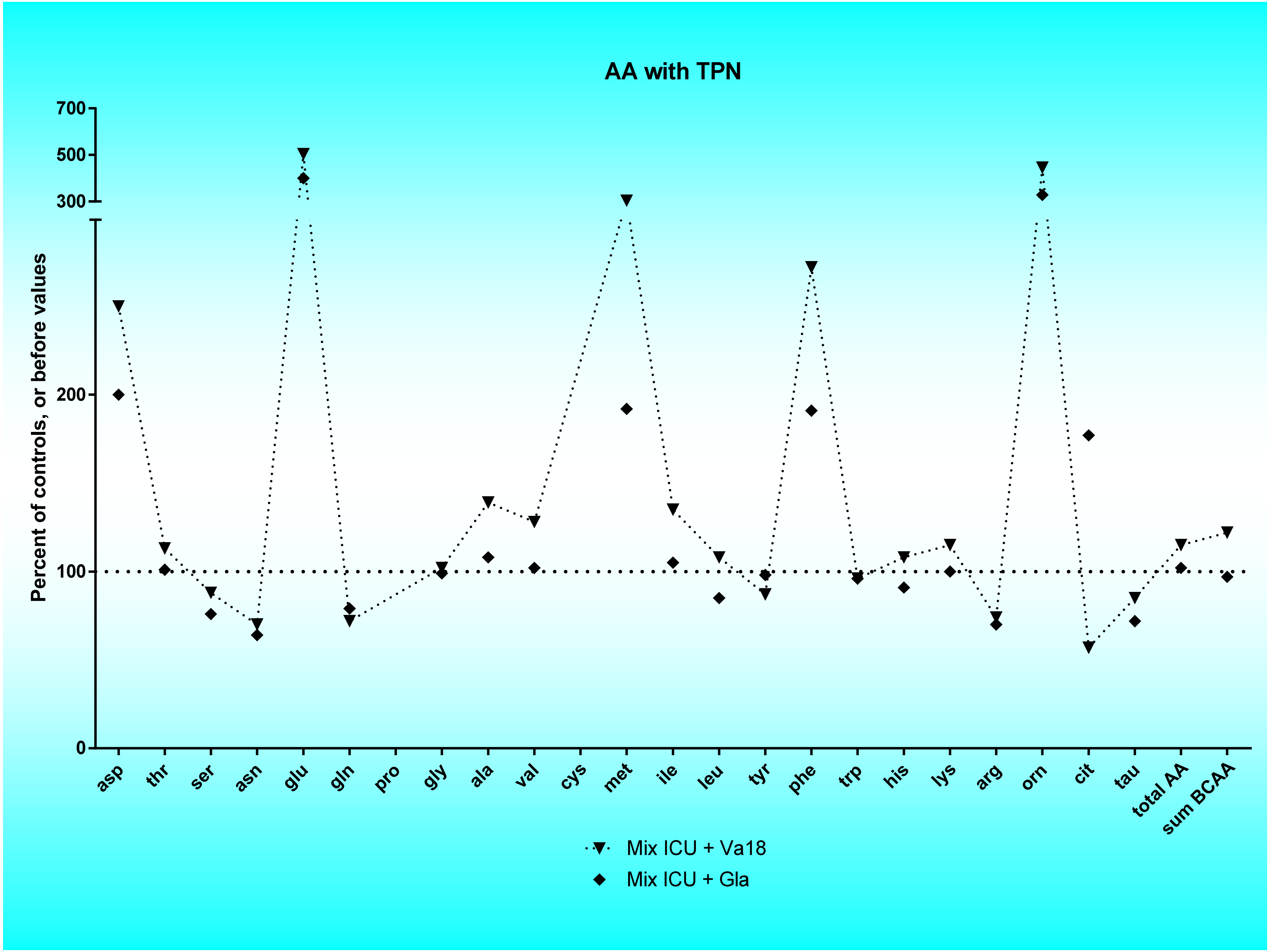
- fordi vi giver de forkerte aminosyrer?

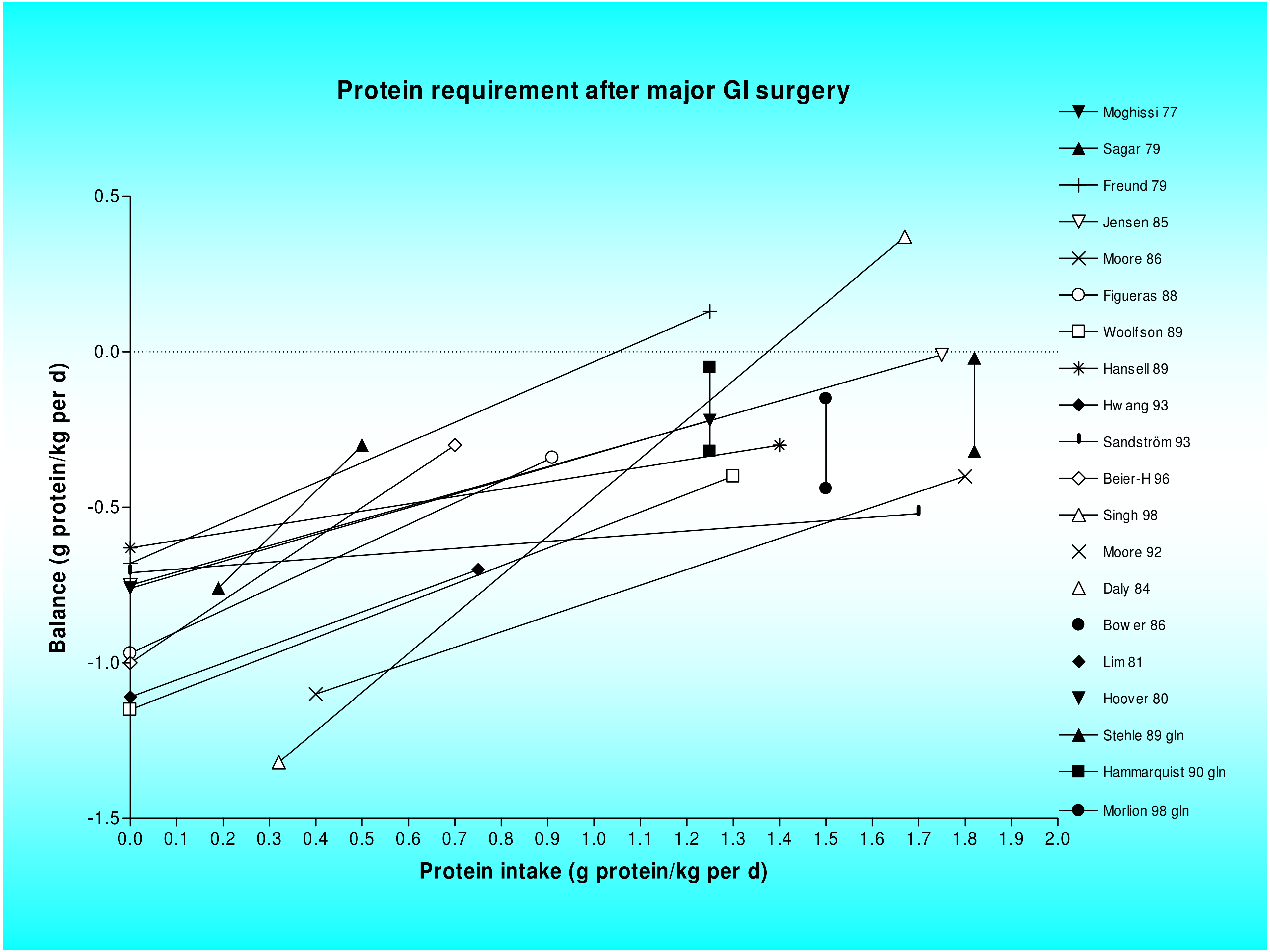
Kondrup J, Nielsen K. Z Gastroenterol 1996;34:26-31.



AA in starvation and sandfly fever
Percent of control values
700
500
300
200
100
0
asp
thr
ser
asn
glu
gln
pro
gly
ala
val
cys
met
ile
leu
tyr
phe
trp
his
lys
arg
orn
cit
tau
total AA
sum BCAA
2 d fast
Sandfly


AA in surgery
Percent of controls, or before values
700
500
300
200
100
0
asp
thr
ser
asn
glu
gln
pro
gly
ala
val
cys
met
ile
leu
tyr
phe
trp
his
lys
arg
orn
cit
tau
total AA
sum BCAA
After/before hip surg
After/before abd surg


AA with TPN
Percent of controls, or before values
700
500
300
200
100
0
asp
thr
ser
asn
glu
gln
pro
gly
ala
val
cys
met
ile
leu
tyr
phe
trp
his
lys
arg
orn
cit
tau
total AA
sum BCAA
Mix ICU + Va18
Mix ICU + Gla


Protein requirement after major GI surgery
Balance (g protein/kg per d)
0.5
0.0
-0.5
-1.0
-1.5
0.0 0.1 0.2 0.3 0.4 0.5 0.6 0.7 0.8 0.9 1.0 1.1 1.2 1.3 1.4 1.5 1.6 1.7 1.8 1.9 2.0
Protein intake (g protein/kg per d)
Moghissi 77
Sagar 79
Freund 79
Jensen 85
Moore 86
Figueras 88
Woolfson 89
Hansell 89
Hw ang 93
Sandström 93
Beier-H 96
Singh 98
Moore 92
Daly 84
Bow er 86
Lim 81
Hoover 80
Stehle 89 gln
Hammarquist 90 gln
Morlion 98 gln

Kroppens reaktion ved faste og stress metabolisme

Konklusioner

- Vigtigt for at forstå den mulige effekt af ernæringsterapi hos den enkelte patient
- Hvis metabolismen kunne behandles, ville almindelig mad være nok
- Proteinbehov: øget,
  - men god nyttevirkning (anabol resistens er 'kompetitiv' hæming)
  - aminosyre-sammensætning svarende til vanlige anbefalinger?