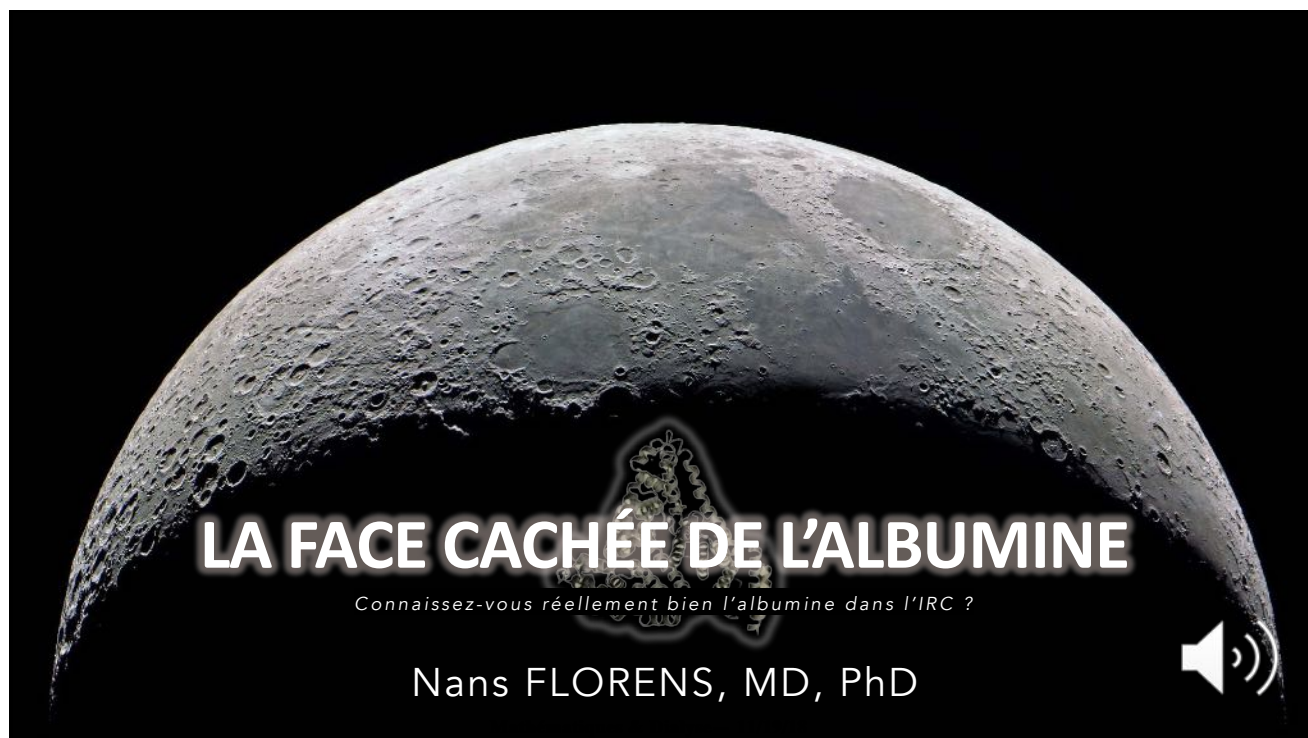




1



2

GÉNÉRALITÉS

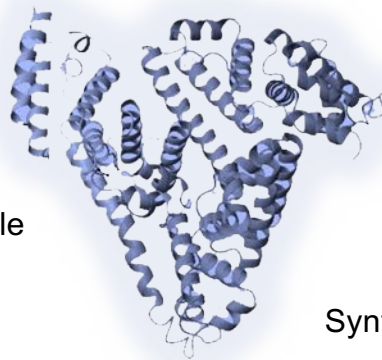
MW : 66.5 kDa

Demi-vie : 21 jours

Monomère hydrosoluble

Synthèse hépatique

Protéine majoritaire du plasma



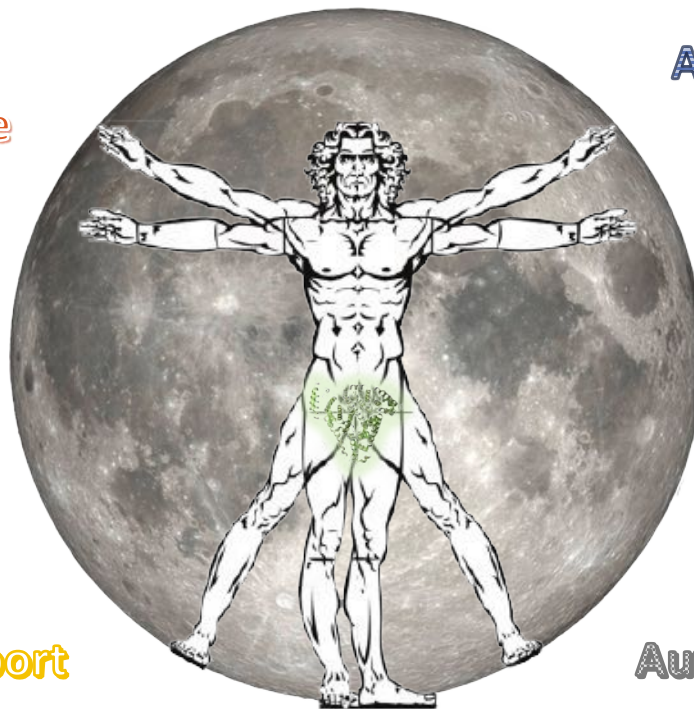
3

pression
oncotique

Anti-oxydant

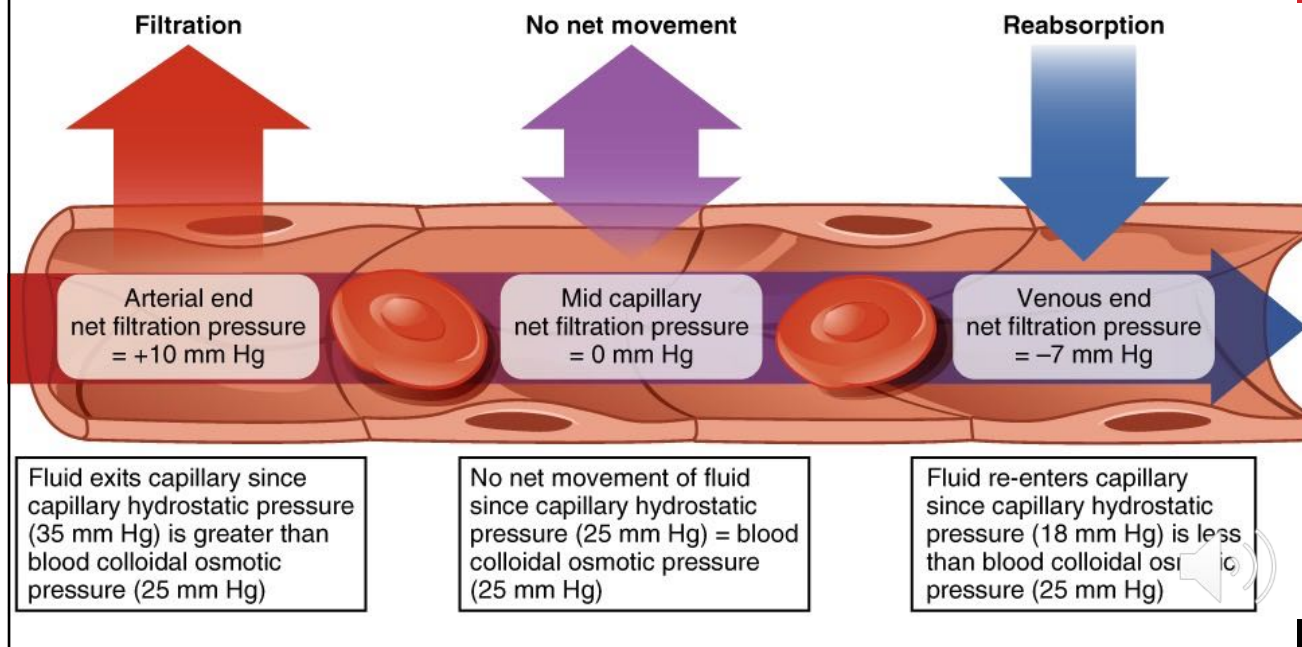
Transport

Autres ?



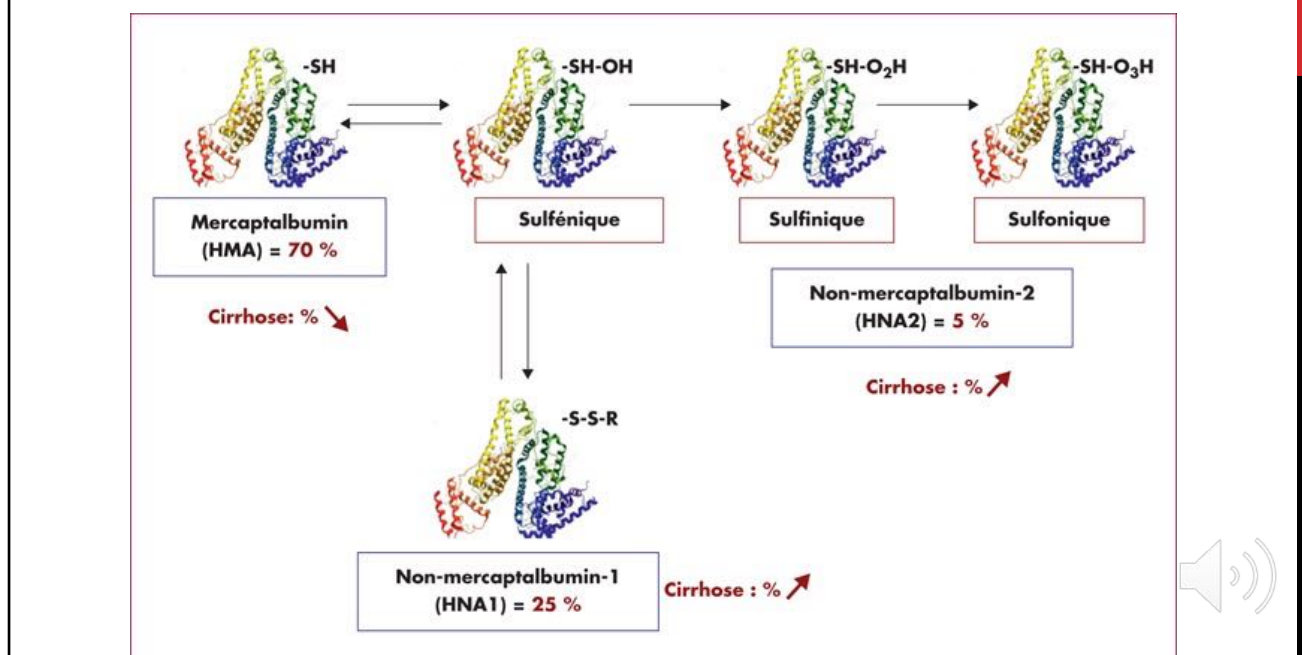
4

LA PRESSION OSMOTIQUE COLLOÏDE



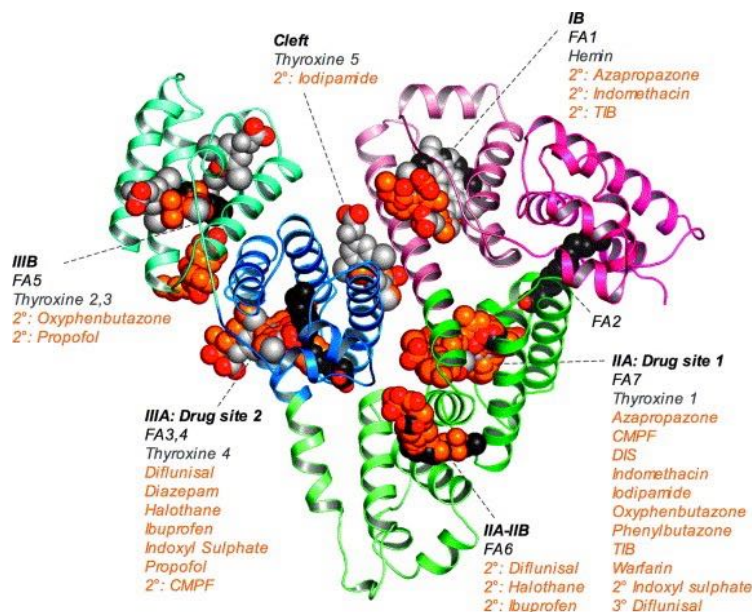
5

RÔLE DE LA 34-CYS



6

PRINCIPALES MOLÉCULES TRANSPORTÉES



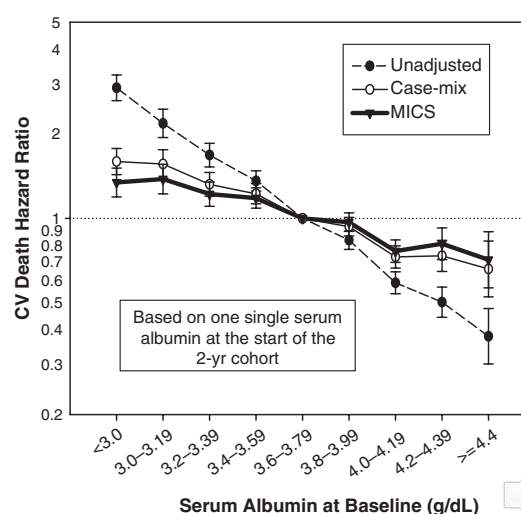
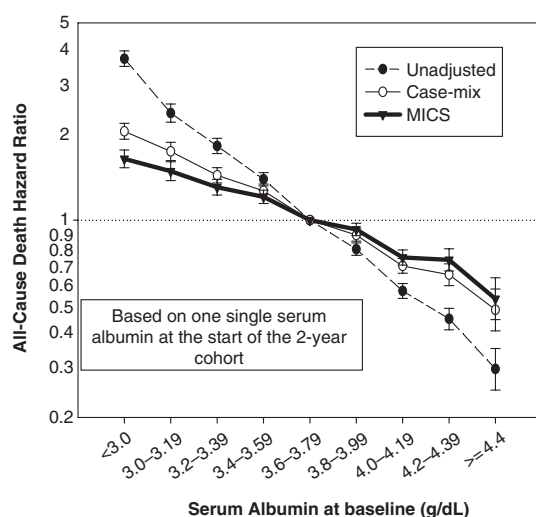
Ghuman et al, JMB, 2005



7

ALBUMINE ET DIALYSE

Albumine au début de la dialyse



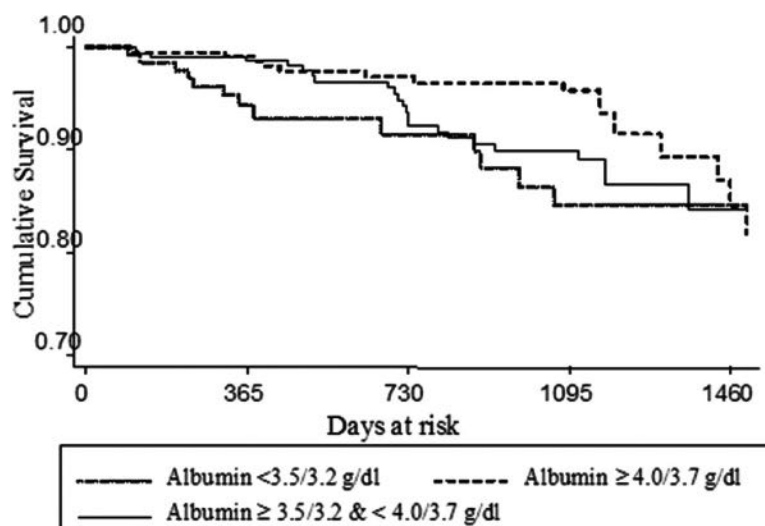
Kalanthar-Zadeh et al, NDT, 2005



8

ALBUMINE ET DIALYSE

Albumine au début de la dialyse, cohorte d'adolescents (12-18 ans)



Amaral et al, CJASN, 2008



9

ALBUMINE ET DIALYSE

Patients with serum albumin ≤ 4 g/dL ($P = 0.032$)

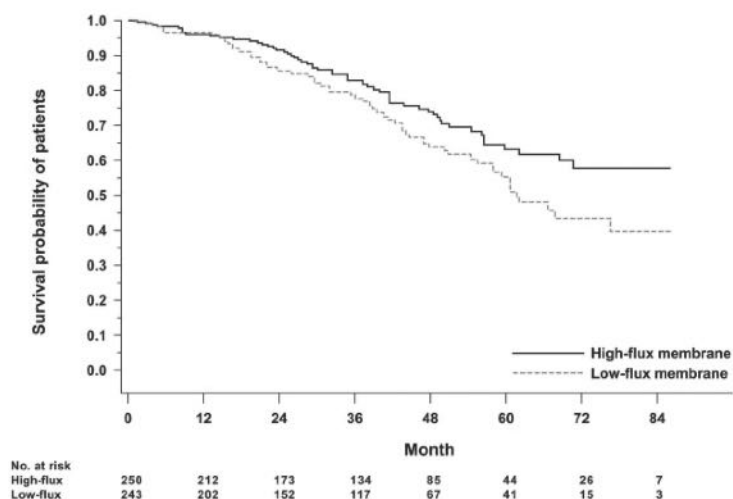


Figure 3. Kaplan-Meier survival curves for the population of patients with serum albumin ≤ 4 g/dl (Log-rank test $P = 0.032$).

Locatelli et al, JASN, 2009



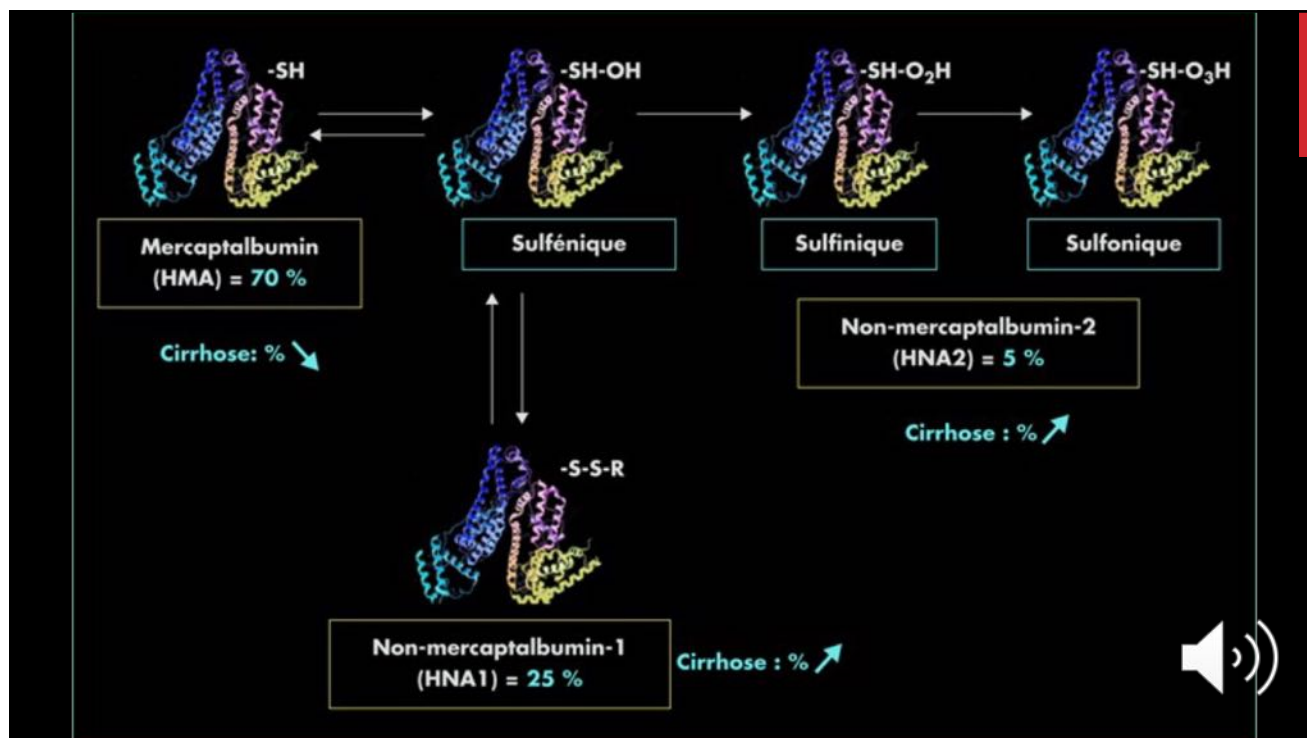
10



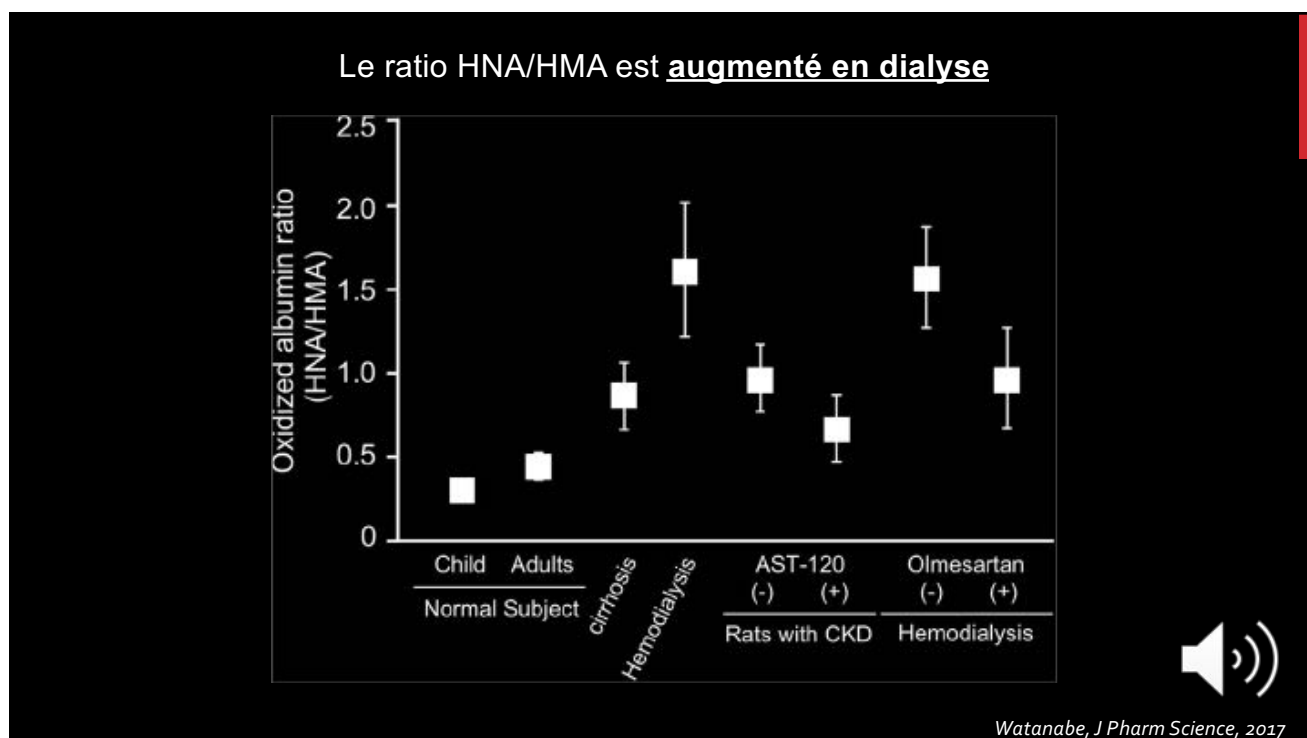
11



12



13



14

La forme HNA-2 irréversible est augmentée en dialyse

Table 2
Determination of serum protein and purified albumin oxidation

	Serum protein		Purified HSA	
	Normal subjects	HD patients	Normal-HSA	HD-HSA
Carbonyl contents (nmol/mg protein)	2.10 ± 0.34	3.12 ± 1.11*	2.13 ± 0.14	2.86 ± 0.45**
f(HMA) (%)	53.6 ± 6.4	40.4 ± 8.7*	46.6 ± 4.9	32.7 ± 6.8**
f(HNA-1) (%)	38.7 ± 6.3	49.7 ± 8.0*	42.0 ± 4.4	54.4 ± 7.1**
f(HNA-2) (%)	7.7 ± 0.9	9.9 ± 1.4*	11.4 ± 0.3	12.9 ± 0.7**

Values are expressed means ± SD.

* $P < 0.01$ as compared with Normal subjects.

** $P < 0.01$ as compared with Normal-HSA.



Mera et al, BBRC, 2005

15



16

Définition

Adduction de produits issus de réactions oxydantes ou non-oxydantes

Médiée par des mécanismes majoritairement **non-enzymatiques**
(adduits de Michael)



Lysine Histidine Cystéine

Enzymatique : rôle des **MPO**



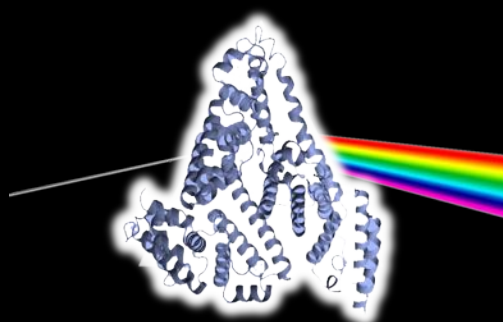
Tyrosine



17

Définition

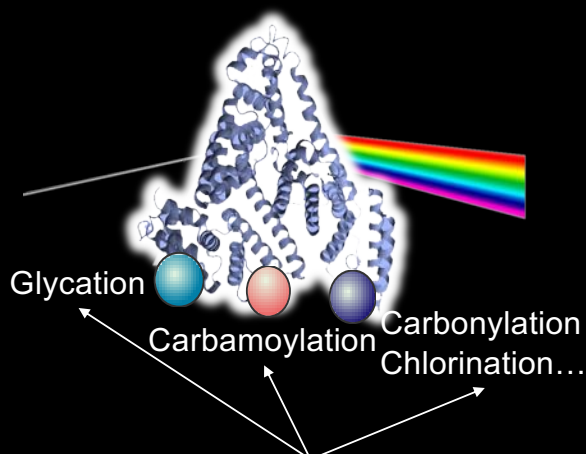
UNE
protéine
normale



18

Définition

UNE
protéine
normale



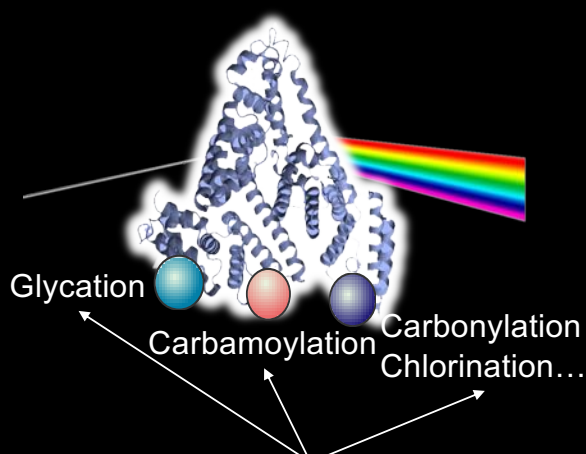
Ajout de molécules issues de réactions oxydatives ou non oxydatives



19

Définition

UNE
protéine
normale

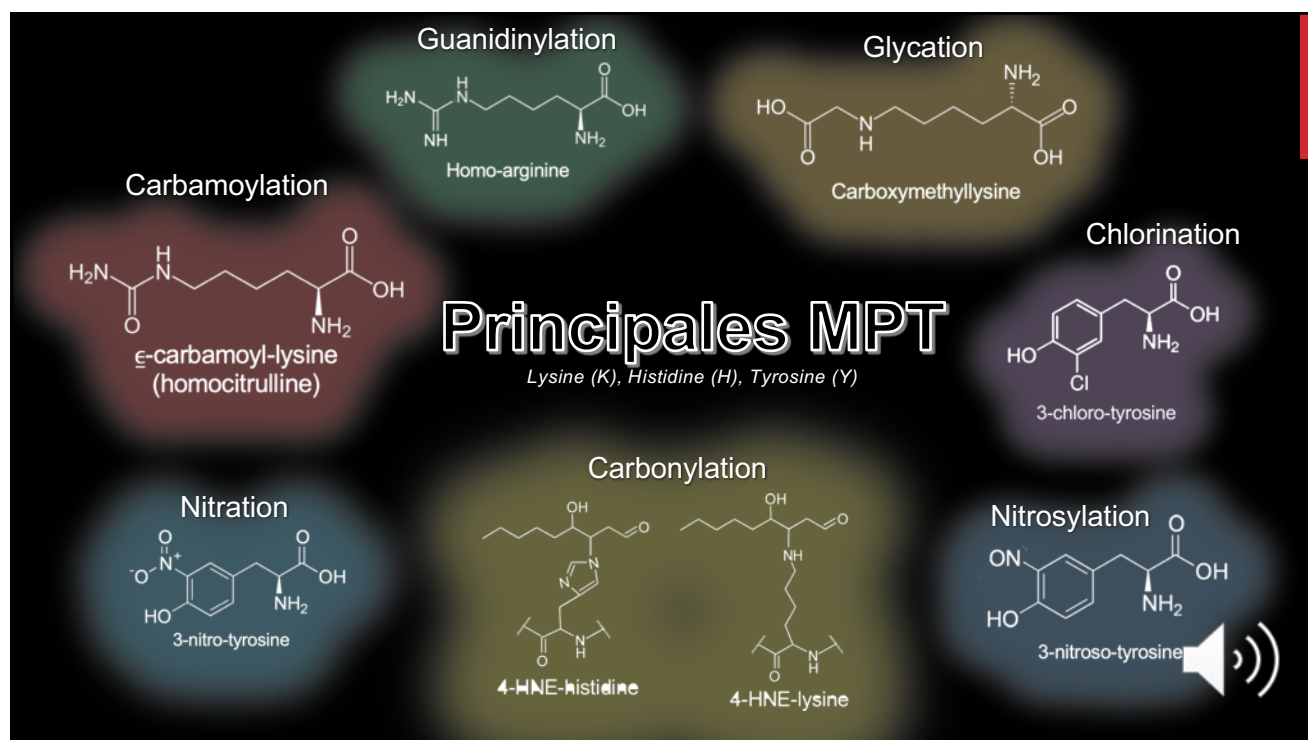


Ajout de molécules issues de réactions oxydatives ou non oxydatives



DES
protéines
modifiées

20



21

Les formes glyquées et carbonylées de l'albumine sont augmentées en dialyse

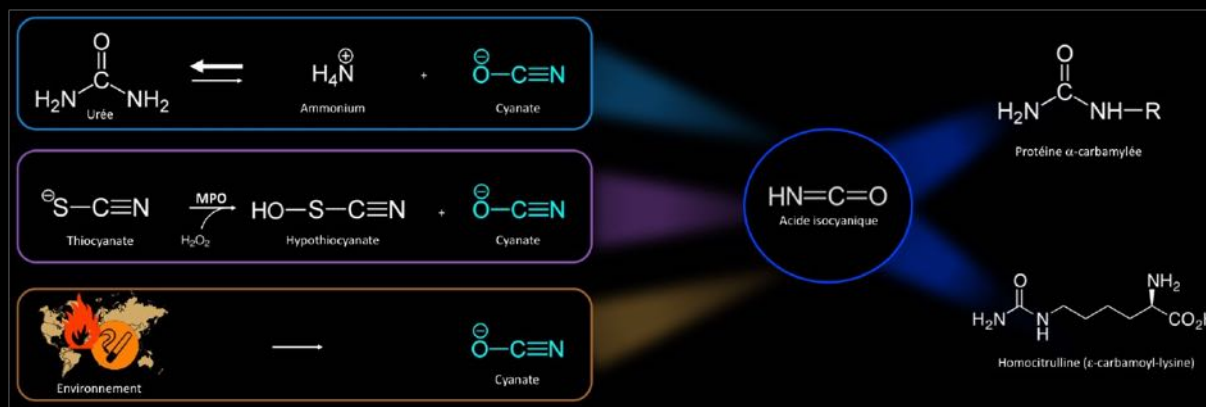
Table 2. Determination of Serum Protein and Purified Albumin Oxidation

	Serum protein			Purified HSA		
	Normal subjects (n=10)	HD patients		normal-HSA	non-DM-HSA	DM-HSA
		non-DM (n=7)	DM (n=10)			
Carbonyl content (nmol/mg protein)	2.06±0.33	2.51±0.18 ^a	2.96±0.48 ^{a,b}	2.13±0.14	2.66±0.07 ^c	2.88±0.22 ^{c,d}
AGE content (fluorescence intensity [a.u.])	232±54	746±58 ^a	1,006±116 ^{a,b}	245±25	722±25 ^c	956±43 ^{c,d}
f(HMA) (%)	55.7±5.9	45.3±7.3 ^a	37.9±6.0 ^{a,b}	50.0±3.9	37.6±4.2 ^c	30.3±5.4 ^{c,d}
f(HNA-1) (%)	36.5±5.8	44.8±6.7 ^a	52.3±5.7 ^{a,b}	38.7±4.1	49.9±4.6 ^c	56.8±5.1 ^{c,d}
f(HNA-2) (%)	7.8±1.0	9.3±0.9 ^a	9.8±1.0 ^a	11.3±0.3	12.6±0.9 ^c	12.9±0.9 ^c

Mera et al, Hypertension Research, 2006

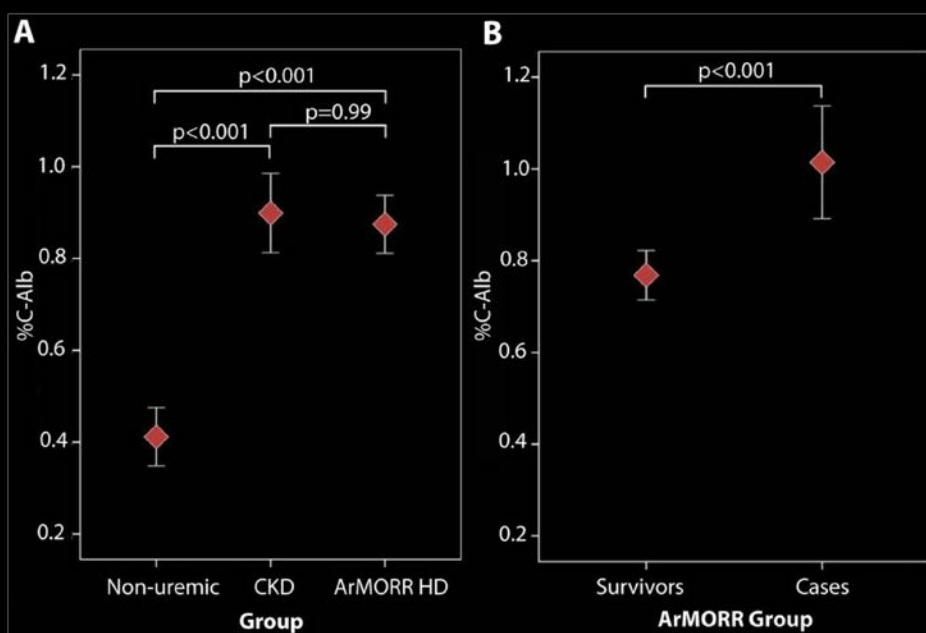
22

La carbam(o)ylation



23

La forme carbamylée est augmentée en dialyse

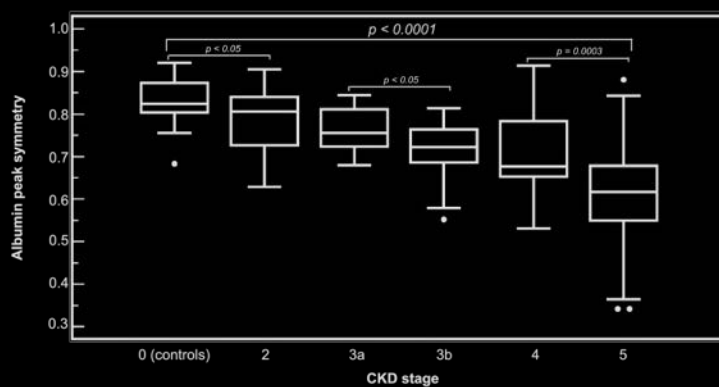
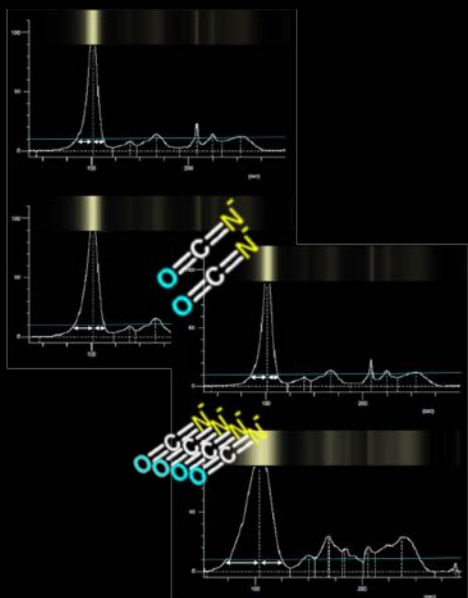


Berg, SciTransl Med, 2013



24

La forme carbamylée est détectable sur l'électrophorèse

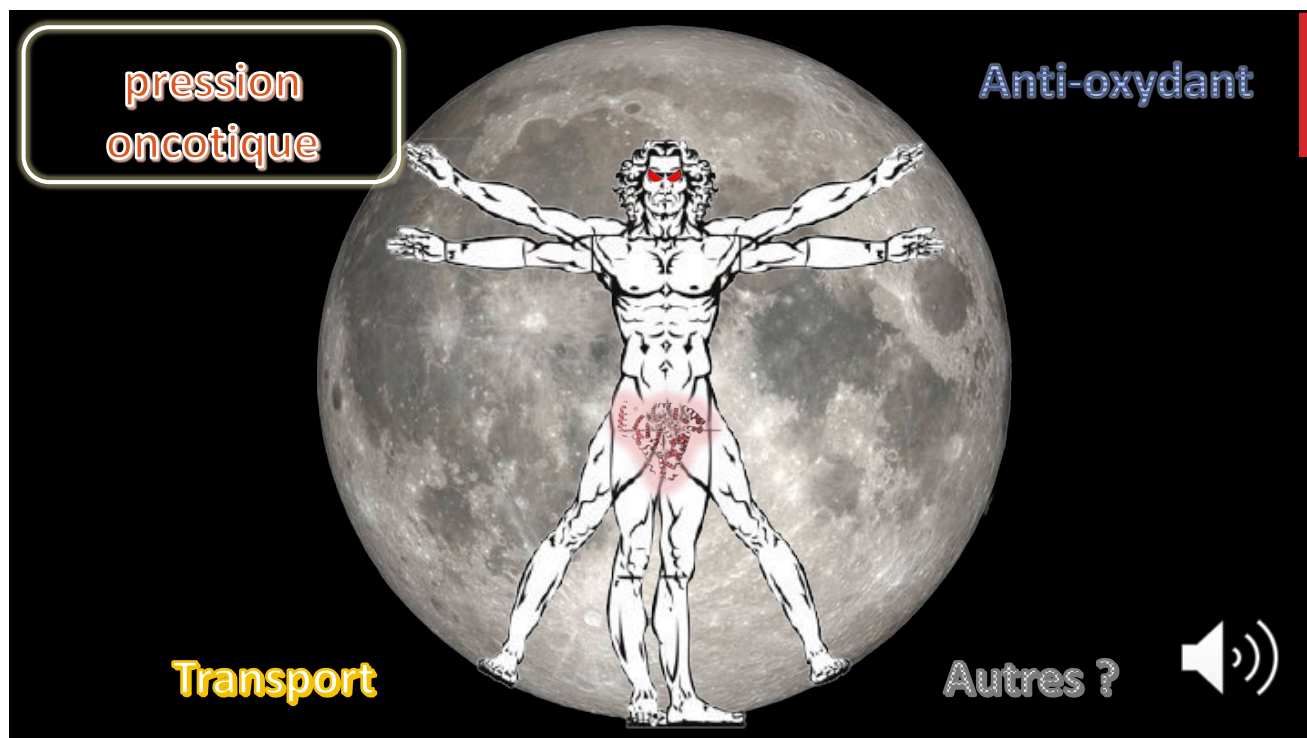


Delanghe, Electrophoresis, 2017

25

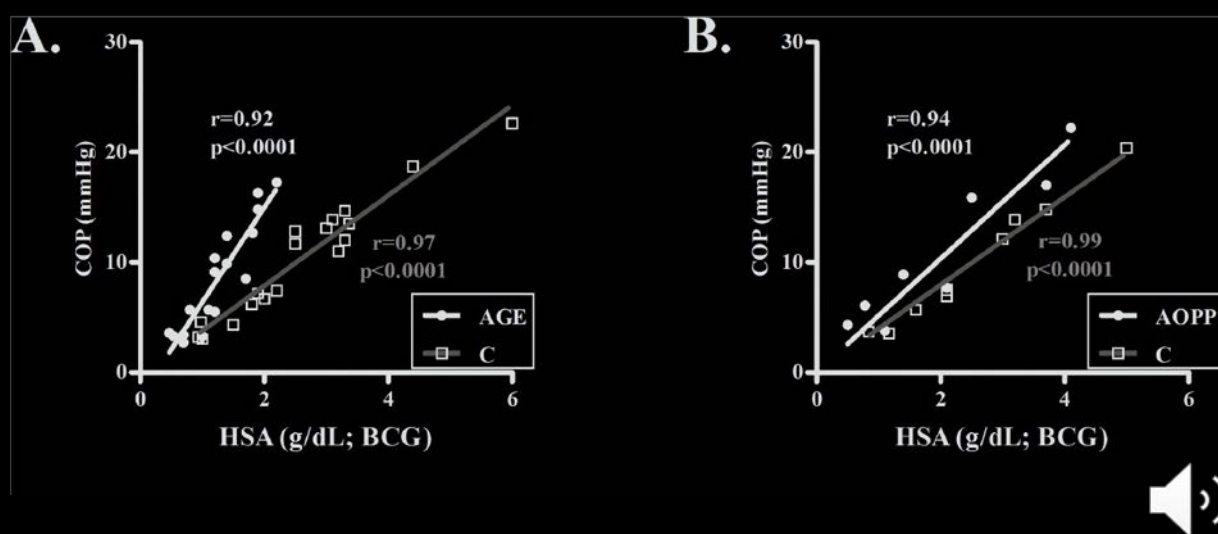


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27

La glycation et la carbonylation modifient la pression oncotique exercée par l'albumine



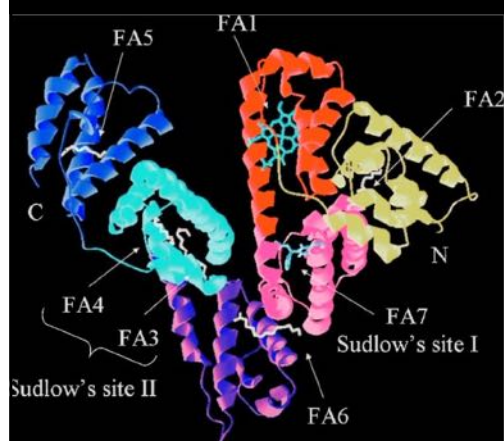
Michelis et al, Plos One, 2016

28



29

Les sites de Sudlow



Fasano et al, IUBMB Life, 2005

Table 2

Domains, subdomains and fatty acid binding sites on HSA.

Domain	Subdomain	Binding sites
I (1–195)	IA(1–112)	FA2, FA8, FA9
	IB(113–195)	FA1, FA8, FA9
II (196–383)	IIA(196–303)	FA2, FA6, FA8, FA9, FA7 (Sudlow's site I)
	IIB(304–383)	FA6
III (384–585)	IIIA(384–500)	FA3-FA4 (Sudlow's site II)
	IIIB(500–585)	FA5

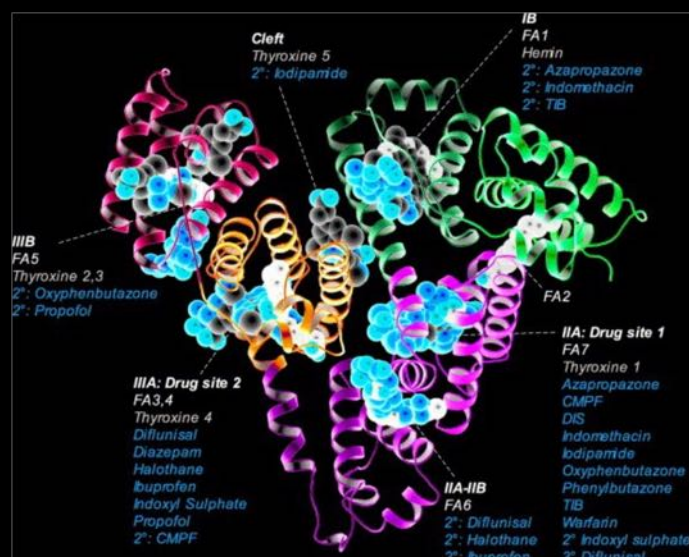
Abbreviations: FA, fatty acids, HSA, human serum albumin.

Florens et al, Biochimie, 2017



30

Les principales molécules

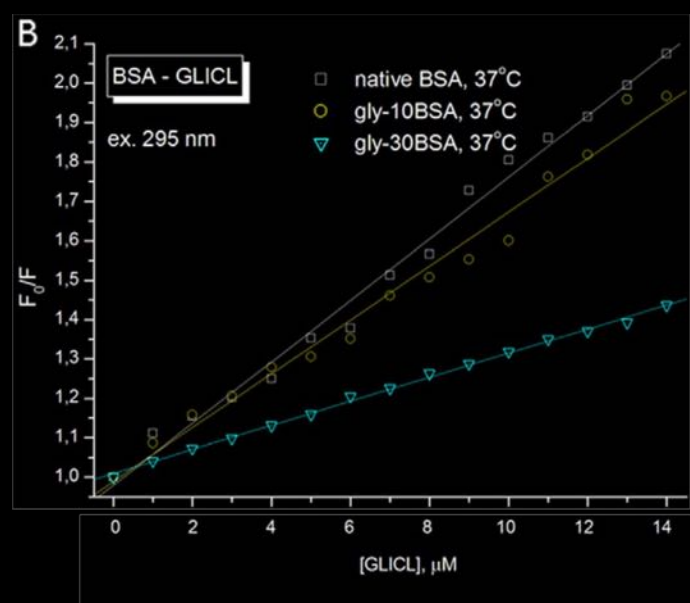


Ghuman et al, JMB, 2005



31

La glycation diminue la liaison du glicazide sur le site I



Zurawska-Płaksej et al, Spectrochimica Acta Par A, 2018



32

Altération de la liaison surtout sur le sites de Sudlow II

Table 3
Binding of warfarin and ketoprofen to Normal-HSA and HD-HSA

	Free fraction (%)	
	Warfarin	Ketoprofen
Normal-HSA	19.6 ± 1.9	5.97 ± 0.75
HD-HSA	23.3 ± 2.0	$9.37 \pm 1.36^*$

Values are expressed means $\pm$ SD.

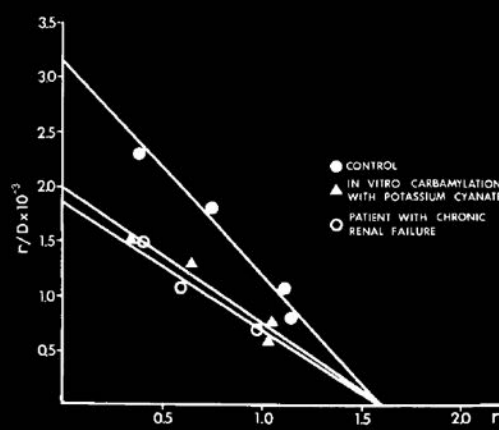
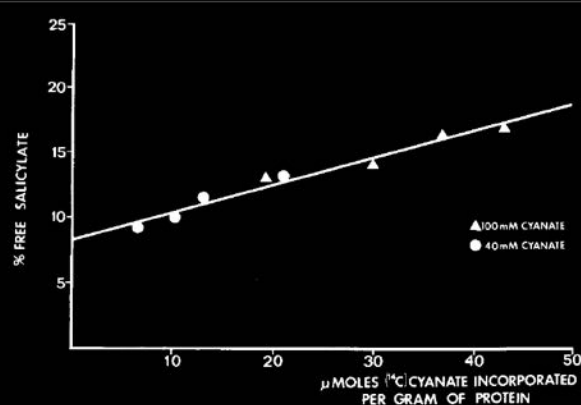
* $P < 0.05$.



Mera et al, BBRC, 2005

33

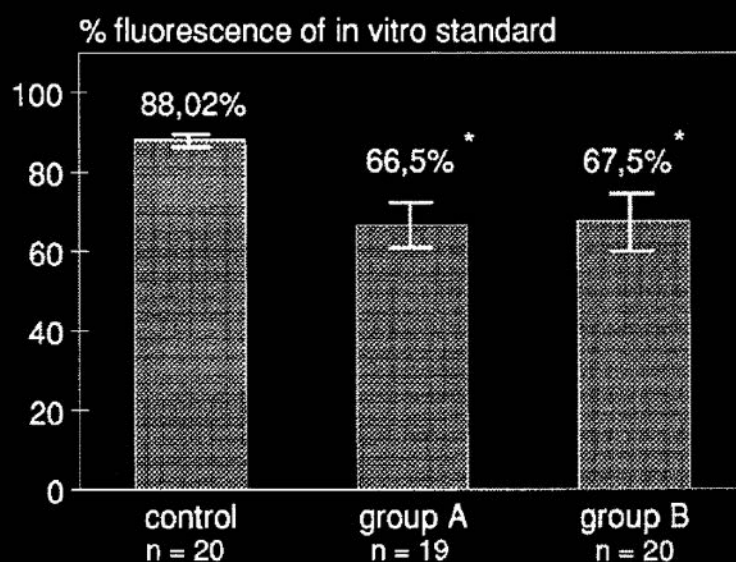
L'albumine carbamylée à des fonctions de liaisons perturbées



Erill et al, Clin Pharmacol Theraph, 1980

34

L'albumine du dialysé présente moins de site disponibles sur le site II



Dengler et al, Eur J Clin Pharmacol, 1992



35

pression
oncotique

Anti-oxydant

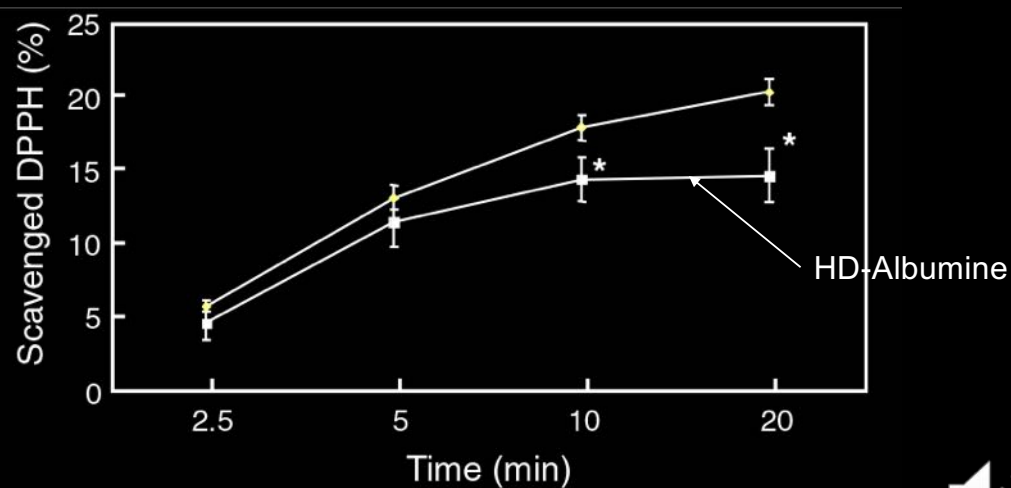
Transport

Autres ?



36

L'albumine du dialysé tamponne moins bien les agressions oxydatives



Mera et al, BBRC, 2005

37

pression
oncotique

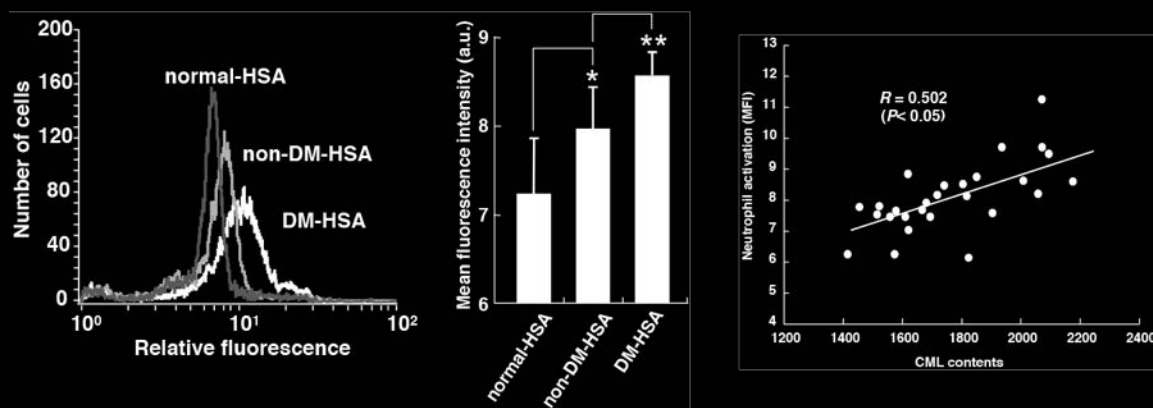
Anti-oxydant

Transport

Autres ?

38

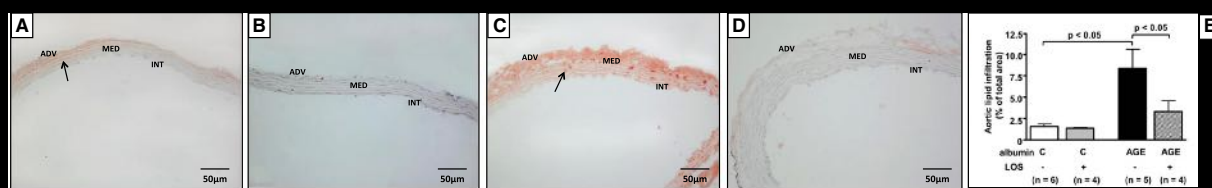
L'albumine du dialysé induit la formation de ROS par les neutrophiles



Mera et al, Hypertension Research, 2006

39

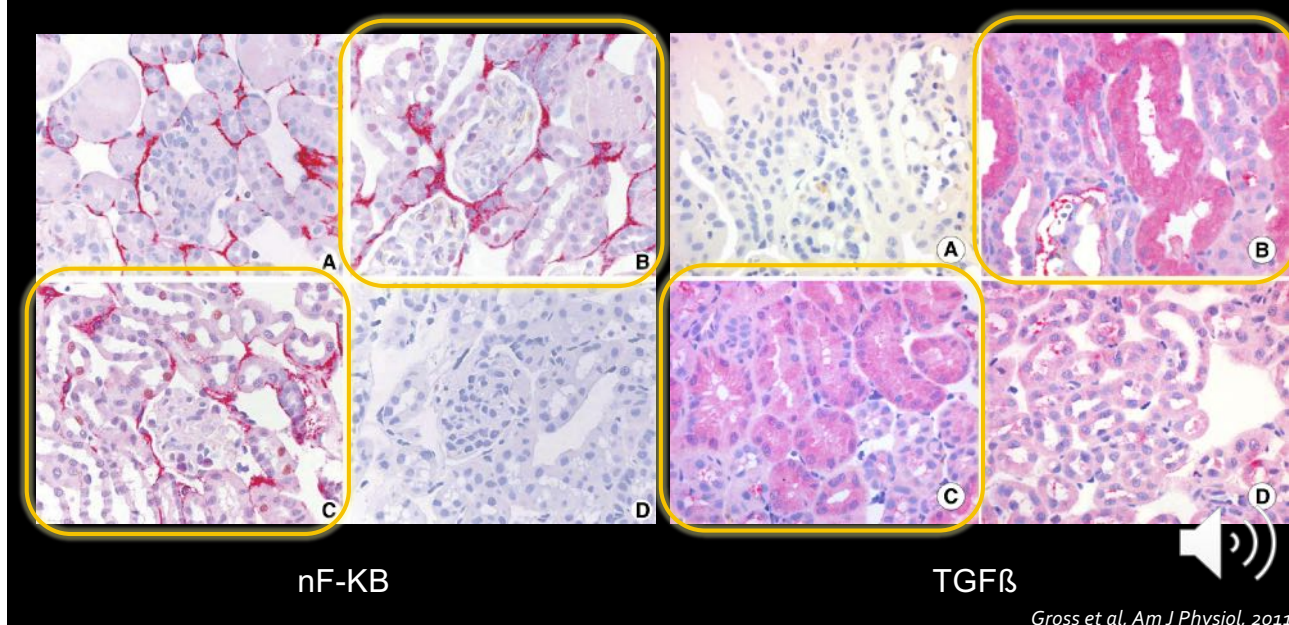
L'albumine glyquée induit une accumulation de lipides dans l'aorte des rats



Juvenal Gomes et al, J Diabetes Complic, 2016

40

Les formes carbamylée et glyquée sont néphrotoxiques



41

L'albumine glyquée a une fonction pro-agrégante sur les érythrocytes

	Controls		Type 1 diabetic patients	
	t_A (s)	$\dot{\gamma}_D$ (s ⁻¹)	t_A (s)	$\dot{\gamma}_D$ (s ⁻¹)
Unglycated	4.25 ± 1.13	43.20 ± 5.07	3.44 ± 1.06	46.98 ± 8.04
Glycated	4.14 ± 1.09 ^a	44.51 ± 4.97 ^b	3.30 ± 1.03 ^a	49.47 ± 9.83 ^a
Mean differences between glycated-unglycated samples ^c	-0.11 ± 0.20	+1.32 ± 3.31	-0.14 ± 0.27 ^d	+2.49 ± 3.97 ^e

Temps d'aggrégation

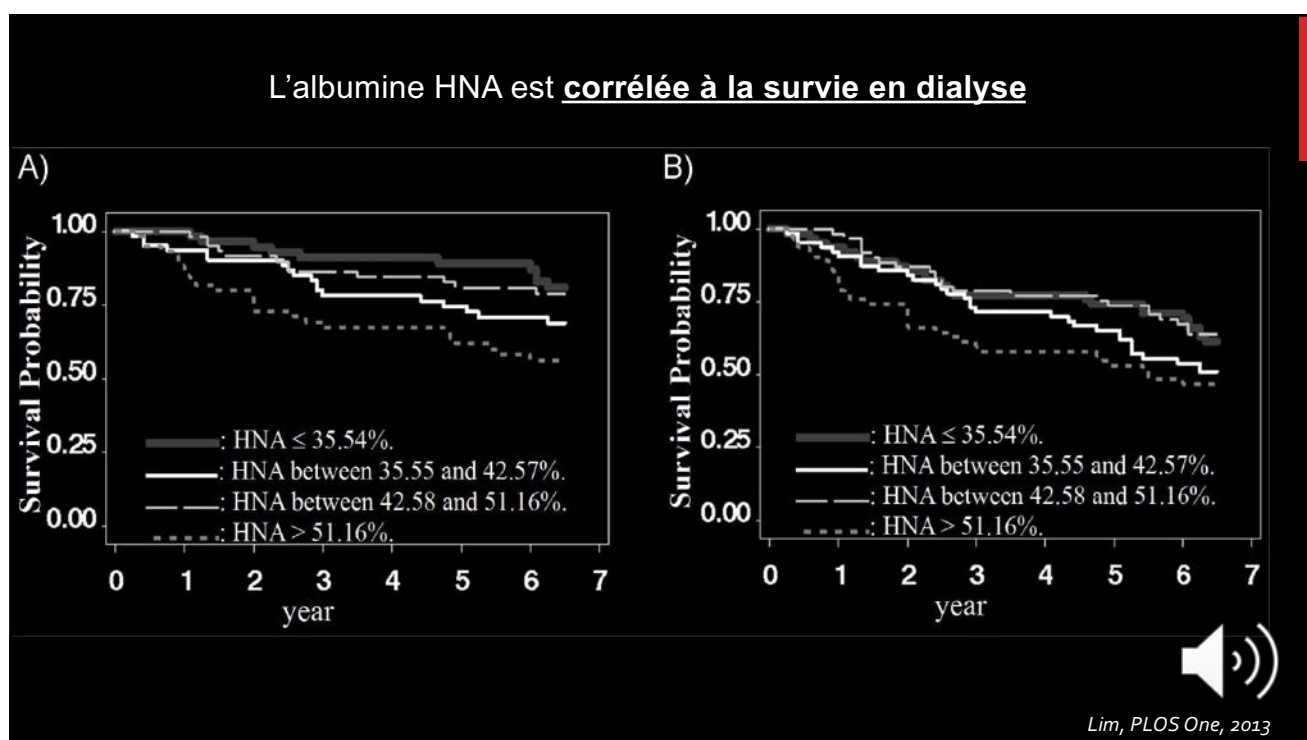
Désaggrégation partielle

Candiloros et al, Diabetes Medecine, 1996

42

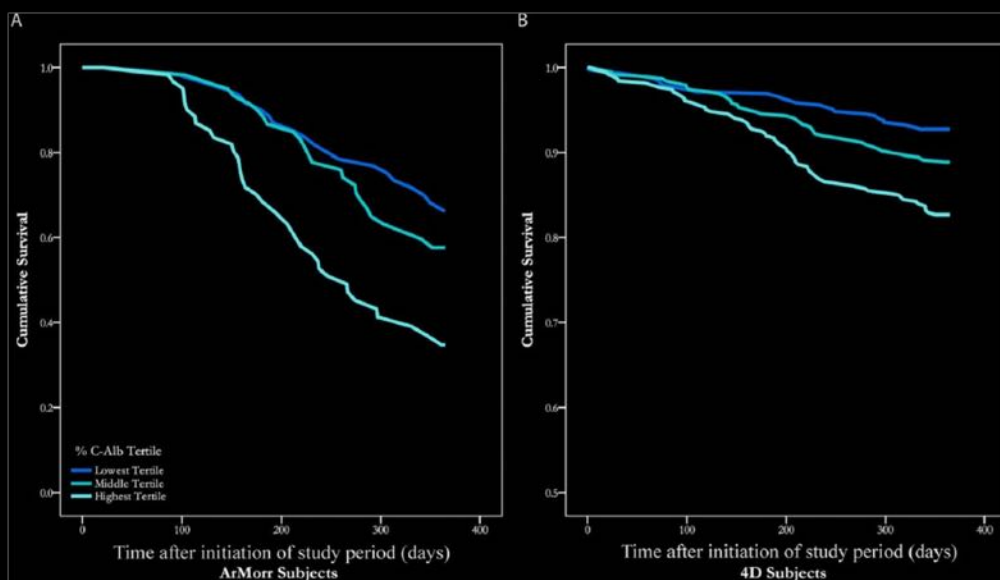


43



44

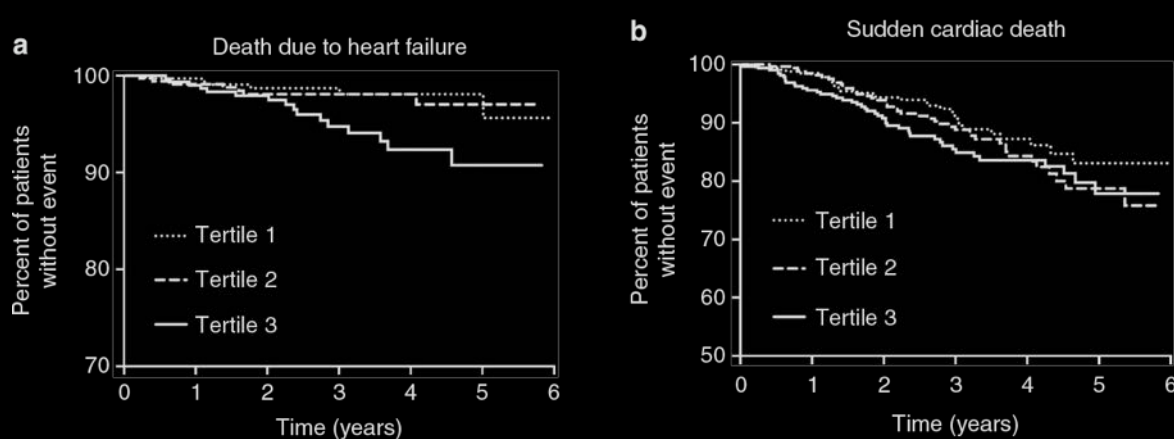
L'albumine carbamylée est corrélée à la survie en dialyse



Berg, SciTransl Med, 2013

45

L'albumine carbamylée est corrélée à la mortalité cardiaque en dialyse



Drechsler, Kidney Int, 2015

46

Sa décroissance est liée à la survie à 1 an

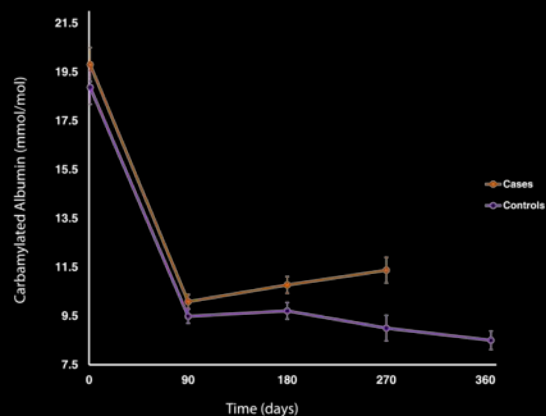


Table 2. Repeated measures analysis of changes in carbamylated albumin, urea reduction ratio, or Kt/V from dialysis initiation to study completion (1 year or death)

Measure	Control, n=244	Patient, n=122	P Value
Carbamylated albumin, mmol/mol	-9.3 (-10.8 to -7.7)	-6.3 (-7.7 to -2.8)	<0.01
Urea reduction ratio	4.1 (3.2 to 5.1)	3.1 (1.7 to 4.5)	0.25
Kt/V	0.2 (0.1 to 0.2)	0.1 (0.0 to 0.2)	0.16

Kalim et al, CJASN, 2016



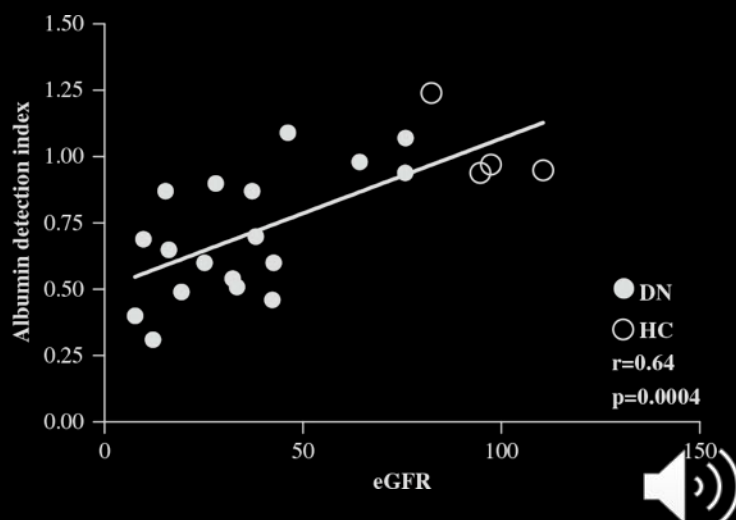
47



48

Le DFG influence le niveau de précision du dosage ?

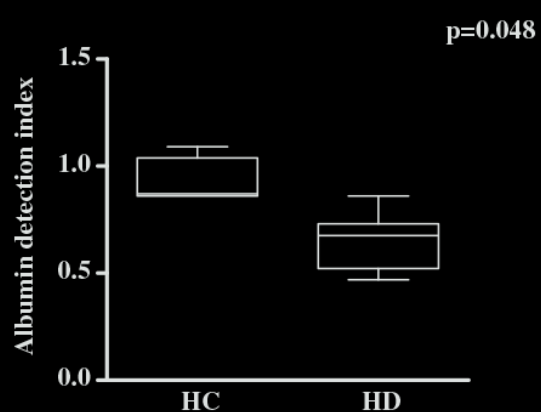
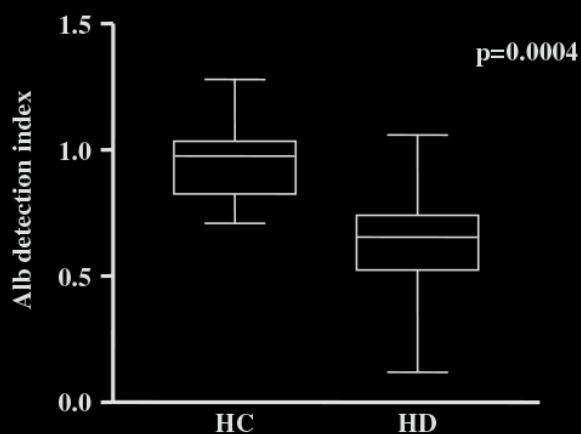
Patient	1	2	3	4	5
Measured Alb [g%]	3.5	3.6	3.7	3.6	3.7
Detection Index	0.49	0.60	0.51	1.16	0.92
Alb. (silver stain)					
Densit. plot					
Densit. [Ux10 ³]	14.2	12.6	10.7	7.8	8.9
Mean densit. [Ux10 ³]	12.5			8.3	



Michelis et al, BBRC, 2010

49

La dialyse influence le niveau de précision du dosage ?

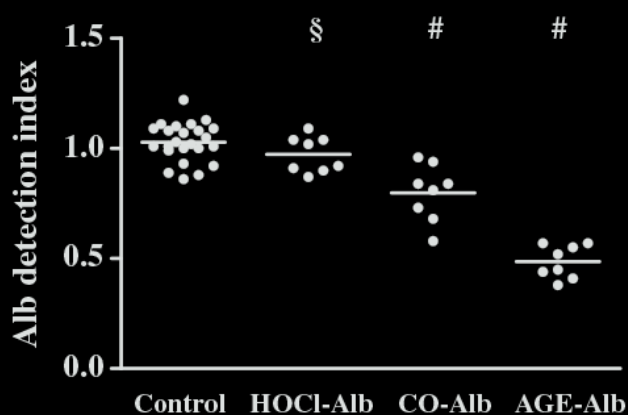


Michelis et al, BBRC, 2010

50

Les modifications influencent le niveau de précision du dosage

C. Albumin detection index

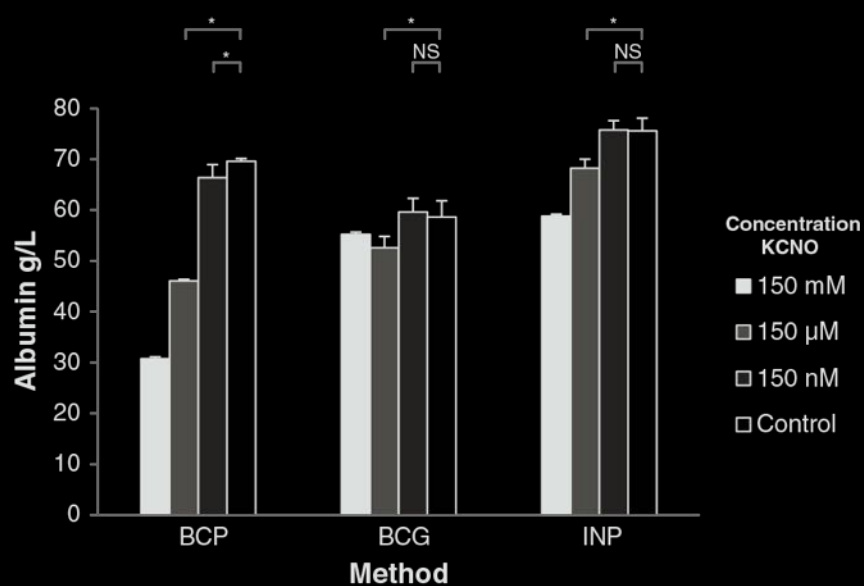


Michelis et al, BBRC, 2010



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La carbamylation de l'albumine perturbe son dosage en immunonéphélométrie



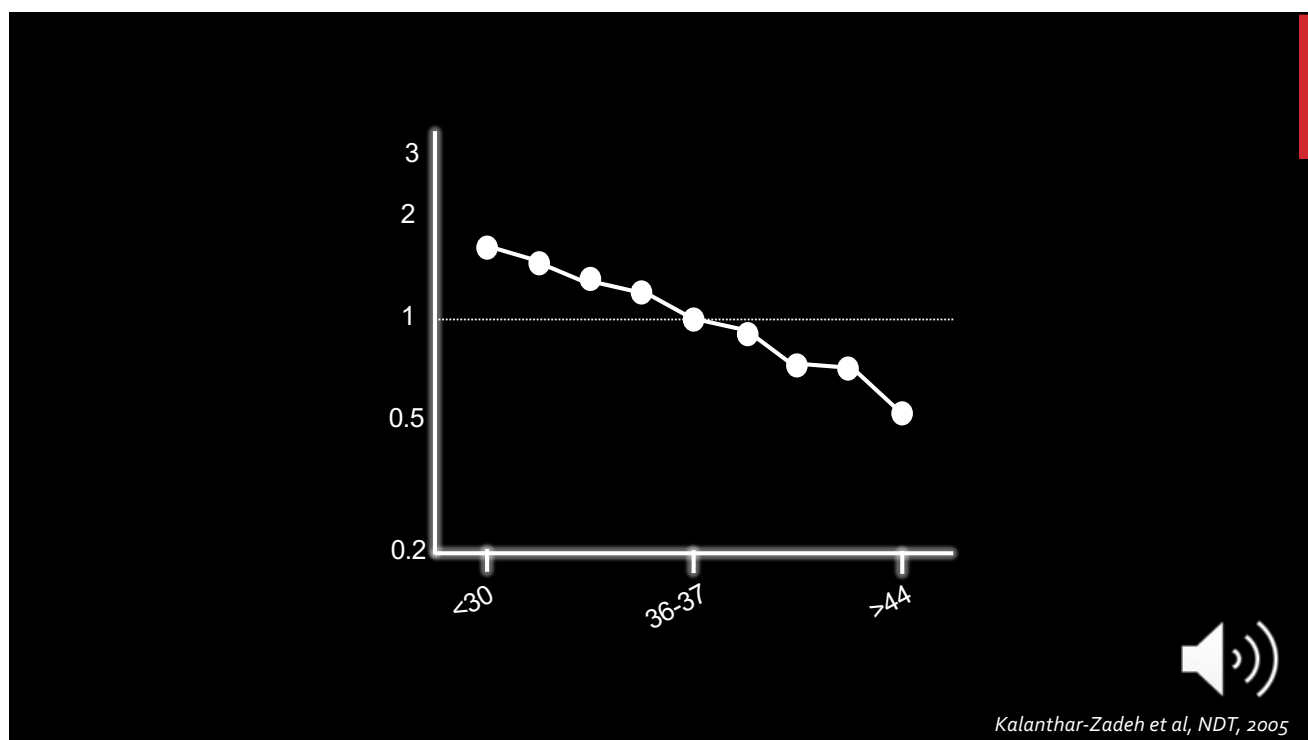
Kok et al, Clin Chim Acta, 2014



52

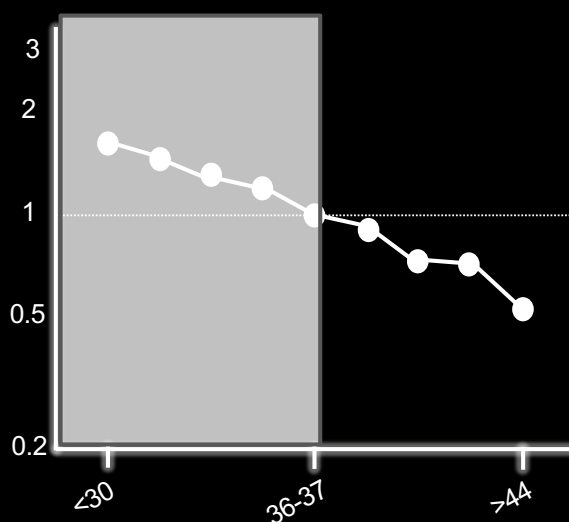


53



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Albuminémie basse

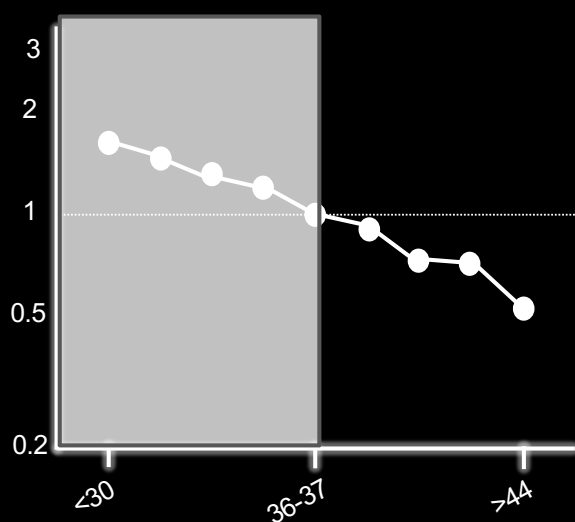


Kalanthar-Zadeh et al, NDT, 2005

55

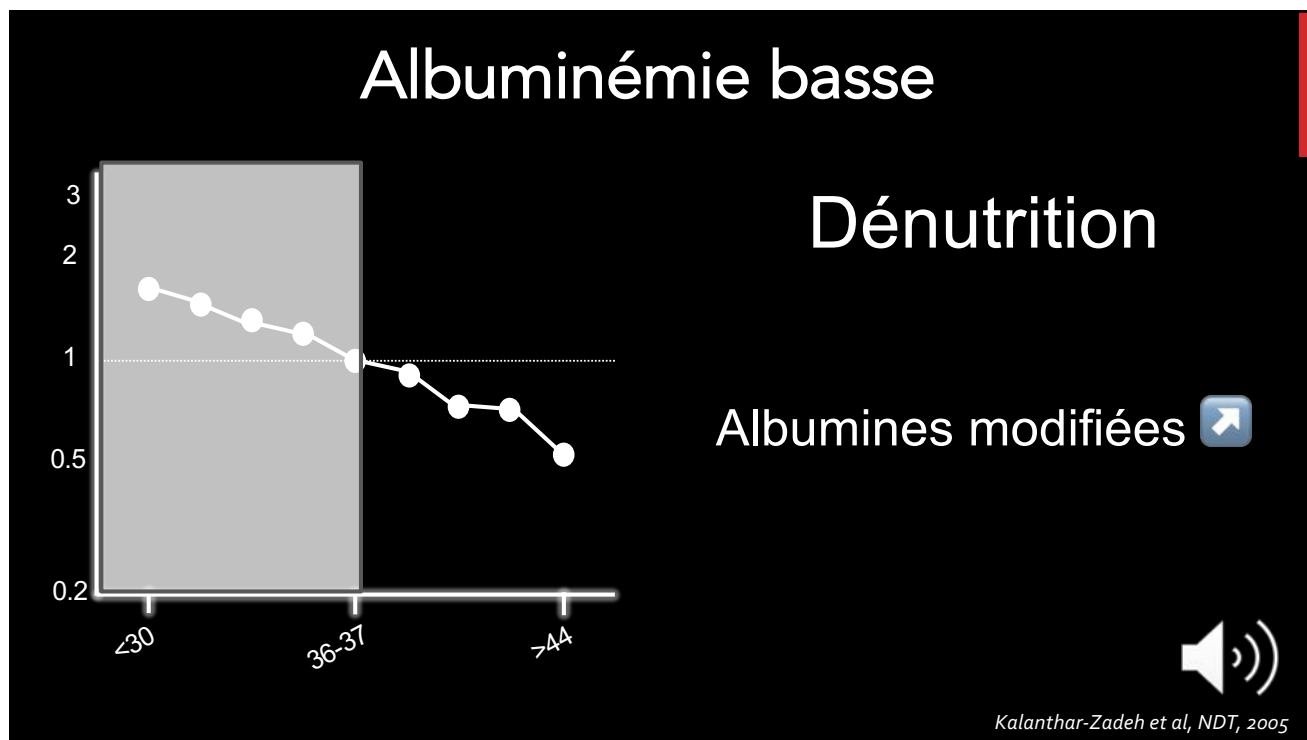
Albuminémie basse

Dénutrition

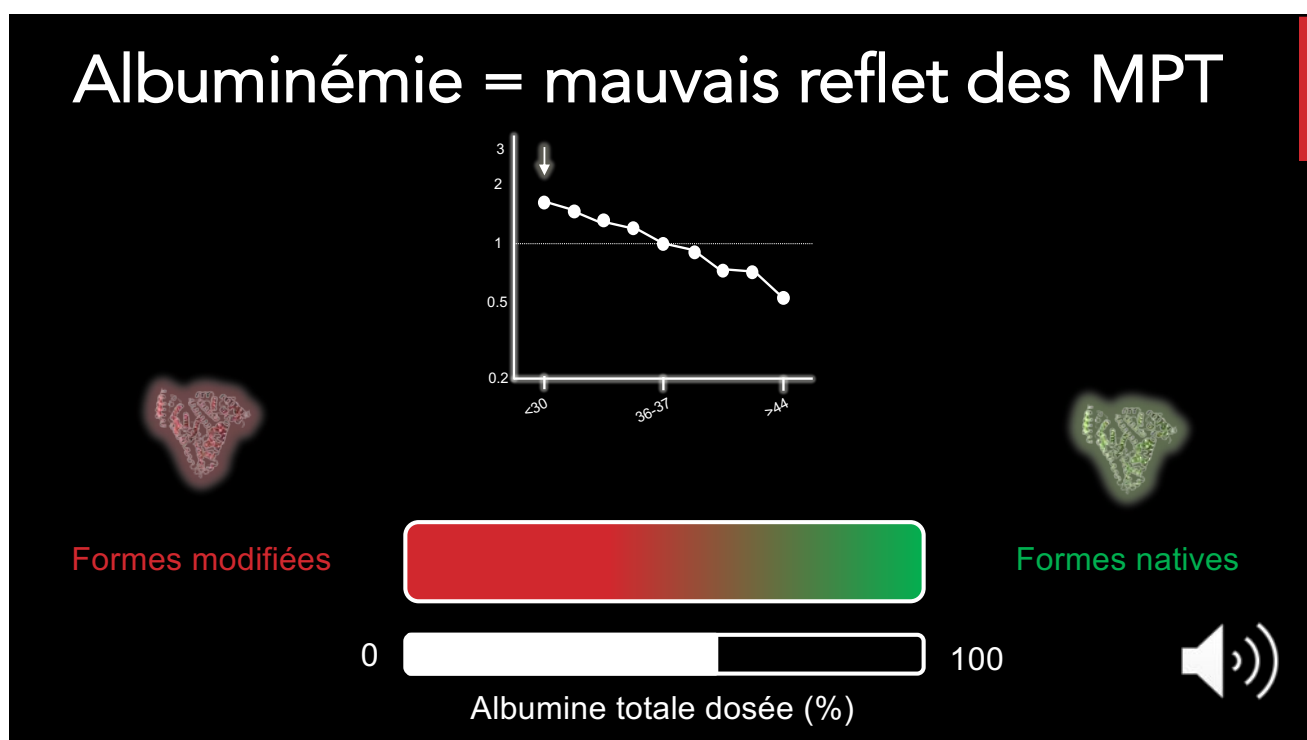


Kalanthar-Zadeh et al, NDT, 2005

56

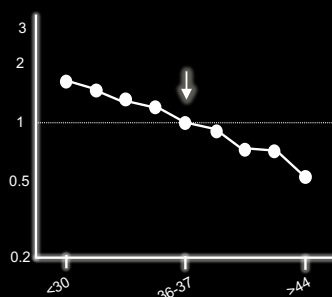


57



58

Albuminémie = mauvais reflet des MPT



Formes modifiées



Formes natives

0



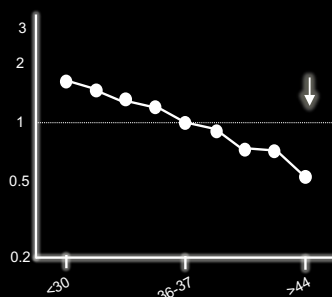
100

Albumine totale dosée (%)



59

Albuminémie = mauvais reflet des MPT



Formes modifiées



Formes natives

0

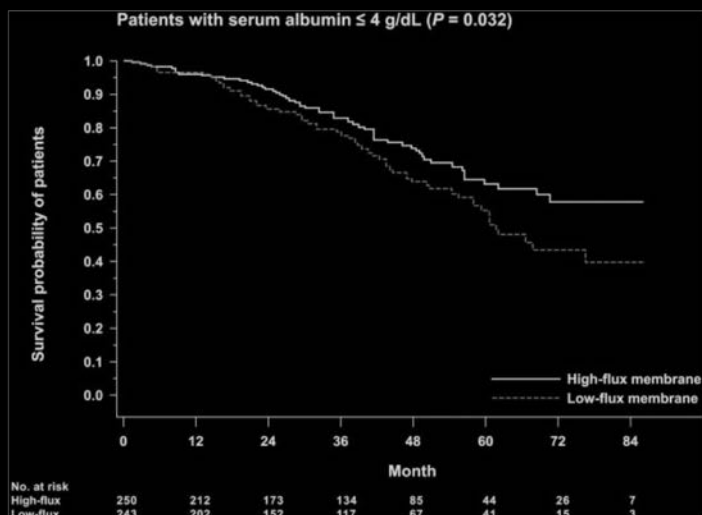


100

Albumine totale dosée (%)



60



Rôle d'une membrane plus permissive sur le turn-over de l'albumine ?



Locatelli et al, JASN, 2009

61

DARK SIDE OF THE ALBUMIN

Devons nous rester aussi stricts sur les pertes d'albumine en dialyse ?

Faut il épurer les formes modifiées de l'albumine ?

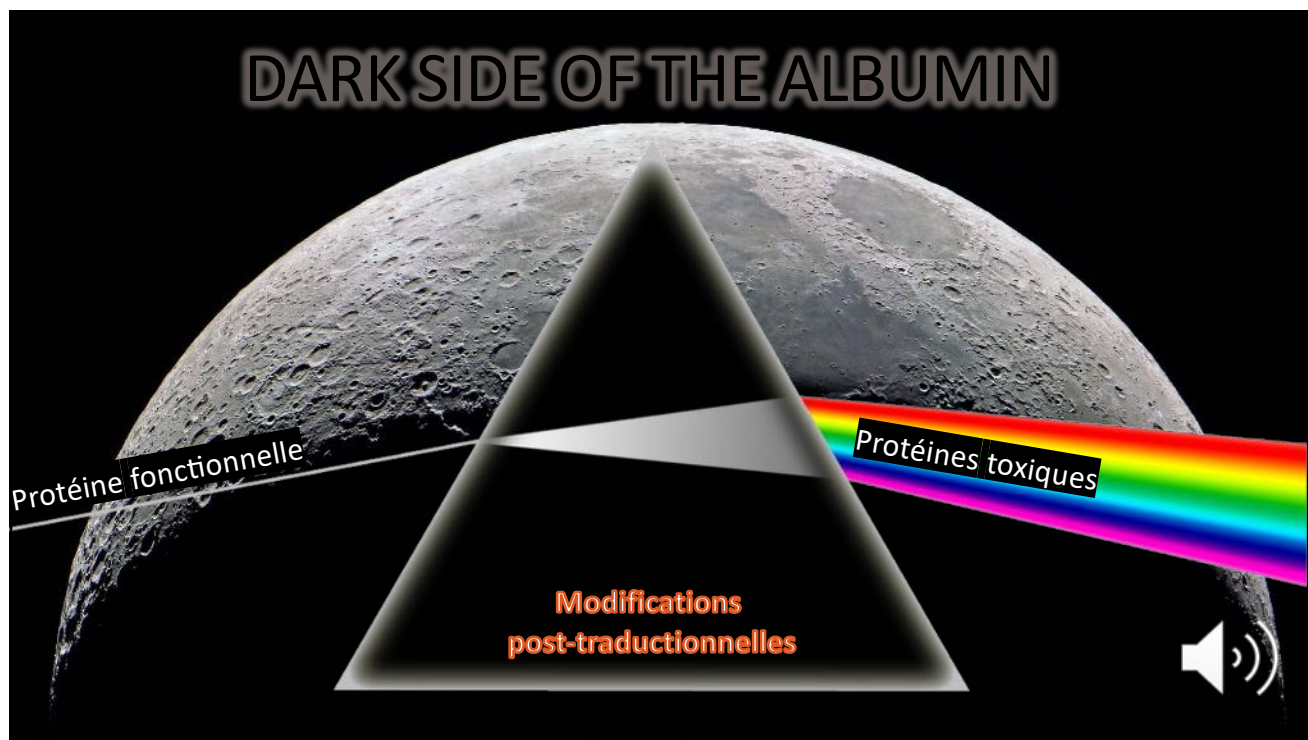
Faut il se méfier d'une albumine basse chez un patient non dénutri ?

Faut il chercher une méthode simple d'évaluer ce pool d'albumine modifiée ?

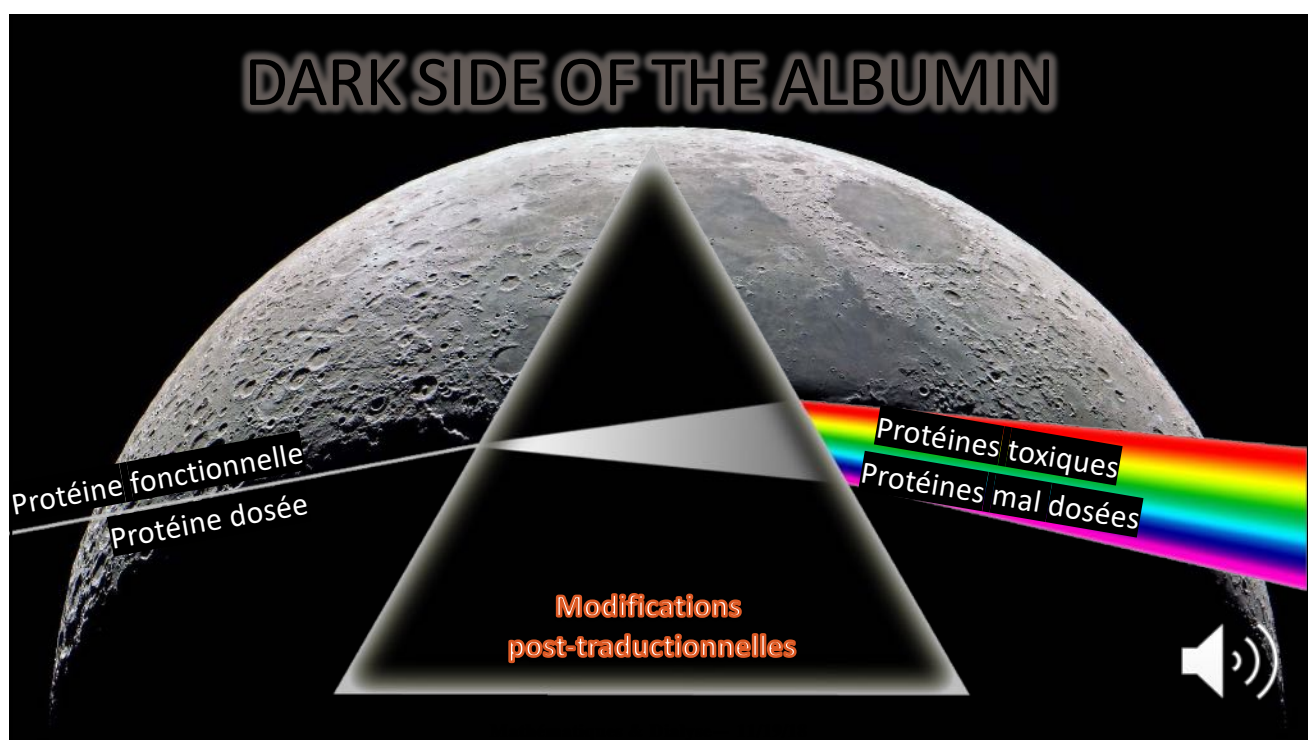
Doit-on se méfier de ces modifications sur d'autres protéines ?



62



63



64



65