A.S.L. CN1

Sessione Congiunta SIMDO - FADOI

Acido urico e diabete: quando e come correggere

Giovanni Gulli
ASL CN1
SC Medicina Interna
Ospedale Maggiore SS. Annunziata
Savigliano, CN

A.S.L. CN1

Agenda

- uric acid (UA) metabolism
- UA and evolution
- UA and type 2 diabetes (T2DM): is there a link?
- when to treat
- how to treat

A.S.L. CN1

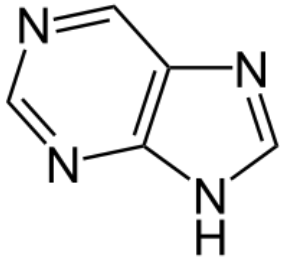
Agenda

- UA metabolism
- UA and evolution
- UA and T2DM: is there a link?
- when to treat
- how to treat

A.S.L. CN1

UA metabolism

- UA is formed from the breakdown of nucleic acids and is an end product of purine metabolism

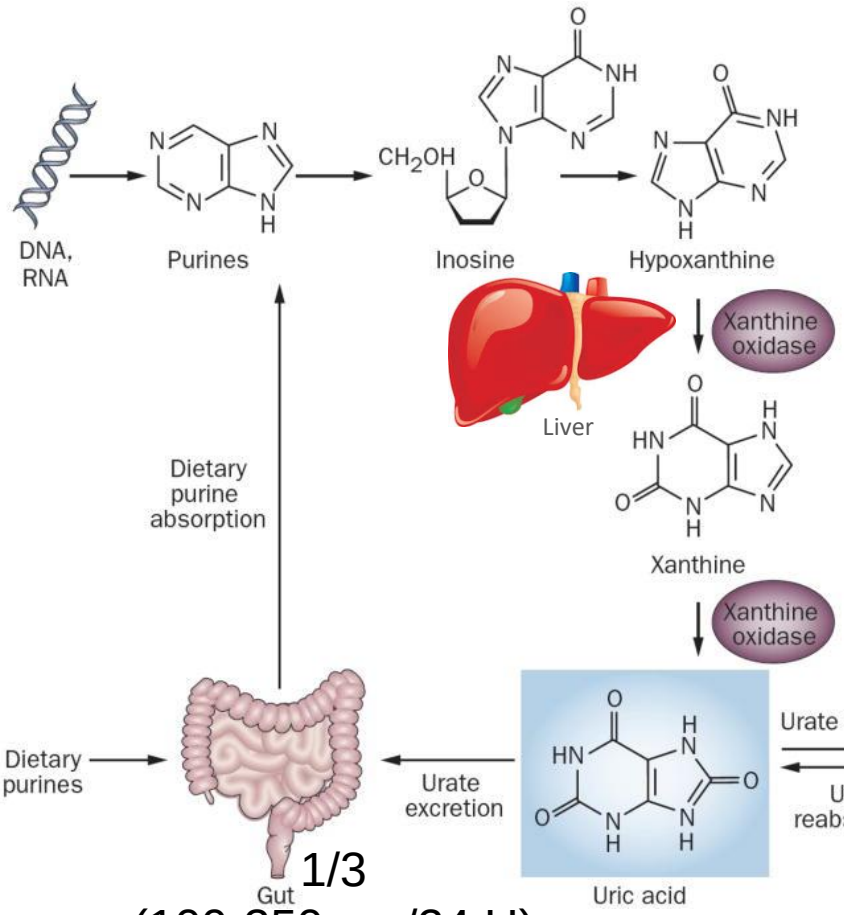


- UA is transported by the plasma from the liver to the kidney, where it is filtered, reabsorbed, and excreted in urine
- The remainder of UA is excreted into the GI tract

Nature reviews Rheumatology 2013;9:13-23

A.S.L. CN1

Biochemistry of UA and its homeostasis



90% of
highly
soluble
filtered
by the
idneys
0-7000
24 H) is
sorbed

1/3
(100-350 mg/24 H)

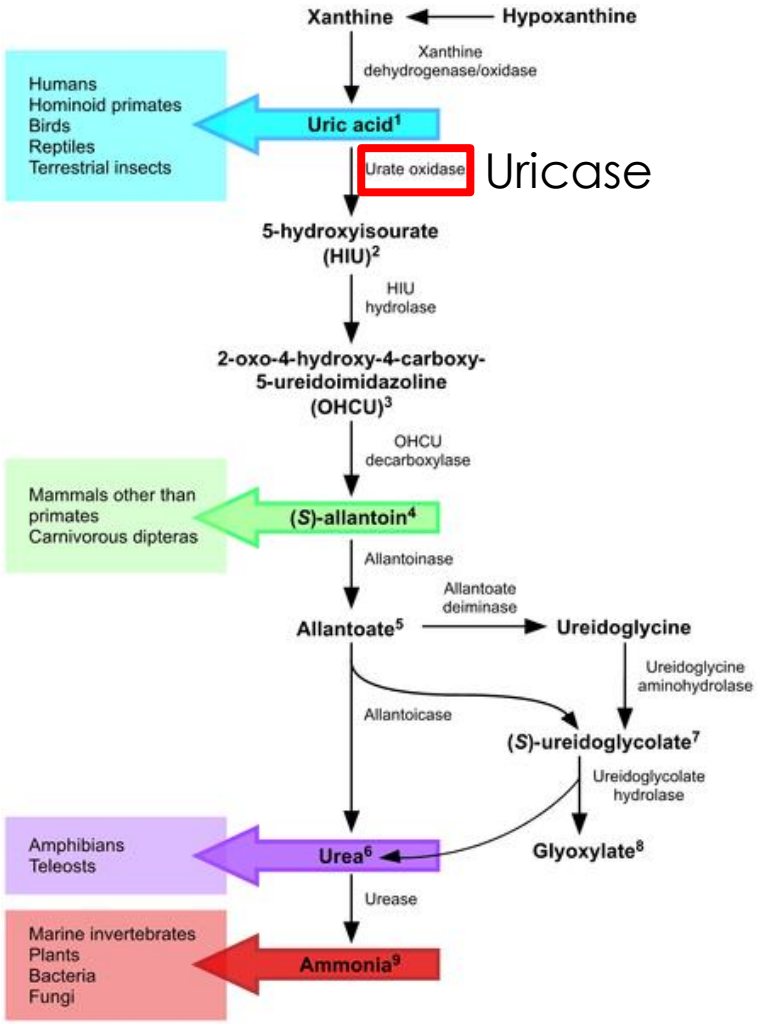
2/3
(200-700 mg/24 H)

Nature reviews Rheumatology 2013;9:13-23

Giovanni Gulli, 2017

A.S.L. CN1

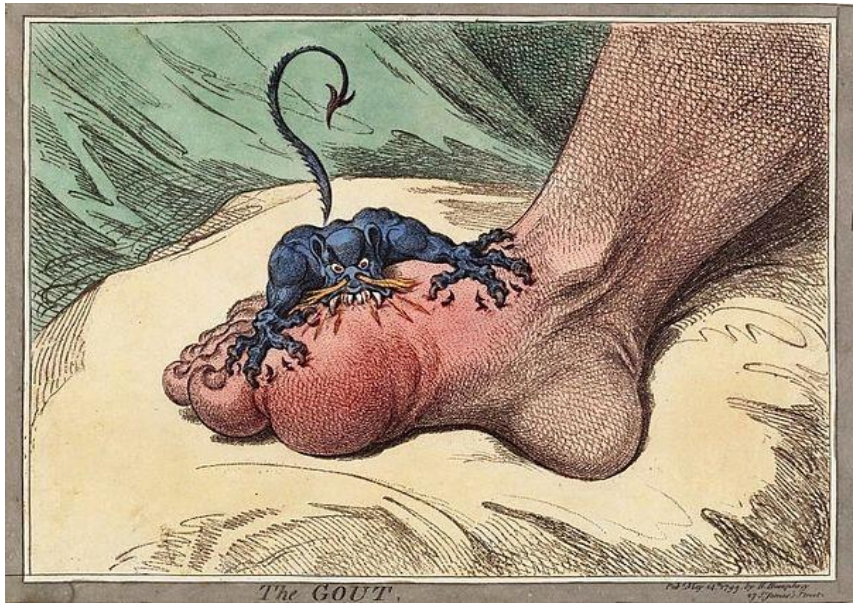
Uricase and UA metabolism



PLoS ONE 2013; 8(5): e64292

Giovanni Gulli, 2017

Gout: a disease of the blessed or a blessing in disguise?



"The patient goes to bed and sleeps quietly until about two in the morning when he is awakened by a pain which usually seizes the great toe, but sometimes the heel, the calf of the leg or the ankle … so exquisitely painful as not to endure the weight of the clothes nor the shaking of the room from a person walking briskly therein."

A.S.L. CN1

Agenda

- UA metabolism
- UA and evolution
- UA and T2DM: is there a link?
- when to treat
- how to treat

A.S.L. CN1

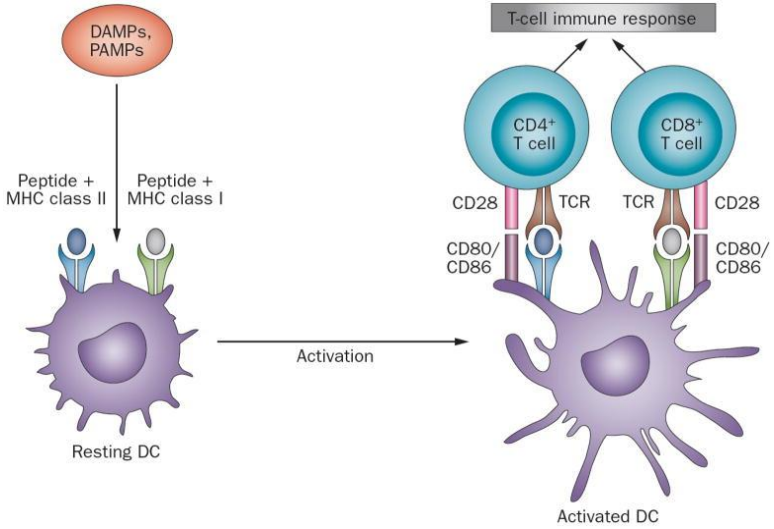
Survival advantage of the loss of uricase

The loss of uricase during the Miocene era may have provided a survival advantage by:

- Endogenous adjuvant during immune presentation and inflammation *
- Higher antioxidant capacity and greater longevity
- Volume and blood pressure control during low salt ingestion *
- Accumulation of fat stores *
- Neuroprotection

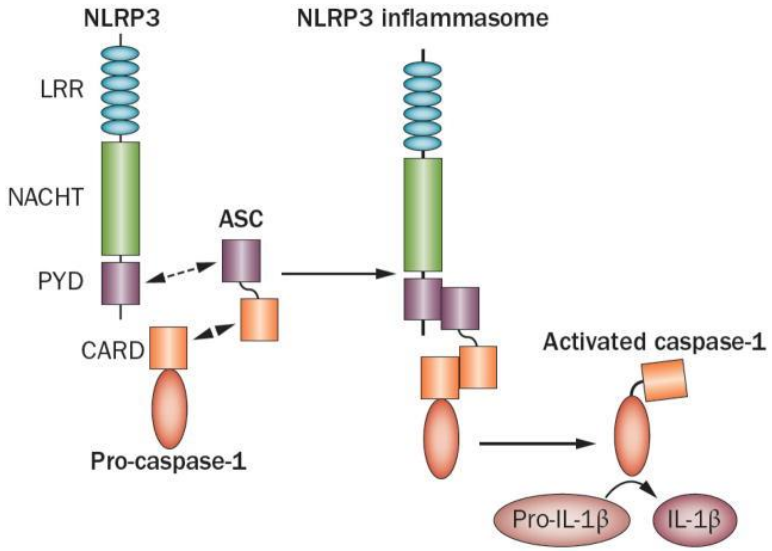
PNAS 2014;111:3763–3768

UA, immunity and inflammation

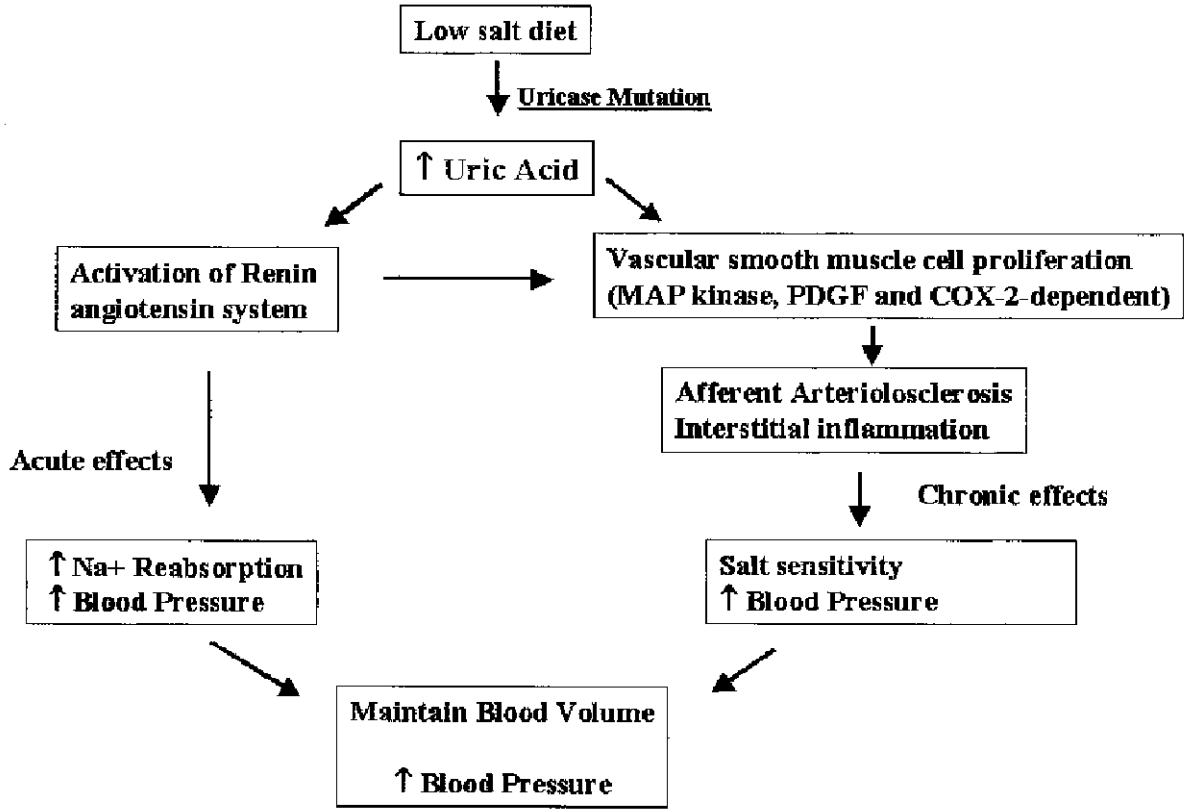


UA is the danger signal that acts as endogenous adjuvant when tissue is injured during immune presentation

UA activates the NALP3 Inflammasome: macrophage generation of IL-1 for cellular secretion



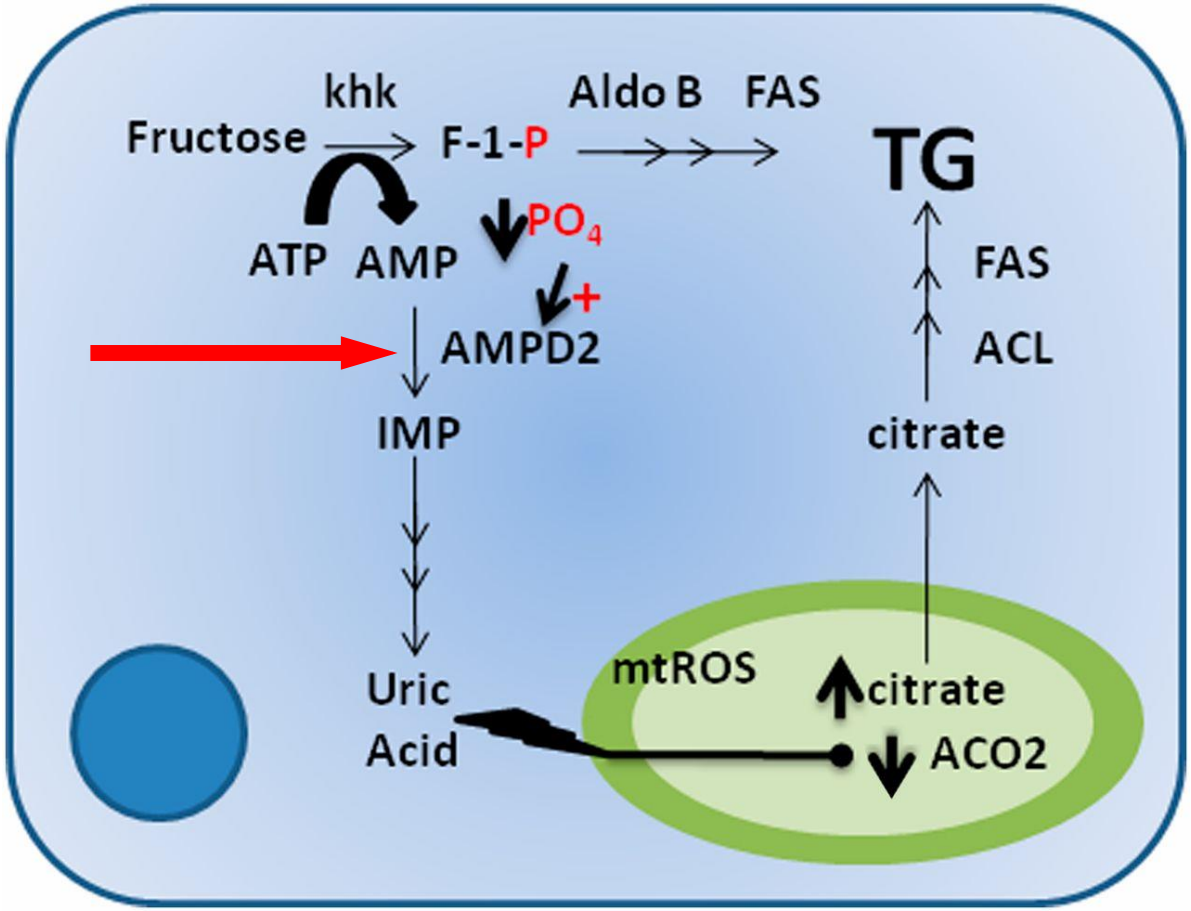
UA and salt-sensitivity



Hypertension 2002;40:355-360

Giovanni Gulli, 2017

UA and lipogenic pathways



Diabetes 2013;62:3307-3315

Giovanni Gulli, 2017

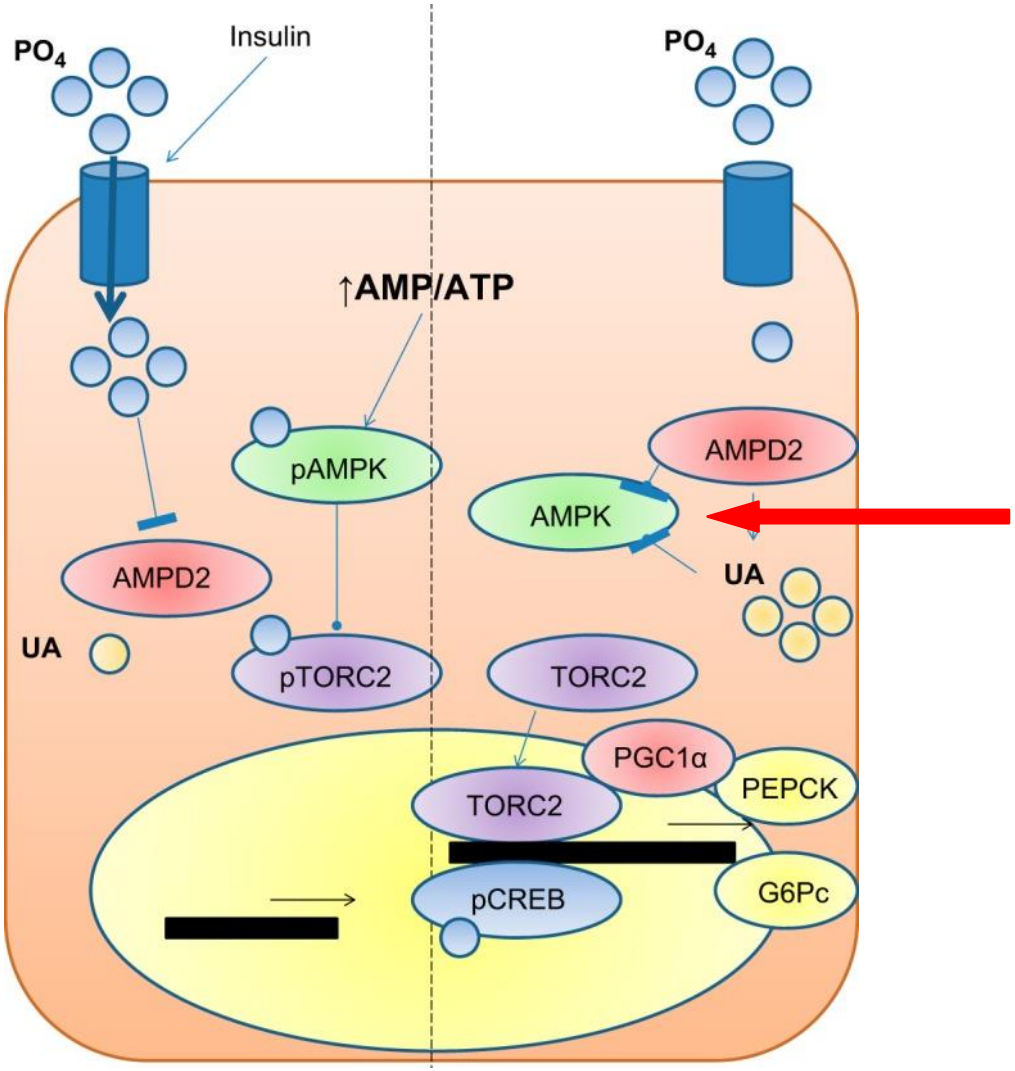
UA and lipogenic pathways (cont)

- AMPD counters the effects of AMP-activated protein kinase (AMPK)
- Whereas activation of AMPK in hepatocytes induces oxidation of fatty acids and ATP generation, AMPD has opposite effects
- Overexpression of AMPD blocks fatty acid oxidation and increases fat accumulation
- The mechanism is mediated in part by the generation of UA, which inhibits AMPK

Diabetes 2013;62:3307–3315,

A.S.L. CN1

UA and gluconeogenesis



FASEB J. 2014;28:3339–3350

Giovanni Gulli, 2017

A.S.L. CN1

Metformin, AMPK and 2DM

- Activation of AMPK by Met reduces protein synthesis, enhances glucose uptake, stimulates mitophagy and mitogenesis, activates autophagy, and significantly reduced intracellular ROS levels
- Activation of SIRT1 by Met protects the cells from metabolic memory through at least two mechanisms: suppressing the cellular inflammatory gene NF-kB and attenuating the expression of the cellular apoptosis gene Bax

Diabetes 2012;61:217-228

A.S.L. CN1

Agenda

- UA metabolism
- UA and evolution
- UA and T2DM: is there a link?
- when to treat
- how to treat

A.S.L. CN1

Potential UA-T2DM link

The loss of uricase during the Miocene era may have provided a survival advantage by:

- Endogenous adjuvant during immune presentation and inflammation *
- Higher antioxidant capacity and greater longevity
- Blood pressure control during low salt ingestion *
- Accumulation of fat stores *
- Neuroprotection

A.S.L. CN1

UA and T2DM: is there a link? Yes!

- Inflammation
- Hypertension
- Fat accumulation
- Reduced glucose uptake
- Increased gluconeogenesis

A.S.L. CN1

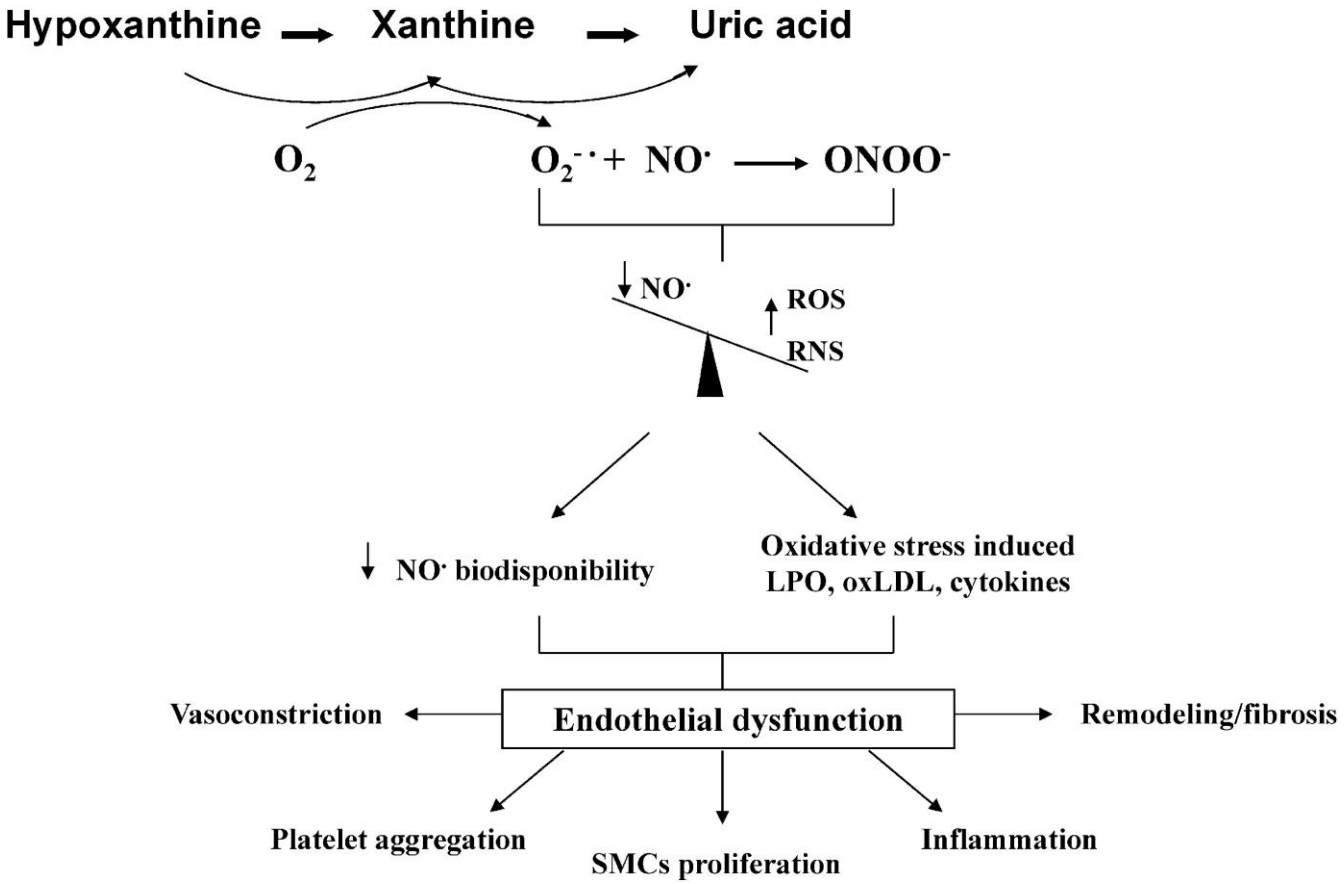
UA predicts the development of MS and T2DM

Location	Population	End point	F/U	Independent	Year	First Author
Israel	10,000 men	diabetes	5 years	Yes	1975	Medalie
U.S.	5,209 adults	diabetes	26 years	Men	1985	Brand
Naura	266 adults	diabetes	6 years	Women	1985	Balkau
Sweden	766 men	type 2 diabetes	13.5 years	Yes	1988	Ohlson
Britain	7,735 men	NIDDM	12.8 years	Yes	1995	Perry
Kinmen (China)	654 high risk	diabetes	3 years	Yes	1998	Chou
Mauritius	2,605 adults	IGT or diabetes	5 years	Yes	2000	Boyko
Japan	6,356 men	type 2 diabetes	9 years	No	2001	Taniguchi
Germany	6,166 adults	type 2 diabetes	3–14 years	Women	2002	Meisinger
U.S.	9,020 adults	↑insulin	11 years	Yes	2003	Carnethon
Japan	2,310 men	IFG or diabetes	6 years	Yes	2003	Nakanishi
Kinmen (China)	641 adults	IFG or diabetes	7 years	Women	2004	Lin
U.S.	60 adults with MI	↑insulin	6 months	Yes	2005	Nakagawa
Finland	522 high risk	type 2 diabetes	4.1 years	No	2006	Niskanen
Netherlands	4,536 adults	type 2 diabetes	10 years	Yes	2008	Dehghan
Mauritius	4,259 adults	diabetes	5 years	Men	2008	Nan
China	2,609 adults	type 2 diabetes	9 years	Yes	2008	Chien
U.S.	9,689 adults	met syn	5.7 years	Yes	2008	Sui
U.S.	566 high risk	type 2 diabetes	13 years	Yes	2009	Kramer
U.S.	9,175 adults	type 2 diabetes	26–28 years	Yes	2010	Bhole
Korea	4,779 men	met syn	3 years	Yes	2011	Ryu
Japan	12,643 adults	IFG and diabetes	5 years	Women	2011	Yamada
China	924 adults	type 2 diabetes	3.5 years	Yes	2011	Wang
Italy	758 adults/BP	type 2 diabetes	3 years	Yes	2011	Viazzi

Diabetes 2013;62:3307–3315

Giovanni Gulli, 2017

Uric acid and endothelial dysfunction



Int J Card 2016; 213:23–27

Giovanni Gulli, 2017

UA and T2DM: is there a link?

ON THE

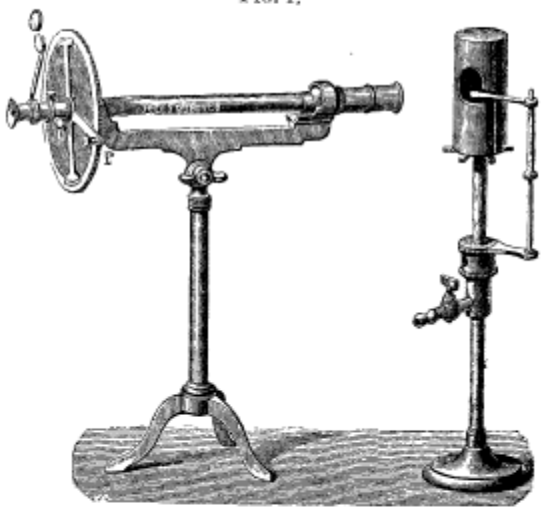
COMMON ORIGIN OF DIABETES AND THE URIC ACID DIATHESIS.

BY DR. DEBOUT D'ESTREES,

OF CONTREXÉVILLE.

THAT diabetes and the uric acid diathesis have a common origin is not a new idea. The subject has been discussed by many writers, some upholding, others opposing, the theory. My own experience classes me with the first, because in all the cases of diabetes brought under my notice at Contrexéville since my appointment in 1868 I have seen the sugar during treatment give place to an excretion of uric acid.

FIG. 1.



Polarimeter or polariscope.

The examination of each sample of urine has on every occasion been carefully made by myself with both microscope and polarimeter (see Fig. 1), the latter instrument giving the proportion of contained sugar with the greatest

Dr. Marchal de Calvi, in a work published in 1864, writes: "*The most obvious factor in the morbid processus of diabetes is the influence of the uric acid diathesis*," and my experience at Contrexéville leads me more than ever to share his opinions as to the connexion of diabetes with gout.

Lancet 127:1886; 964-965

A.S.L. CN1

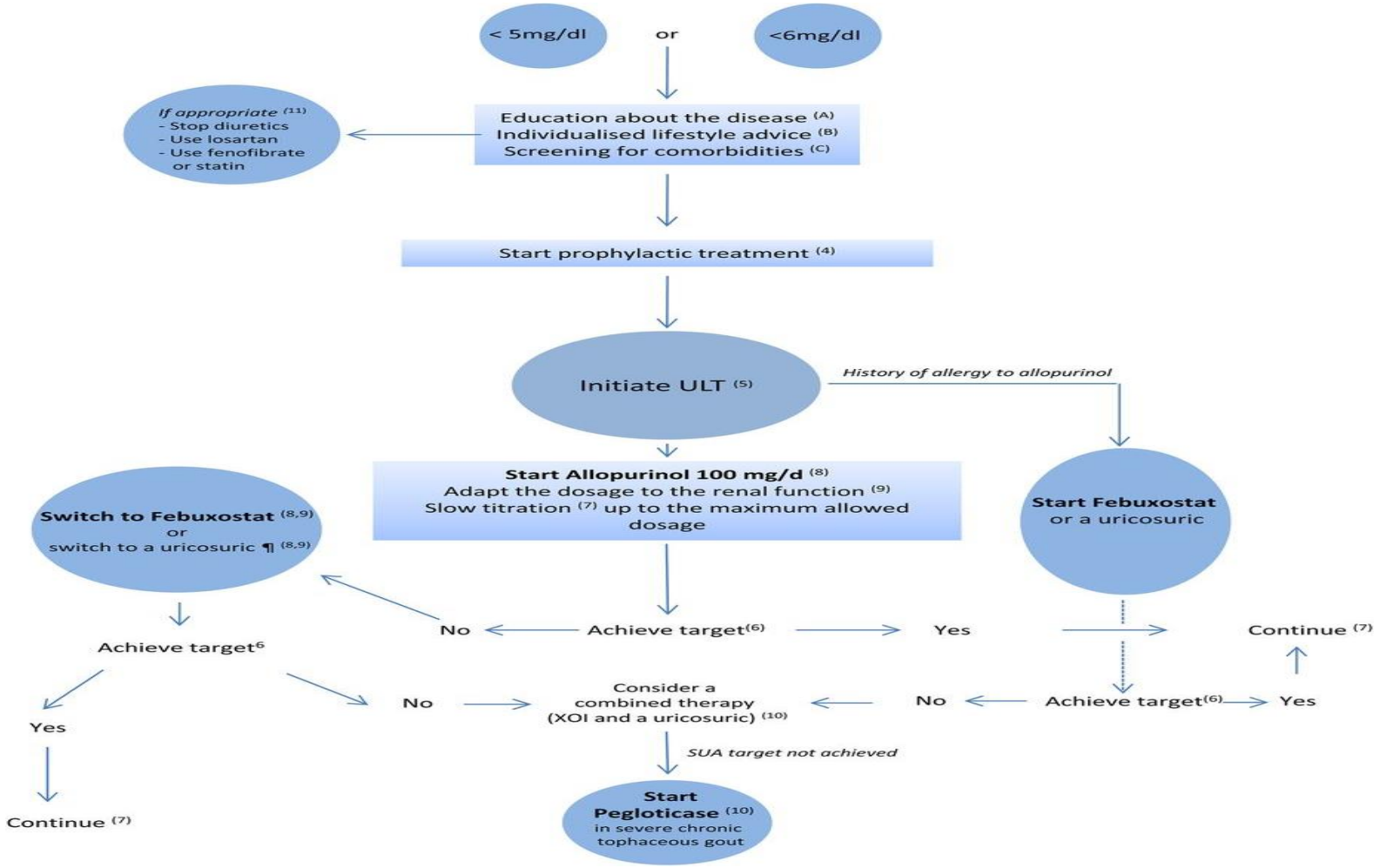
Conclusion

- The possibility has been raised that high uric acid levels might contribute to the development of hypertension, metabolic syndrome and atherosclerosis
- Determining cause and effect of high uric acid levels and its comorbidities, and elucidating the mechanisms underlying these epidemiological associations, is not trivial and at this point is unresolved

Nature Rev Rheumatol 2013;9:13–23

A.S.L. CN1

SUA target and management of gout



Ann Rheum Dis 2017;76:29-42

Giovanni Gulli, 2017

A.S.L. CN1

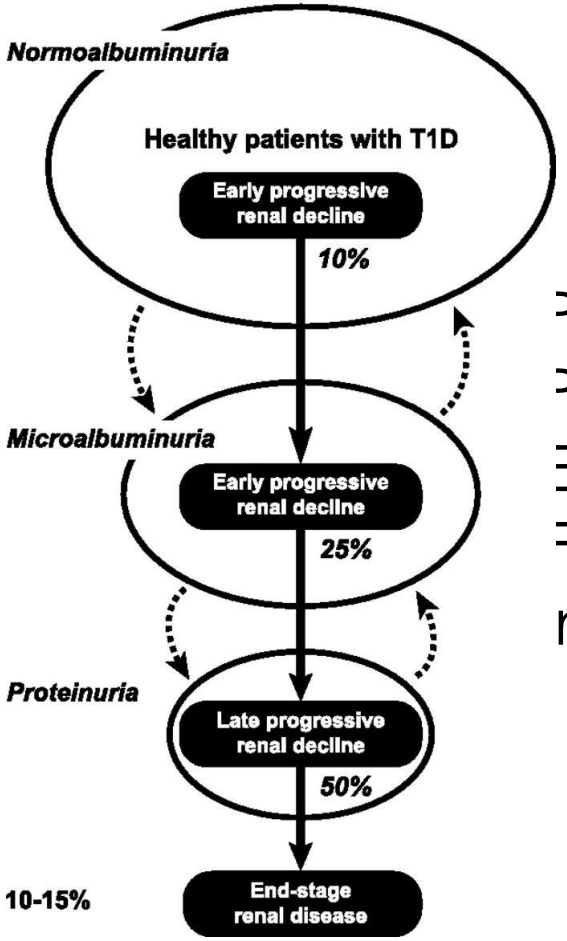
Management of asymptomatic hyperuricaemia

- Asymptomatic hyperuricemia (AH) is a common clinical condition associated with increased risk for gout and other urate crystal–related clinical events
- AH is also associated with cardiovascular, metabolic, and renal disease, although the clinical significance and causal relationship of these associations remain the subject of controversy
- Pharmacologic treatment of AH is not recommended, but management includes further evaluation and lifestyle changes known to reduce serum urate

Ann Rheum Dis 2017;76:29-42

Giovanni Gulli, 2017

A new paradigm of T1DM nephropathy



PERL:
Preventing
Early Renal
Function Loss
in Diabetes

Diabetes Care 2015;38:954-962

Giovanni Gulli, 2017

A.S.L. CN1

Sessione Congiunta SIMDO - FADOI

Acido urico e diabete: quando e come correggere

Giovanni Gulli
ASL CN1
SC Medicina Interna
Ospedale Maggiore SS. Annunziata
Savigliano, CN

A.S.L. CN1

Il dopo Campanini: oltre la corsa c'è di più

Skydive Garz

Giovanni Gulli, 2017

A.S.L. CN1

Sessione Congiunta SIMDO - FADOI

Acido urico e diabete: quando e come correggere

Giovanni Gulli
ASL CN1
SC Medicina Interna
Ospedale Maggiore SS. Annunziata
Savigliano, CN