Stone Composition

- Stone analysis 43,545 at Mayo Stone Lab (2010)

Calcium oxalate	67%
Hydroxyapatite	16%
Uric acid	**8%**
Struvite	3%
Brushite	0.9%
Cystine	0.35%

Lieske et al. Clinical Journal of American Society of Nephrology, 9:2141, 2014.

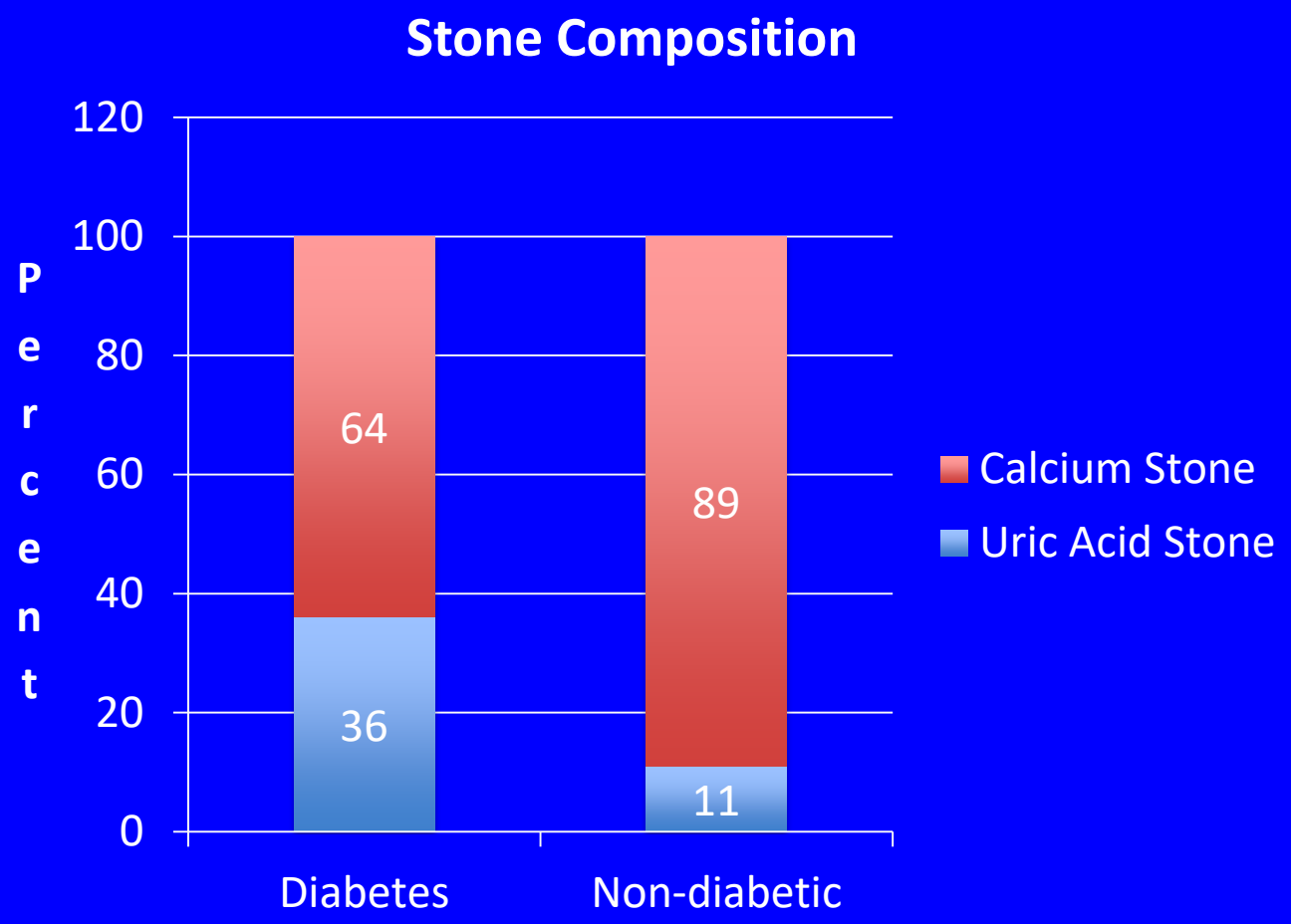
Associations

- Diabetes
- Metabolic Syndrome
- Obesity
- Gout
- Bowel disease
- States of increased uric acid production

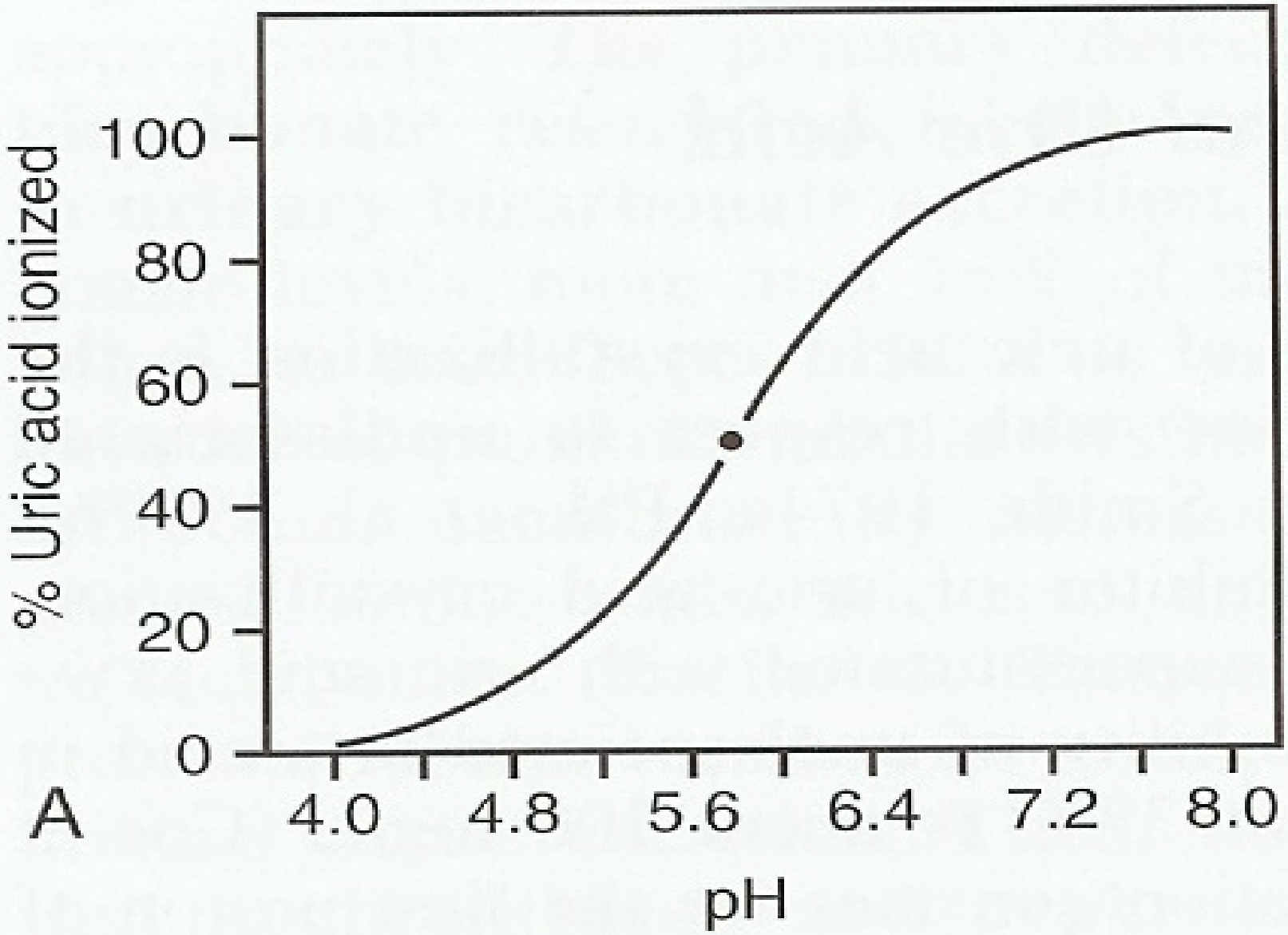
Percent Stone Composition and Obesity

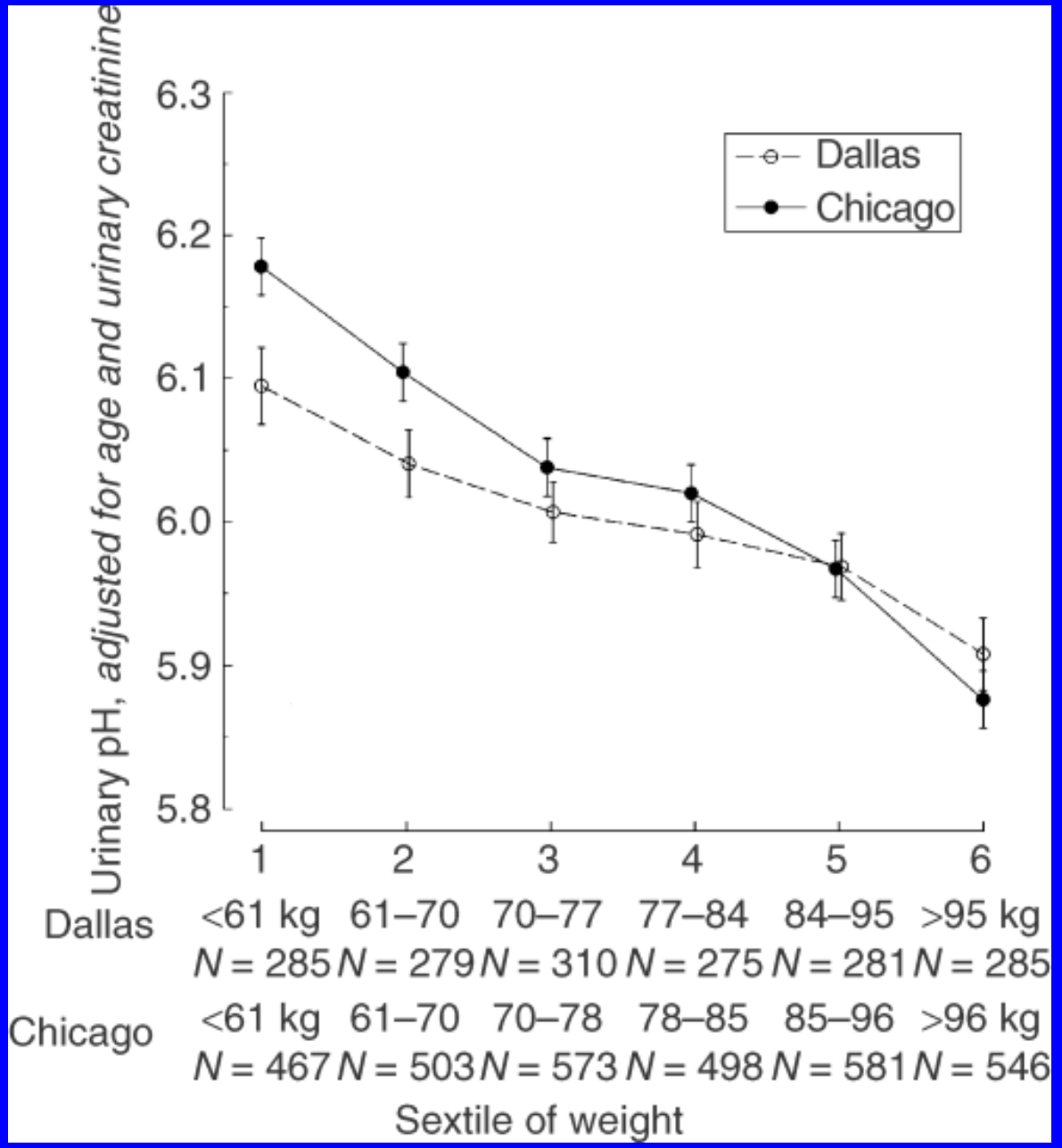
Ekeruo et al. Journal of Urology, 172:159,2004

	Obese	Non-Obese
COM	66	88
COD	31	68
Uric Acid	**63**	**11**
Apatite	31	68
Brushite	16	9

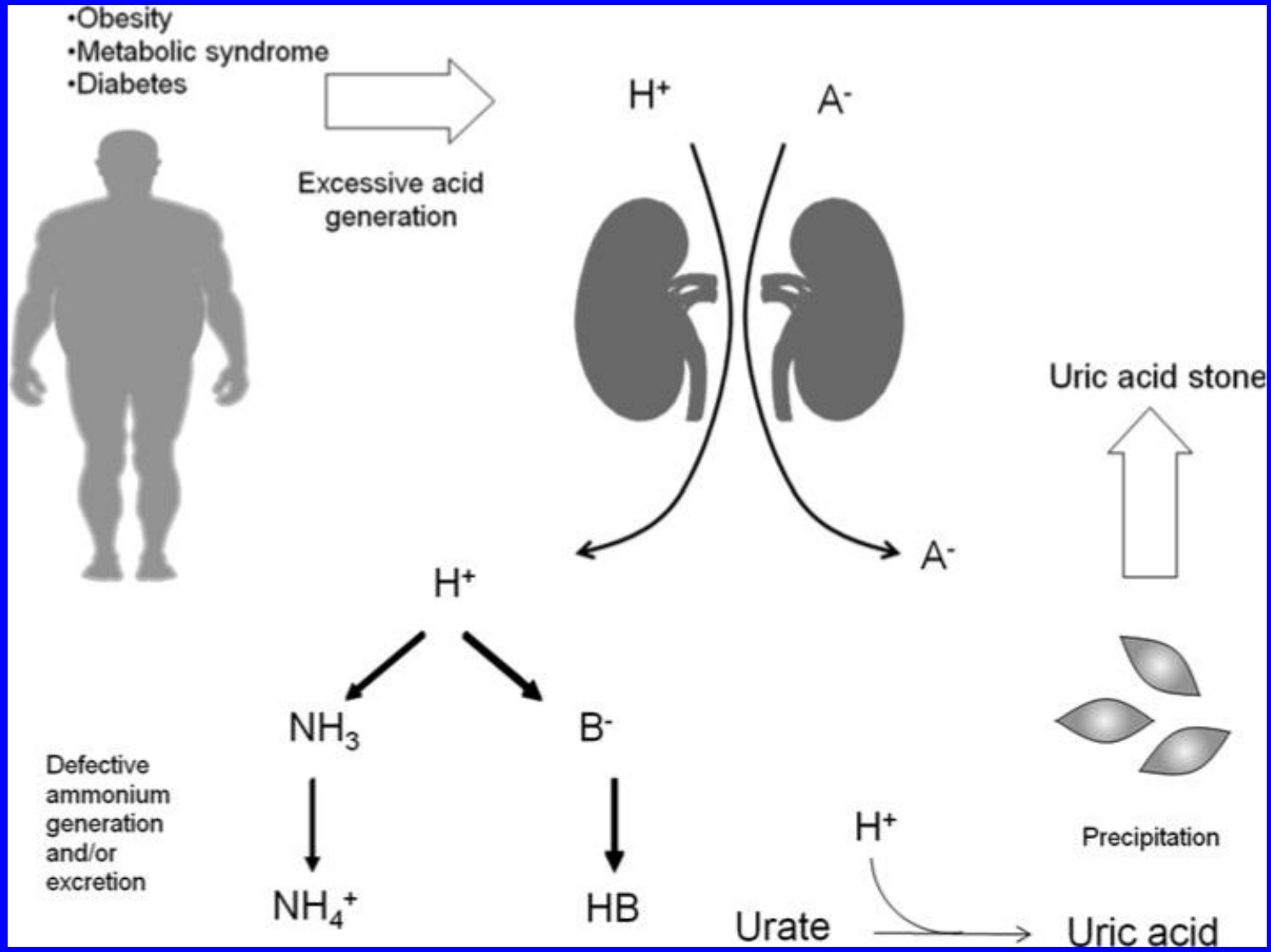


Daudon et al. Journal of the American Society of Nephrology, 17:2026, 2006.


% Uric acid ionized
100
80
60
40
20
0
4.0
4.8
5.6
6.4
7.2
8.0
pH
A

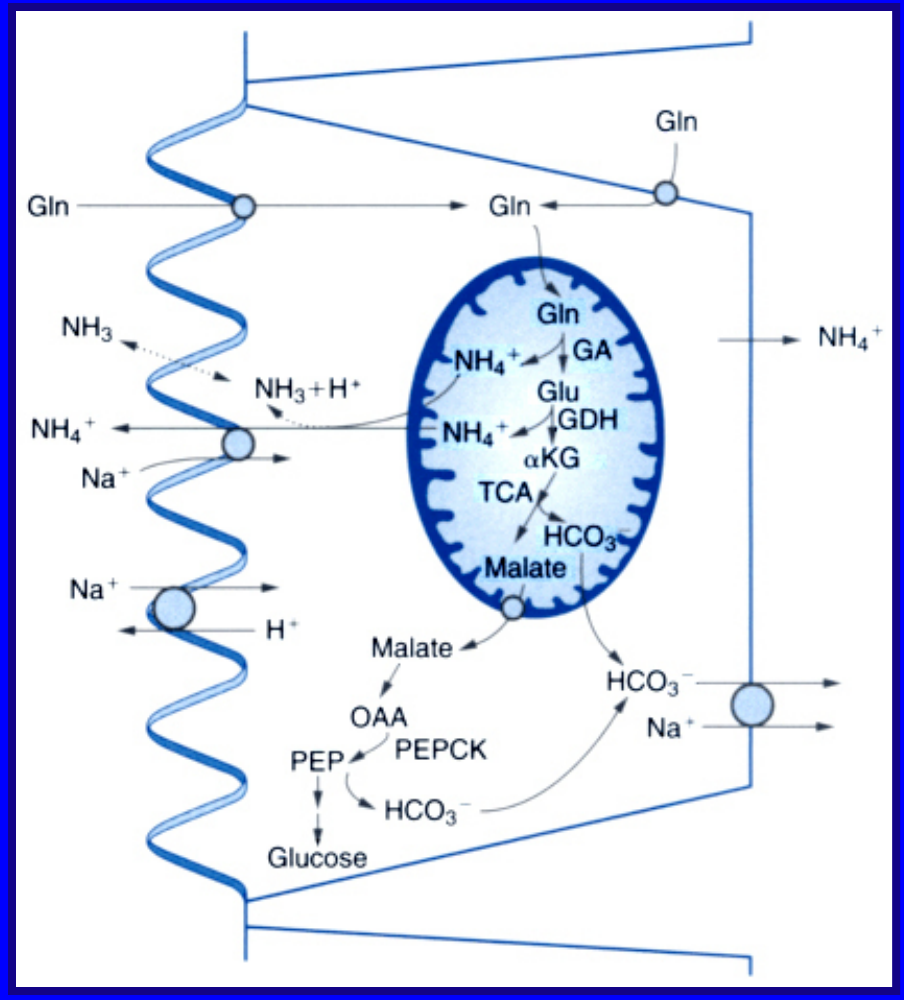


Maalouf et al. Kidney International, 65:1422,2004.



Wiederkehr and Moe. Clinical Reviews in Bone and Mineral Metabolism, 9:207, 2011.

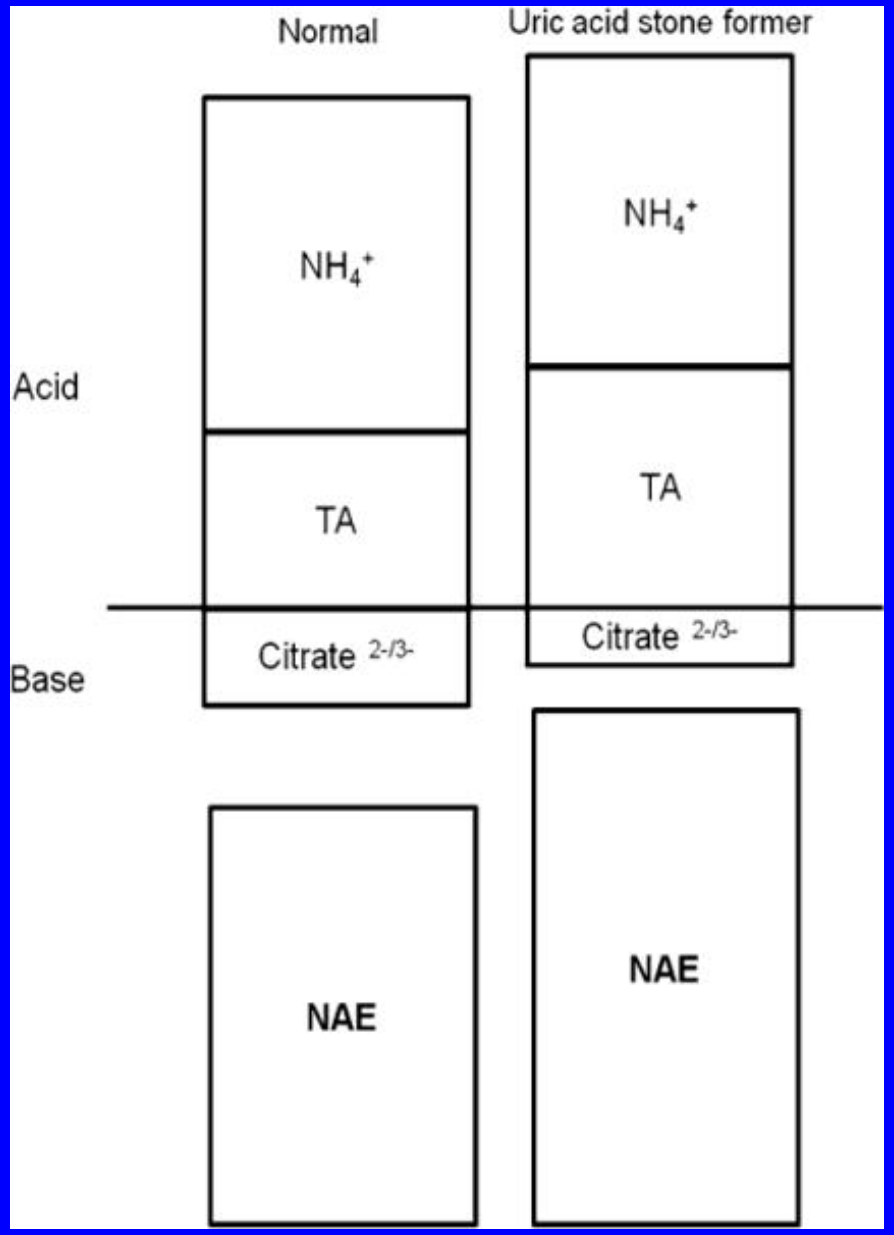
Ammonium/Acid Elimination



"The Kidney", WB Saunders, 2004.

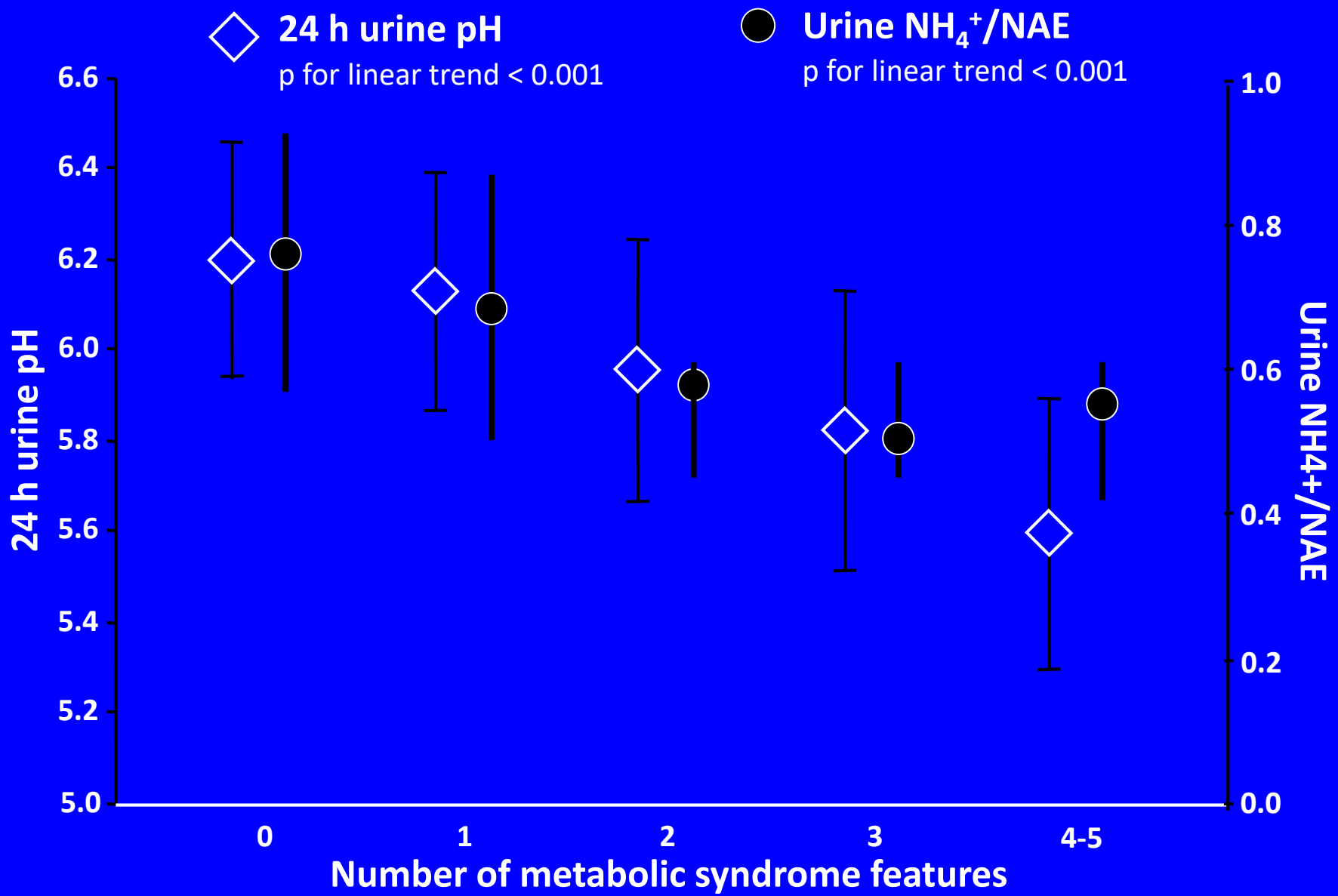
Ammonium Generation

- Mitochondrial metabolism of glutamine → glutamate → **α**-ketoglutarate releasing NH_3 in renal proximal tubule
- NH_3 can cross brush border and be trapped in the tubular lumen with protonation to NH_4^+
- NH_3 can be protonated in the cell and transported as NH_4^+
- Na^+/H^+ exchanger 3 (NHE3) extrudes H^+ and Na^+/NH_4^+ exchanger



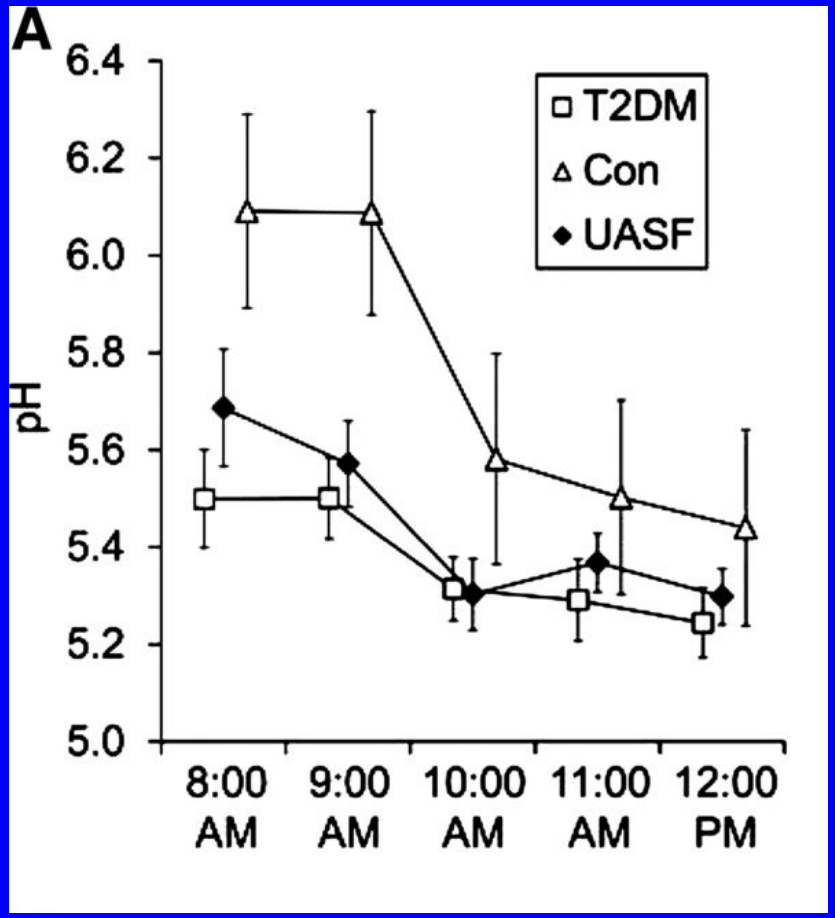
Wiederkehr and Moe. Clinical Reviews in Bone and Mineral Metabolism, 9:207, 2011.

Metabolic Syndrome Features and Renal Acidification



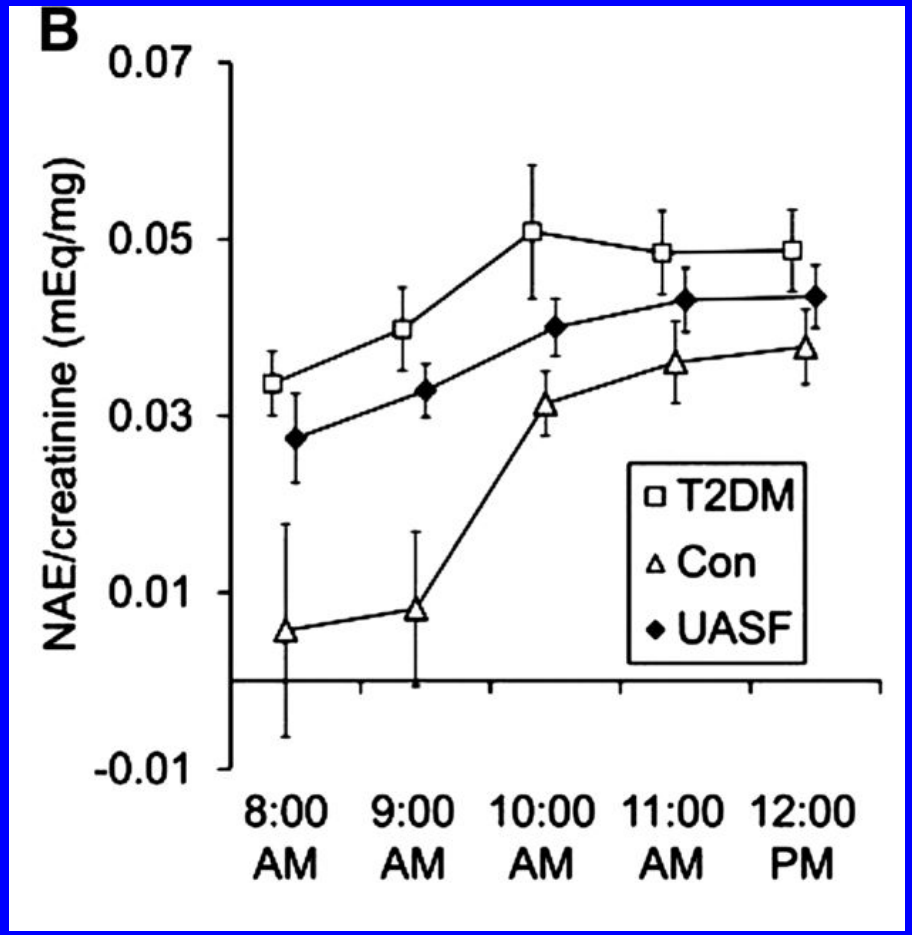
Maalouf, Semin Nephrol, 2008.

Response to Acid Load



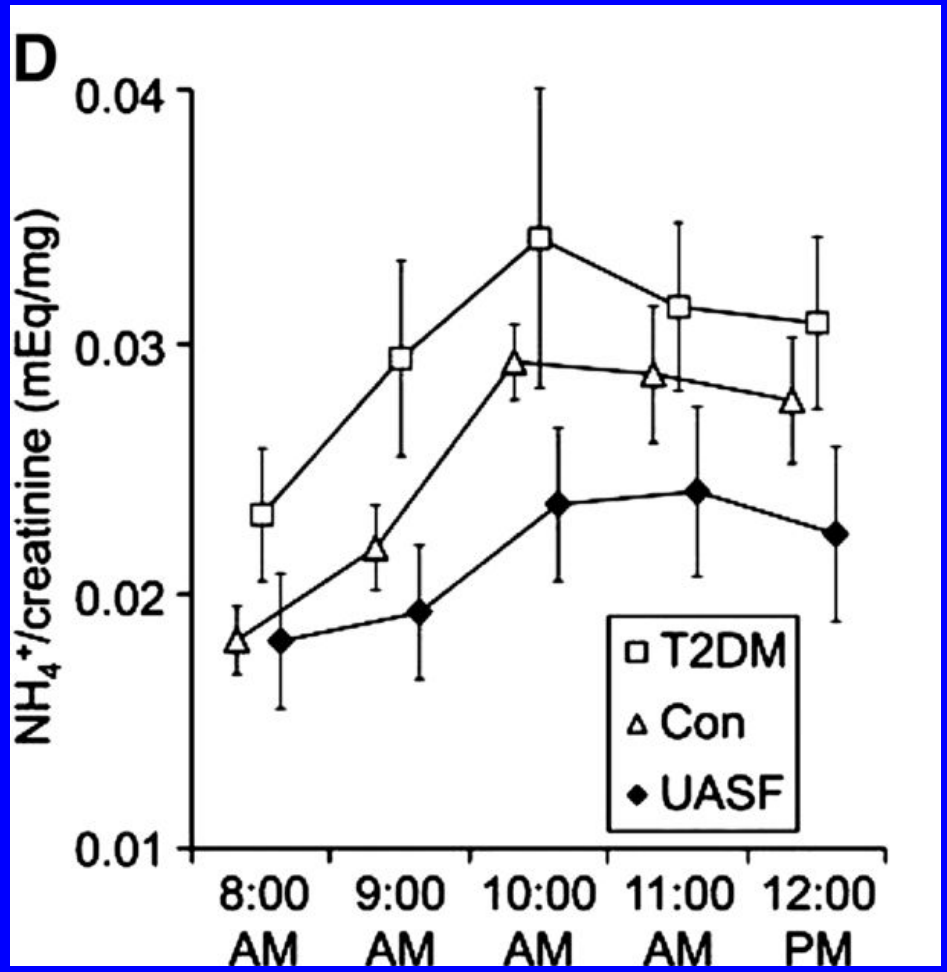
Bobulescu et al. American Journal of Physiology, 305:1498, 2013.

Response to Acid Load



Bobulescu et al. American Journal of Physiology, 305:1498, 2013.

Response to Acid Load



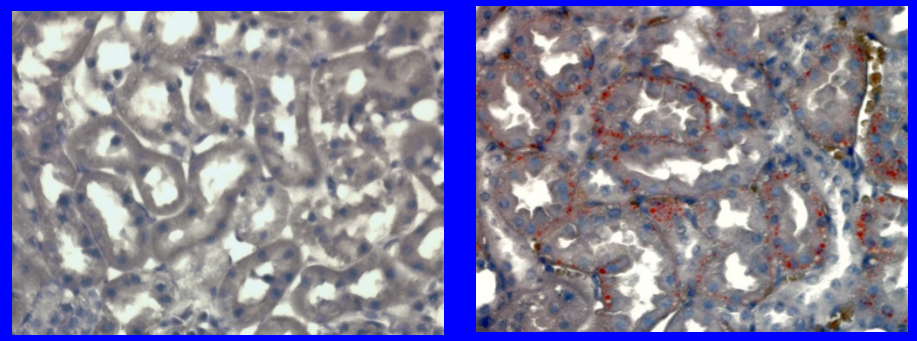
Bobulescu et al. American Journal of Physiology, 305:1498, 2013.

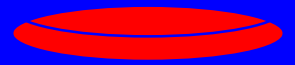
Unknown Source of Increased Net Acid Excretion

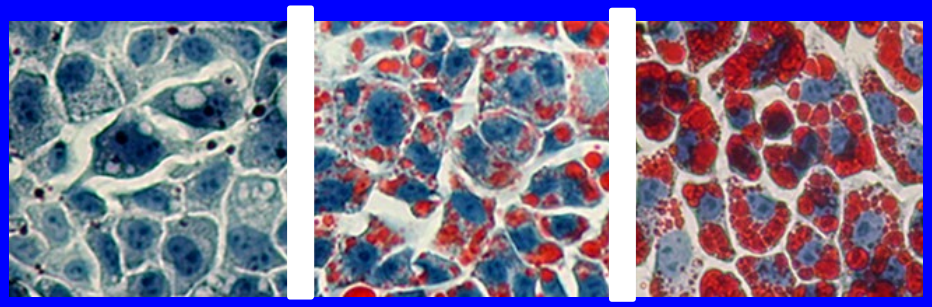
- Uric acid stone formers and matched controls
- Controlled metabolic diet
- + correlation with NAE and BMI both groups
- Uric acid stone formers higher NAE and lower NH_4^+ excretions
- Urinary metabolomics to identify excess organic acids did not account for the higher NAE.

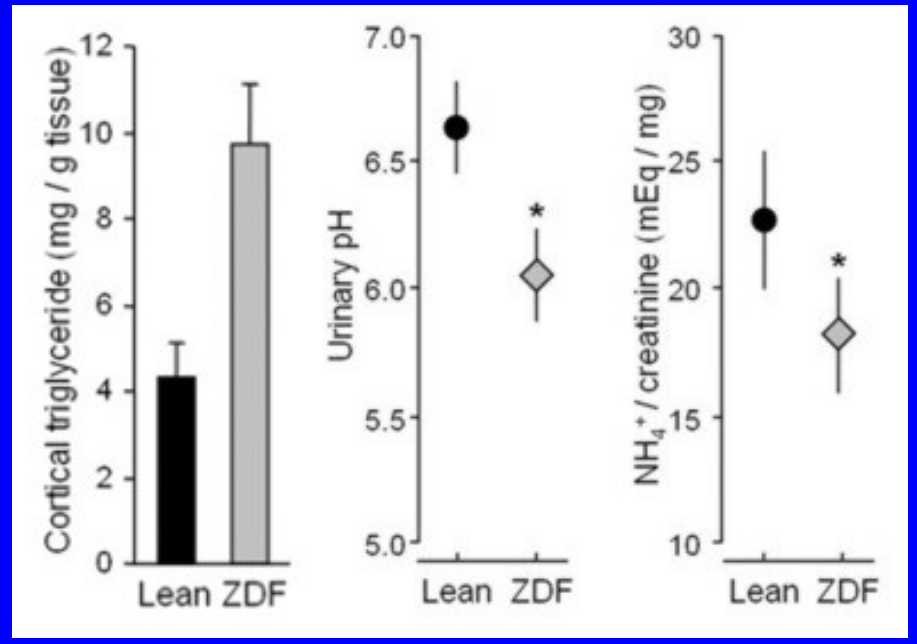
Bobulescu et al. Clinical Journal of American Society of Nephrology, 14:411, 2019

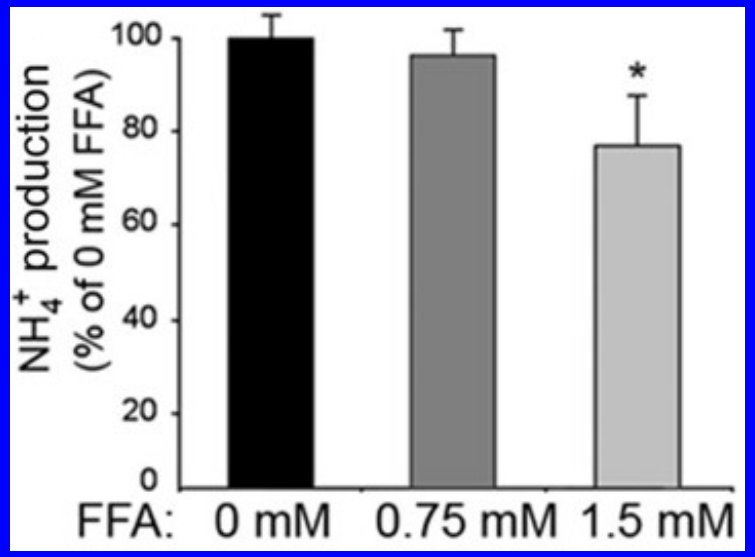
Renal Fat Accumulation and Ammoniagenesis











Bobulescu et al. American Journal of Physiology, 294:315, 2008.

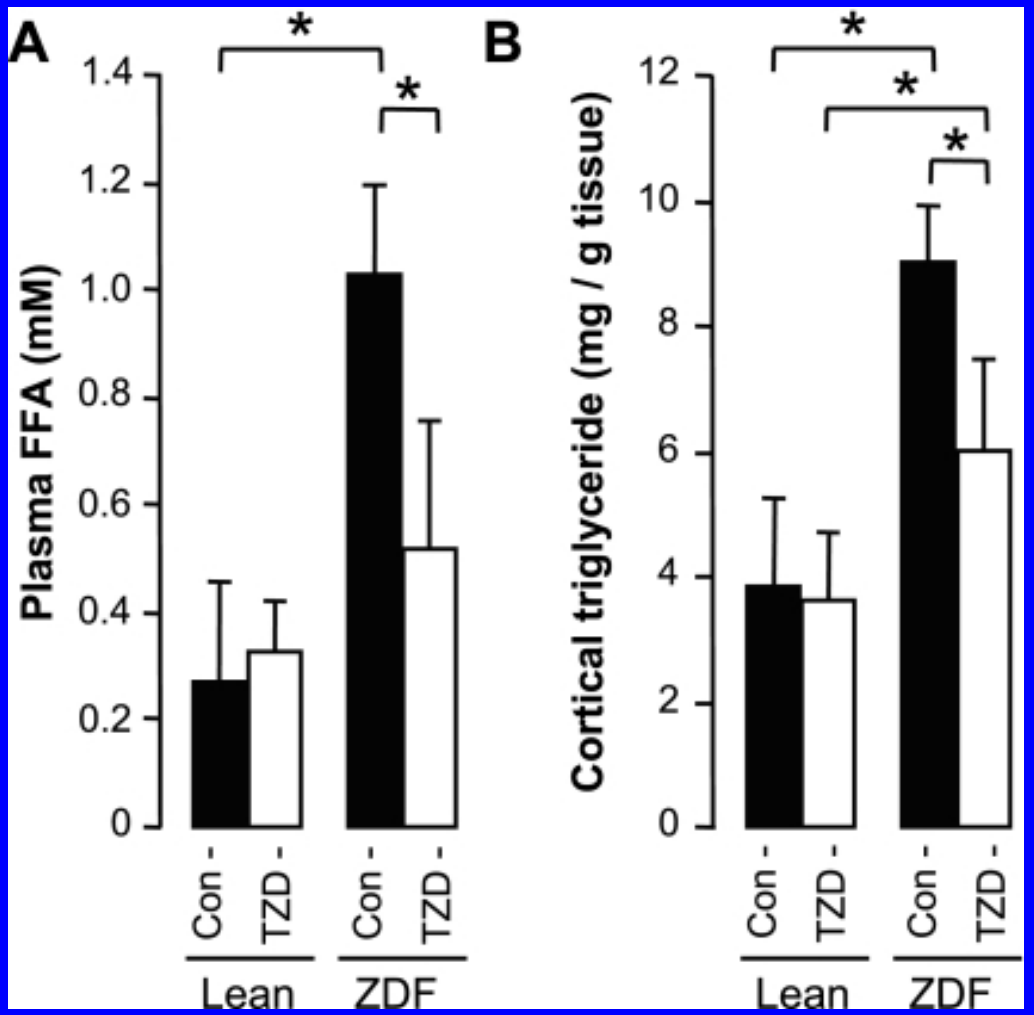
Body Fat Content

- Urine pH and supersaturation of uric acid are more closely correlated to total body fat and truncal fat than lean mass or body weight. (DEXA)
- Visceral fat negative correlation with urine pH (CT)
- Hepatic steatosis associated with low urine pH.

Pigna et al. Clinical JSAN, 9:159, 2014.
Patel et al. Journal of Urology, 198:1085, 2017.

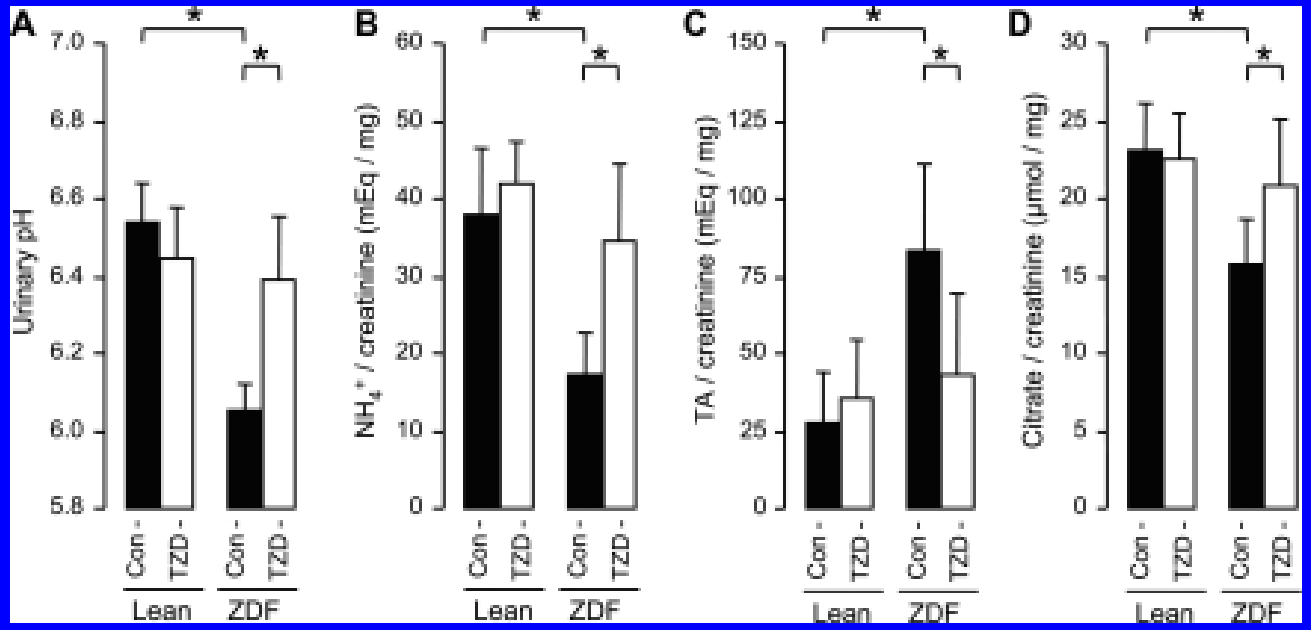
Thiazolidinedione

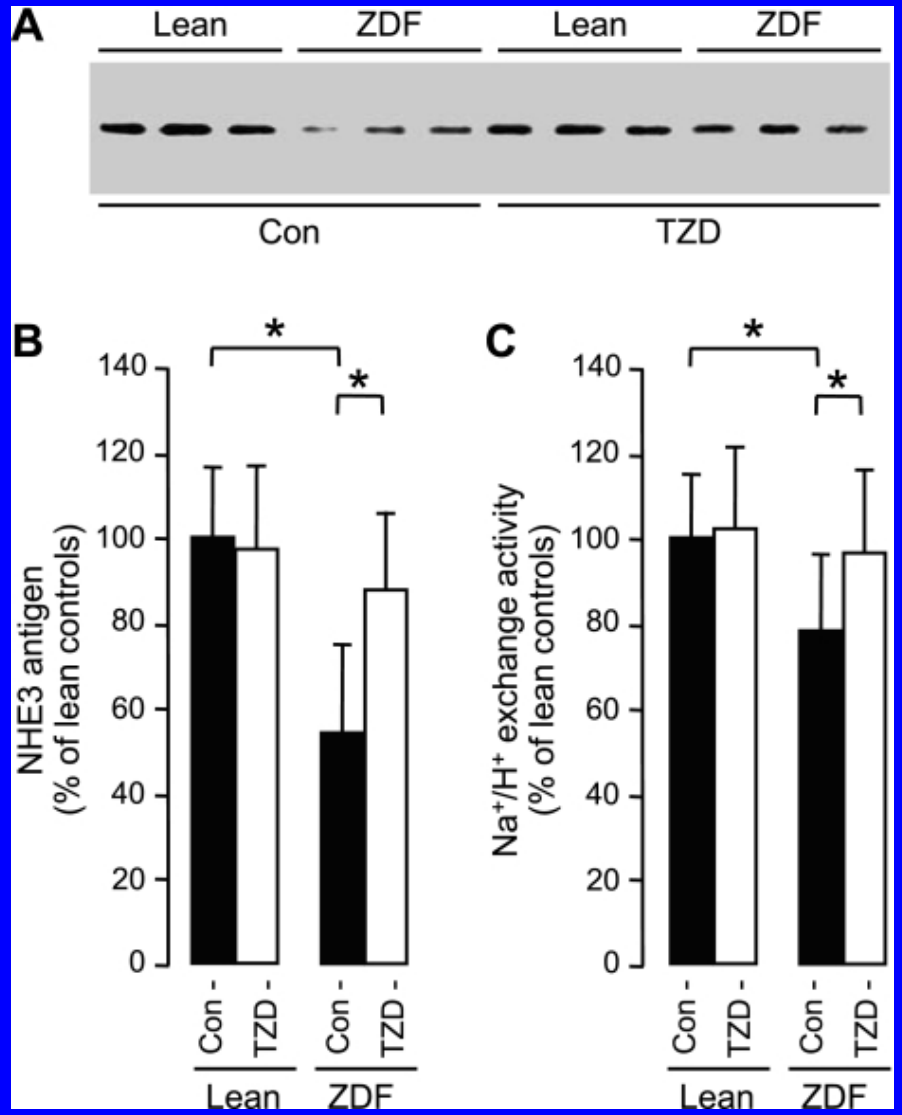
- Agonists of nuclear transcription factor peroxisome proliferator –activated gamma receptor (PPAR)
- Reduce insulin resistance
- Promote fatty acid uptake in adipose tissue
- Attenuate the release of adipokines
- Decrease fat accumulation in organs (liver, heart, skeletal muscle)

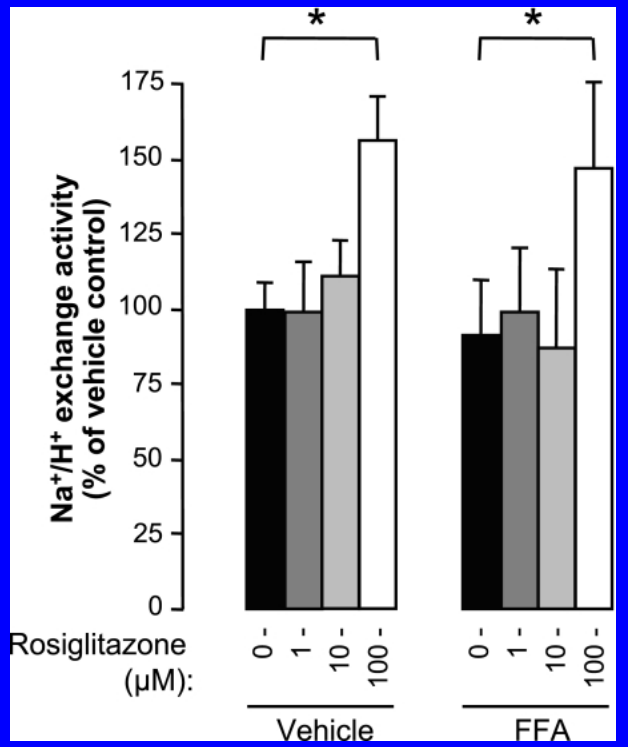


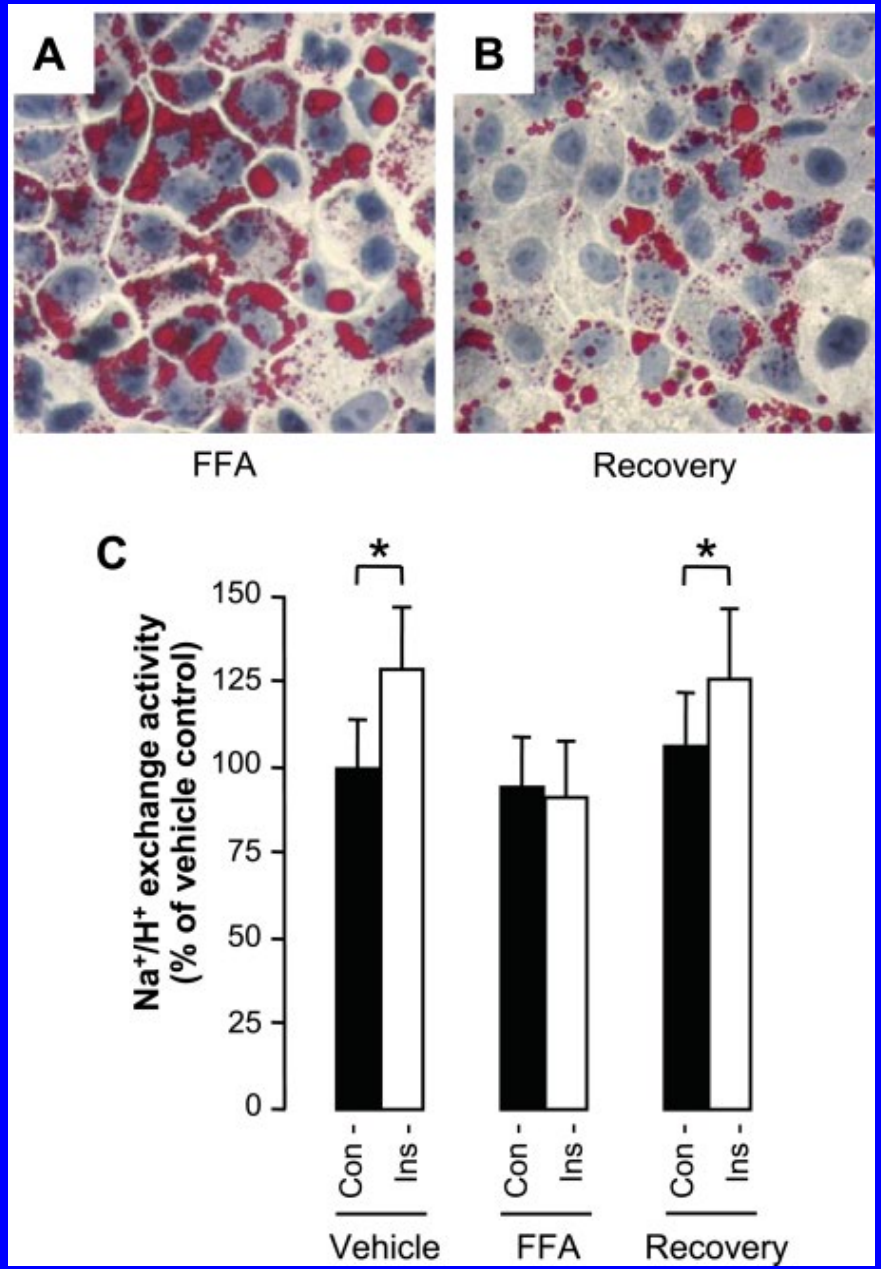
Rosiglitazone

Bobulescu et al. American Journal of Physiology, 297:1419, 2009.


A
Urinary pH
7.0
6.8
6.6
6.4
6.2
6.0
5.8
Con -
TZD -
Con -
TZD -
Lean
ZDF
B
NH4+ / creatinine (mEq / mg)
60
50
40
30
20
10
0
C
TA / creatinine (mEq / mg)
150
125
100
75
50
25
0
D
Citrate / creatinine (µmol / mg)
30
25
20
15
10
5
0


A
Lean
ZDF
Lean
ZDF
Con
TZD
B
NHE3 antigen
(% of lean controls)
140
120
100
80
60
40
20
0
*
*
Con -
TZD -
Con -
TZD -
Lean
ZDF
C
Na+/H+ exchange activity
(% of lean controls)
140
120
100
80
60
40
20
0
*
*
Con -
TZD -
Con -
TZD -
Lean
ZDF

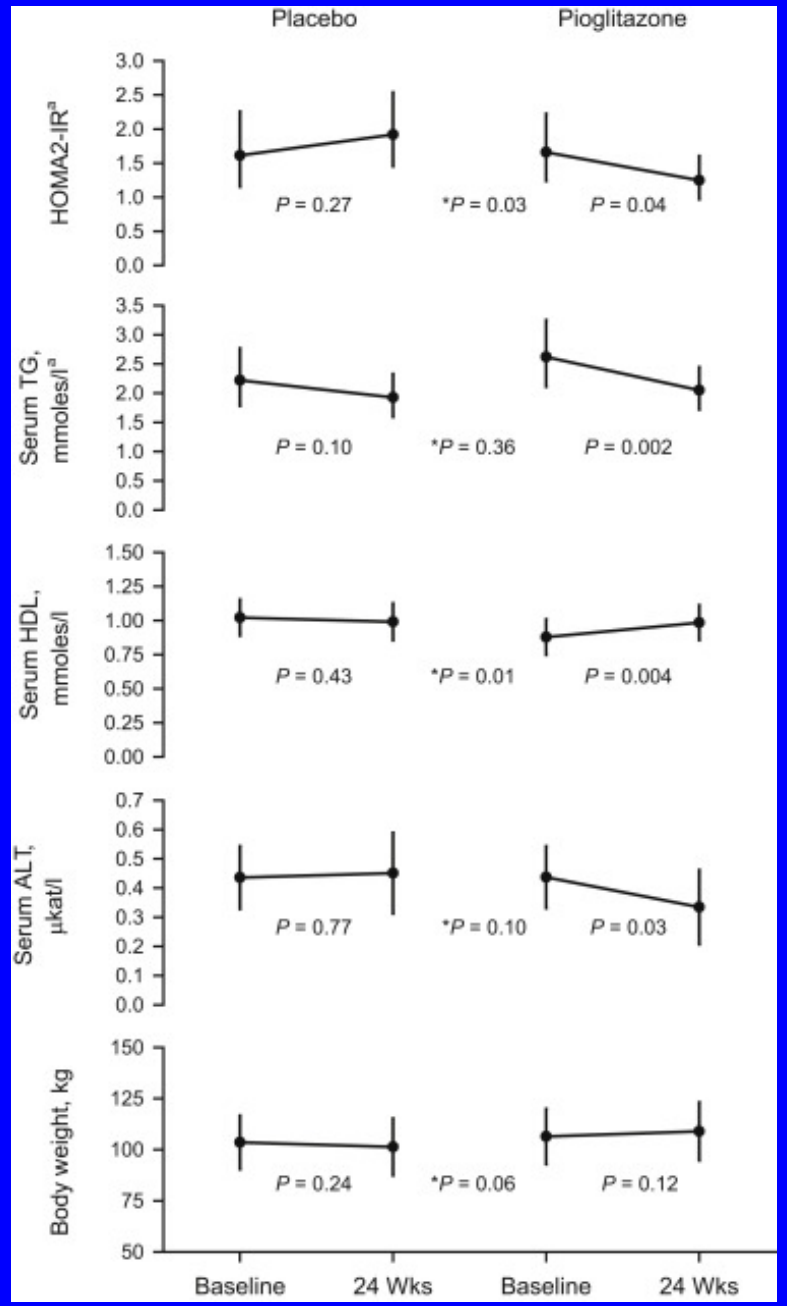

*
*
175
150
125
100
75
50
25
0
Na+/H+ exchange activity
(% of vehicle control)
Rosiglitazone
(μM):
0
1
10
100
0
1
10
100
Vehicle
FFA

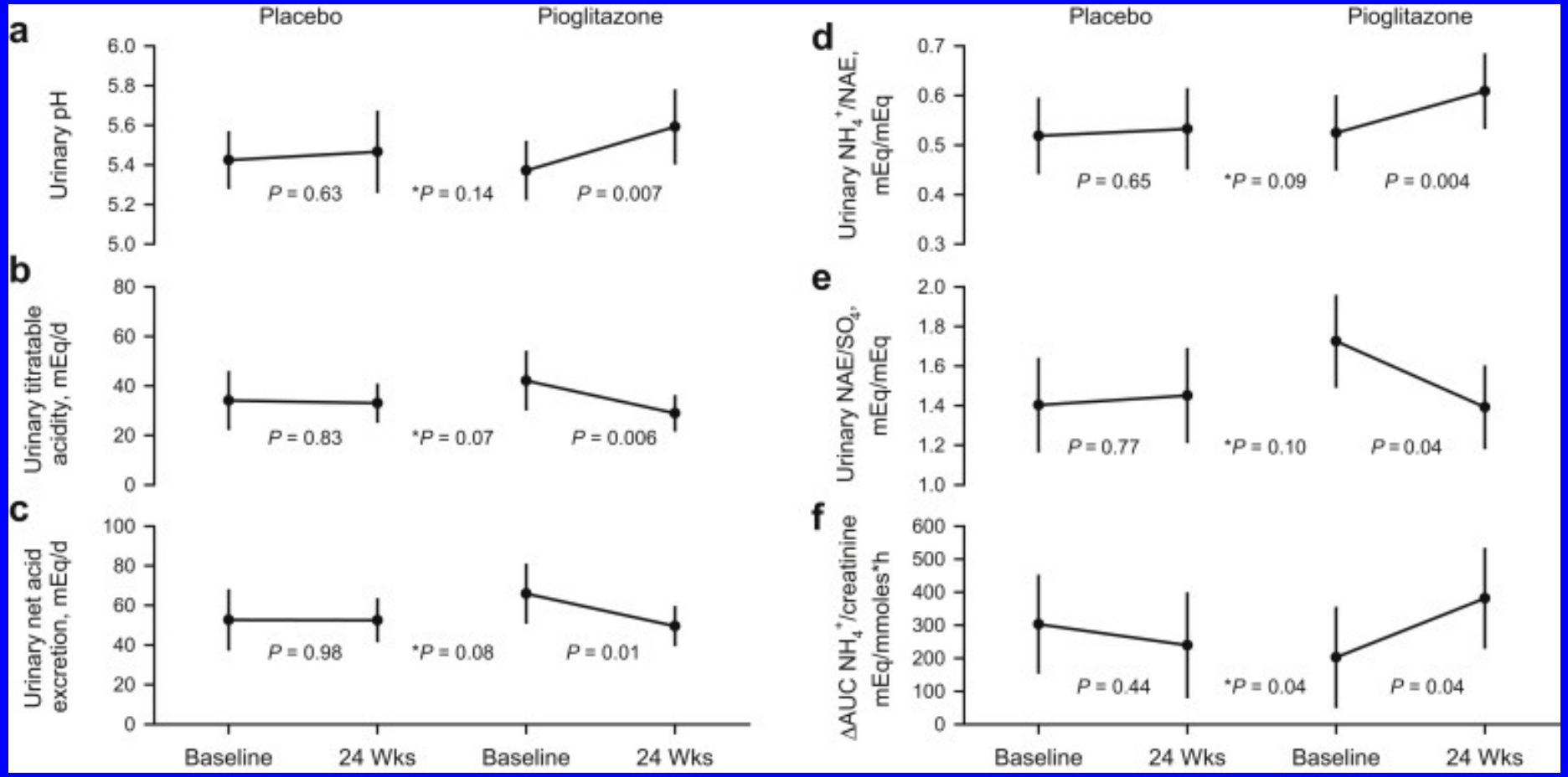

A
B
FFA
Recovery
C
*
*
150
125
100
75
50
25
0
Na+/H+ exchange activity
(% of vehicle control)
Con -
Ins -
Con -
Ins -
Con -
Ins -
Vehicle
FFA
Recovery

Pioglitazone

- Thiazolidinediones (TZD)
- Reverses insulin resistance
- Decrease fat load within the liver, kidney, heart and skeletal muscle
- Clinical trial
- Uric acid stone formers administered agent versus placebo for 24 weeks
- Assessed metabolic responses on controlled diet.

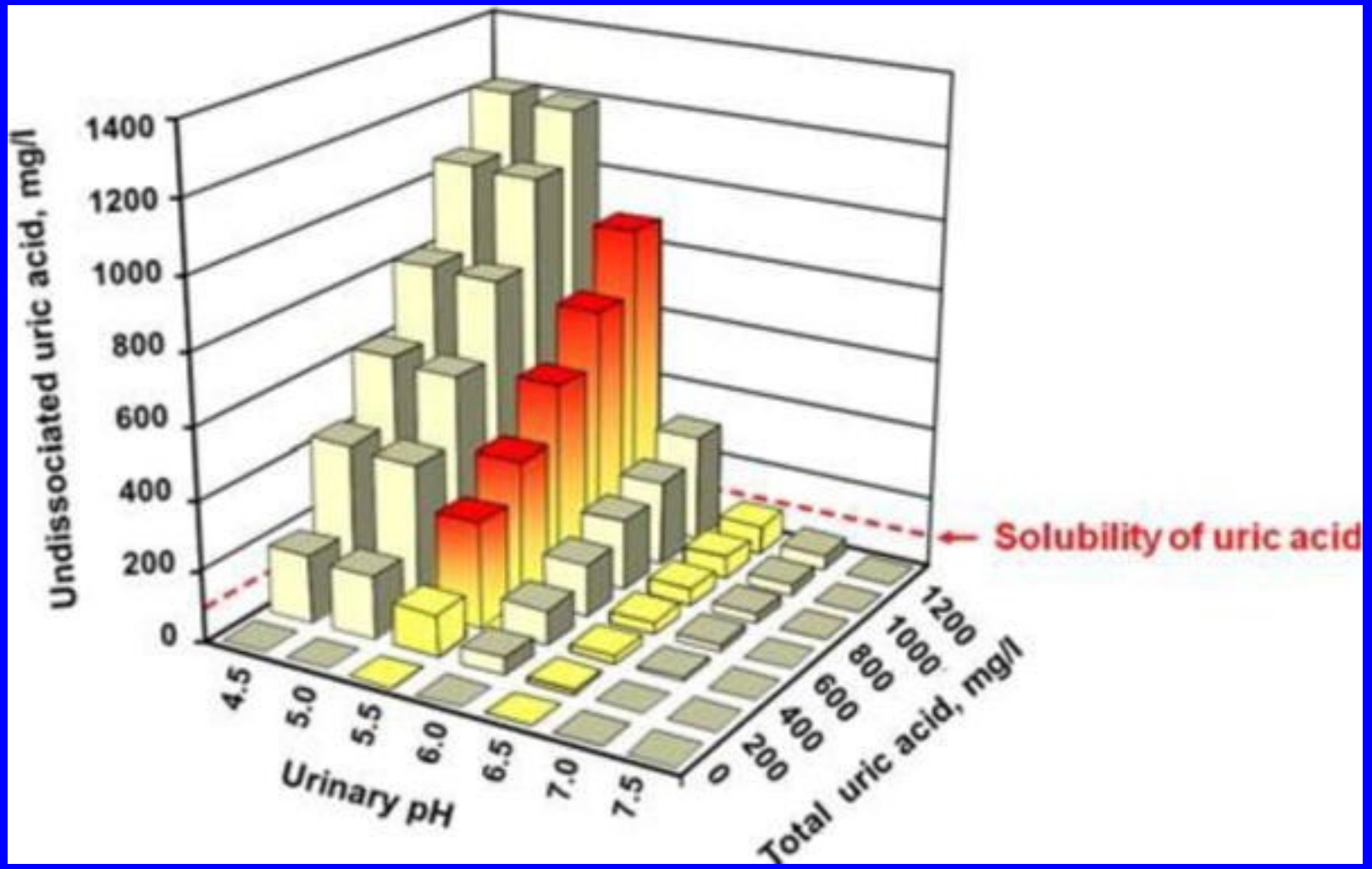
Maalouf et al. Kidney International, 95:1262, 2019.


Placebo
Pioglitazone
HOMA2-IR[a]
3.0
2.5
2.0
1.5
1.0
0.5
0.0
P = 0.27
*P = 0.03
P = 0.04
Serum TG, mmoles/l[a]
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
P = 0.10
*P = 0.36
P = 0.002
Serum HDL, mmoles/l
1.50
1.25
1.00
0.75
0.50
0.25
0.00
P = 0.43
*P = 0.01
P = 0.004
Serum ALT, µkat/l
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
P = 0.77
*P = 0.10
P = 0.03
Body weight, kg
150
125
100
75
50
P = 0.24
*P = 0.06
P = 0.12
Baseline
24 Wks
Baseline
24 Wks


a
Placebo
Pioglitazone
Urinary pH
6.0
5.8
5.6
5.4
5.2
5.0
P = 0.63
*P = 0.14
P = 0.007
b
Urinary titratable acidity, mEq/d
80
60
40
20
0
P = 0.83
*P = 0.07
P = 0.006
c
Urinary net acid excretion, mEq/d
100
80
60
40
20
0
P = 0.98
*P = 0.08
P = 0.01
Baseline
24 Wks
Baseline
24 Wks
d
Placebo
Pioglitazone
Urinary NH4+/NAE, mEq/mEq
0.7
0.6
0.5
0.4
0.3
P = 0.65
*P = 0.09
P = 0.004
e
Urinary NAE/SO4, mEq/mEq
2.0
1.8
1.6
1.4
1.2
1.0
P = 0.77
*P = 0.10
P = 0.04
f
ΔAUC NH4+/creatinine mEq/mmoles*h
600
500
400
300
200
100
0
P = 0.44
*P = 0.04
P = 0.04
Baseline
24 Wks
Baseline
24 Wks

Guidelines Statements
Uric Acid Stones

- High fluid intake to achieve a urine volume of at least 2.5 liters.
- Limit non-dairy animal protein intake.
- Potassium citrate to raise urine pH

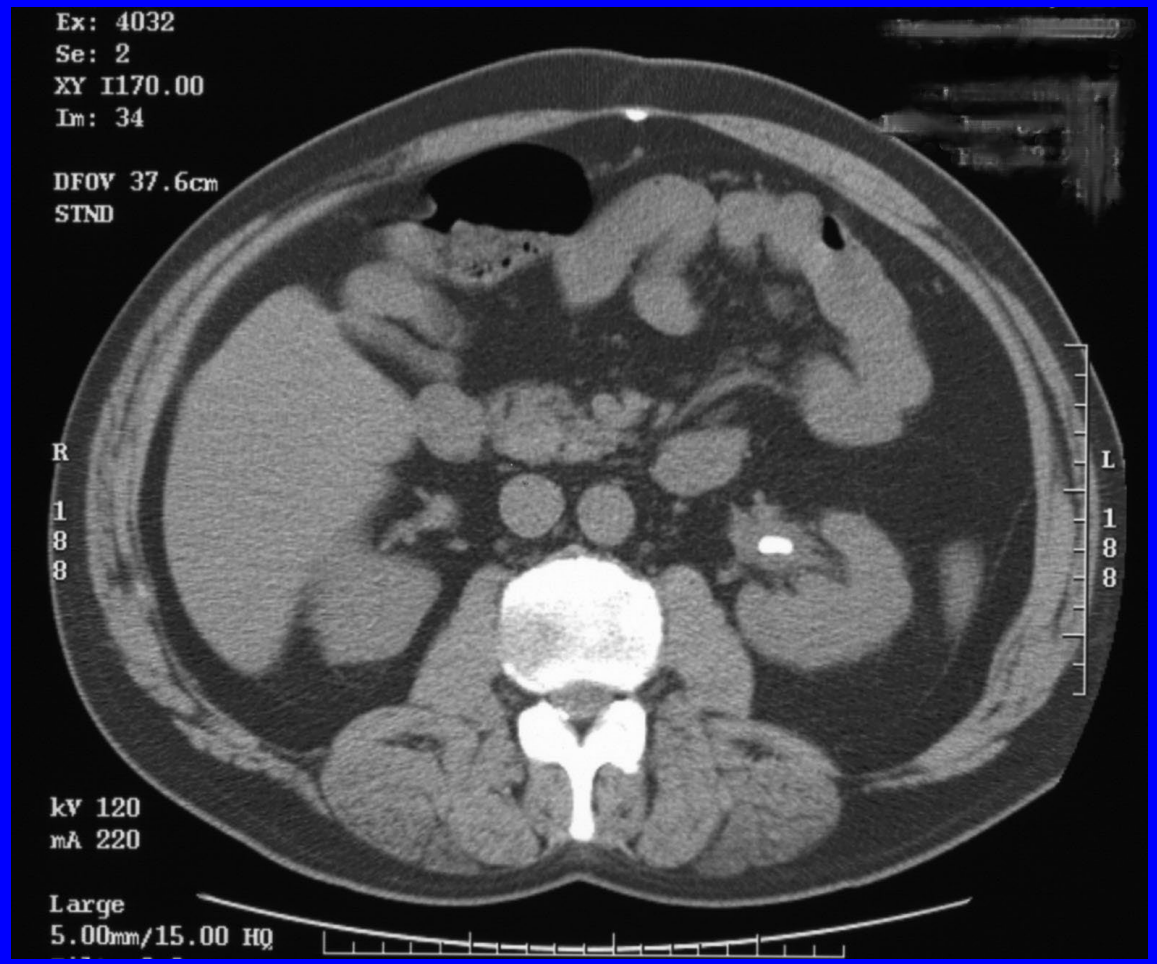


Maalouf et a. Current Opinions in Nephrology and Hypertension, 13:181, 2004.

Other Options

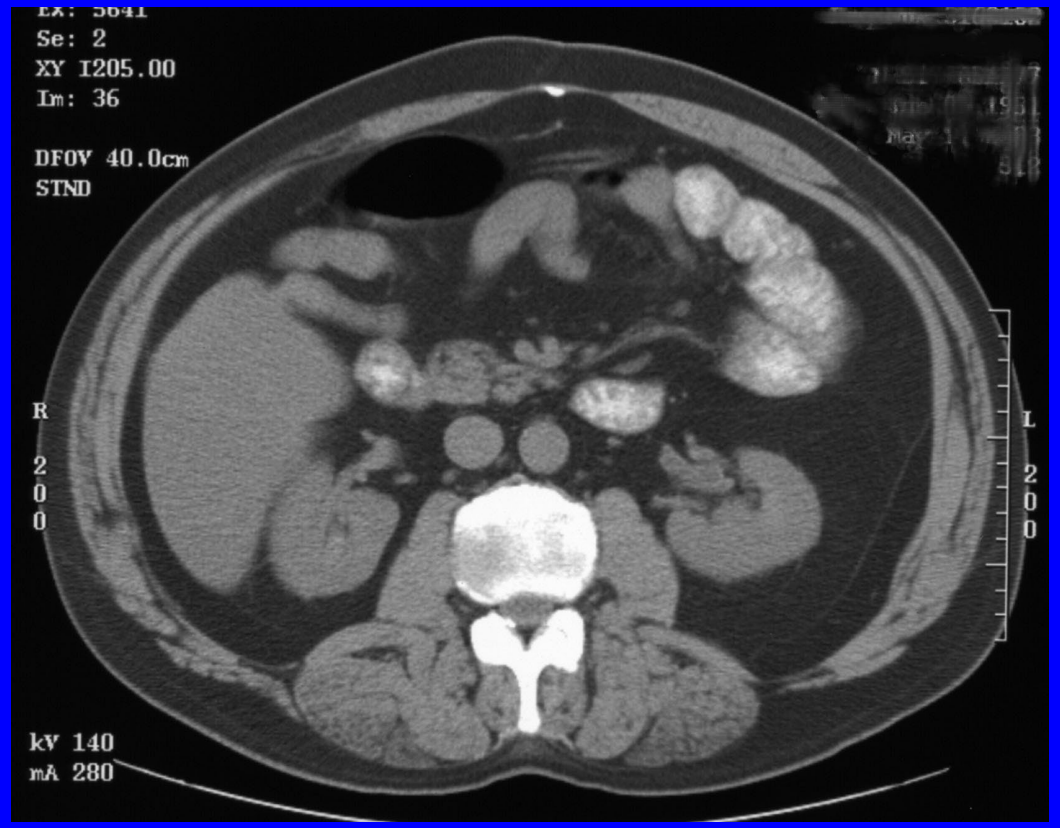
- Sodium bicarbonate
- Sodium citrate
- Potassium bicarbonate
- Pioglitazone (Actos) ????

52 year old ♀
Left flank pain
Type 2 diabetes
Urine pH 5
Stone attenuation 350 HU



Potassium citrate 20 mEq bid
pH 6.5-7.0

CT in 6 weeks later



Other Considerations

- Weight loss
  - Diet
  - Exercise