Vitamins & kidney

Sepideh Hajian,MD

Gazvin university of medical sciences

Introduction

- ✓Complementary and alternative medicine (CAM) is widely practiced all over the world & one of the commonest are multivitamins.
- ✓They are considered by the US Food and Drug Administration (FDA) as a “food” and not as “pharmaceutical drugs”, hence manufacturers do not require FDA approval before marketing.

✓Kalra EK Nutraceutical – definition and introduction. AAPS PharmSci. 2003; 5: E25. [PMC free article] [PubMed] [Google Scholar] [Ref list]

Introduction

- ✓The various label claims associated with these products have a variable level of regulation .While dietary supplements are advertised and consumed with the promise of providing significant health benefits without side effects, evidence suggests minimal benefits and potential harm to human health
- ✓In addition to damage to other organs ,a diverse range of nephrotoxicities have been reported with dietary supplements Despite these safety concerns, a significant number of patients do not report dietary supplement use, and physicians often do not inquire about them.

- ✓ **Trivedi R Salvo MC Utilization and Safety of Common Over-the-Counter Dietary/Nutritional Supplements, Herbal Agents, and Homeopathic Compounds for Disease Prevention. Med Clin North Am. 2016; 100: 1089–1099.**
- ✓ **Guallar E Stranges S Mulrow C Appel LJ Miller ER Enough is enough: Stop wasting money on vitamin and mineral supplements. Ann Intern Med. 2013; 159: 850–851.**

Nephrotoxicity

- ✓Acute tubolointerstitial nephritis(ATIN)
- ✓Chronic tubolointerstitial nephritis(CTIN) =CKD
- ✓Glomerulonephritis(FSGS,…)
- ✓Interstitial fibrosis
- ✓Tubolar atrophy

Prevalence and trends in dietary supplement use among US adults with diabetes: the National Health and Nutrition Examination Surveys, 1999–2014

Jing Li1, Xinli Li2, Wambui Gathirua-Mwangi3, http://orcid.org/0000-0002-2097-7332Yiqing Song4

PREVALANCE OF MULTIVITAMIN USE

- ✓Overall, the prevalence of any supplement use (52%–58%; P for trend=0.08) and that of any mineral use (47%–51%; P for trend=0.23) seemed stable over the years studied.
- ✓Reported use of MVMM slightly decreased from 36% to 32% (P for trend=0.006). Use of any vitamin products significantly increased from 47% to 52% (P for trend=0.03). Use of some individual supplements, especially vitamin D, choline, lycopene, and fish oil supplements, significantly increased, while some vitamins, minerals and NVNM supplements decreased over the years.
- ✓In addition, the trend of any supplement use varied by age, sex, race/ethnicity, or education, but not by diabetes duration or diabetic comorbidities.

Medicine (Baltimore)
2022 Jan 28;101(4):e28638. doi: 10.1097/MD.0000000000028638.

Prevalence and characteristics of multivitamin-multimineral (MVMM) use among Saudi populations in Riyadh, Saudi Arabia: A cross-sectional study

Saleh I Alwalan 1, Abdullah A Alrasheed 2, Khaled K Aldossari 3, Jamaan M Al-Zahrani 3, Abdullah Mohammed Alshahrani 4, Mohammed A Batais 2, Turky H Almigbal 2

A cross-sectional study was conducted at 6 shopping malls located in the different regions of Riyadh city for 6 months from February 01, 2019, to July 31, 2019.

A P value of ≤.05 and 95% confidence intervals were used to report the statistical significance.Out of 1200 surveys distributed, 1105 were returned by the participants (response rate 92%). **Prevalence of MVMM supplements use turned out to be 47%.** The study revealed statistically significant association between MVMM use and gender, marital status, education, regular exercise, smoking, following special diet, and eating fruits and vegetables (P ≤ .05). Majority of the participants used MVMM on daily basis (57.9%), and hospital prescriptions (57.9%) were the most common reason of MVMM use.

Majority of the participants used MVMM for **diet supplements (32.2%), health promotion (29.4%), and treatment of disease (16%).**The MVMM use is prevalent in Saudi population, warranting sound regulatory policies for their judicial use and increase awareness about the benefits and side effects of dietary supplements.


Vitamin A

the recommended dietary allowances for vitamin A are:

14 to 18 years **14 to 18 years/breastfeeding**	**900 mcg for males, 700 mcg for females**
14 to 18 years/pregnant females	750 mcg female,900 mcg for males
19+ years	1,200 mcg
19+ years/pregnant	900 for males, 700 for females
19+ years/breast-feeding	770 Mcg
	1300 Mcg

Potential complications of hypervitaminos A

- ✓Potential complications of excess vitamin A include:
- ✓liver damage
- ✓osteoporosis (a condition causing bones to become brittle, weak, and prone to breaks)
- ✓excessive calcium buildup in your body
- ✓kidney damage due to excess calcium

vitamin A toxicity

✓Acute toxicity:

The most common cause of acute vitamin A toxicity is the ingestion (generally accidental) of over 300,000 IU of vitamin A.

✓Chronic toxicity:

The most common cause of chronic vitamin A toxicity is the regular ingestion of over 100,000 IU daily, which is sometimes prescribed for dermatological conditions such as acne.

Br Med J (Clin Res Ed). 1981 Jun 20; 282(6281): 1999–2002.
doi: 10.1136/bmj.282.6281.1999
Vitamin A toxicity and hypercalcaemia in chronic renal failure.
K Farrington, P Miller, Z Varghese, R A Baillod, and J F Moorhead

VITAMIN A IN CKD & ESRD

- ✓Patients taking vitamin A supplements had significantly higher vitamin A concentrations than those not taking them (p less than 0.05), and hypercalcaemic patients had higher concentrations than normocalcaemic patients (p less than 0.005). Withdrawal of vitamin A supplements in seven patients caused significant falls in serum vitamin A concentrations and plasma calcium concentrations (p less than 0.01 at two and three months in both cases) and in **plasma alkaline phosphatase** concentrations (p less than 0.01 at two months).
- ✓Vitamin A toxicity can contribute to hypercalcaemia in patients undergoing haemodialysis, **probably by an osteolytic effect**. Multivitamin preparations containing vitamin A should therefore be prescribed with caution in these patients.

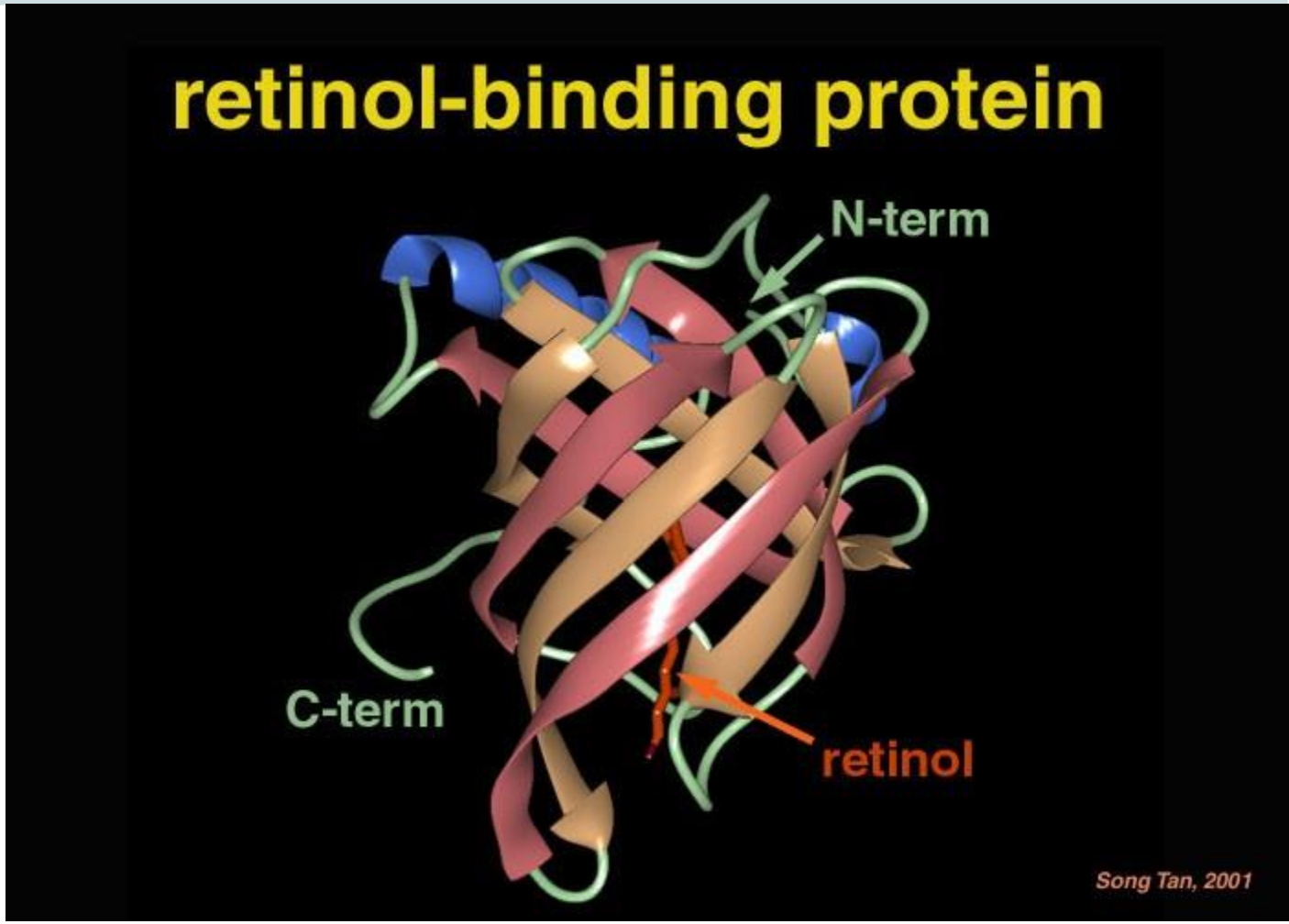
Hypervitaminosis A symptoms in Advanced Chronic Renal Failure

anorexia
nausea
vomiting
skin dryness
headache
pruritus
muscle fasciculation
peripheral Paraesthesias
bleeding
and bone changes

are common in severe uraemia

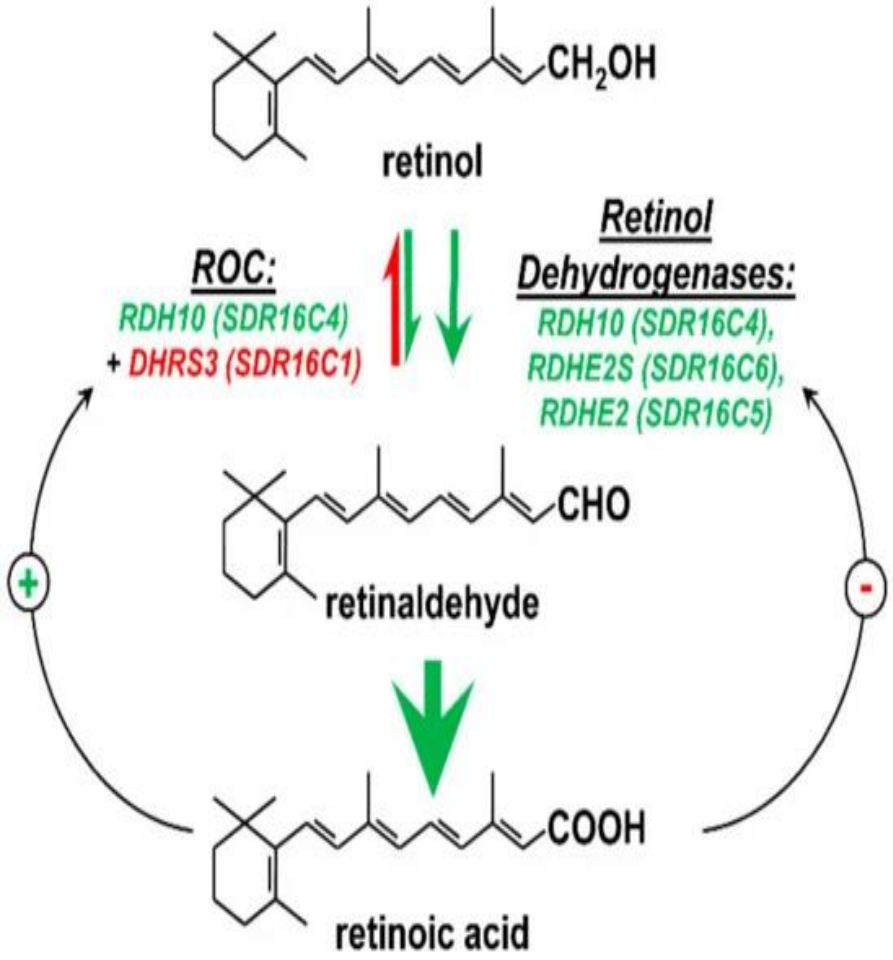
For significant increase of serum vitamin A in patients with advanced chronic renal failure there are two hypotheses:

(a) the increase may result from a previous rise in serum **Retinol-Binding Protein**. The simultaneous increase of serum vitamin A and retinol binding protein noted in patients suffering from renal disease supports this possibility.



For significant increase of serum vitamin A in patients with advanced chronic renal failure there are two hypotheses:

(b) The increase may be due to reduced excretion. Vitamin A is stored as **Retinol Palmitate** in the liver, from which it is liberated to maintain a normal level in the blood. Retinol is excreted in the bile after its transformation to retinoic acid together with glucoronide. **Because retinoic acid seems to be formed in the kidney** the loss of renal tissue may cause a decreased production and, consequently, a reduced excretion of vitamin A derivatives.



What are the implications of this vitamin A accumulation in the patient with advanced renal failure ?

Such accumulation may play a role in the development of renal osteodystrophy.

Two pathogenic mechanisms have been recognized in the development of renal bone disease: **secondary hyperparathyroidism and vitamin D resistance.**

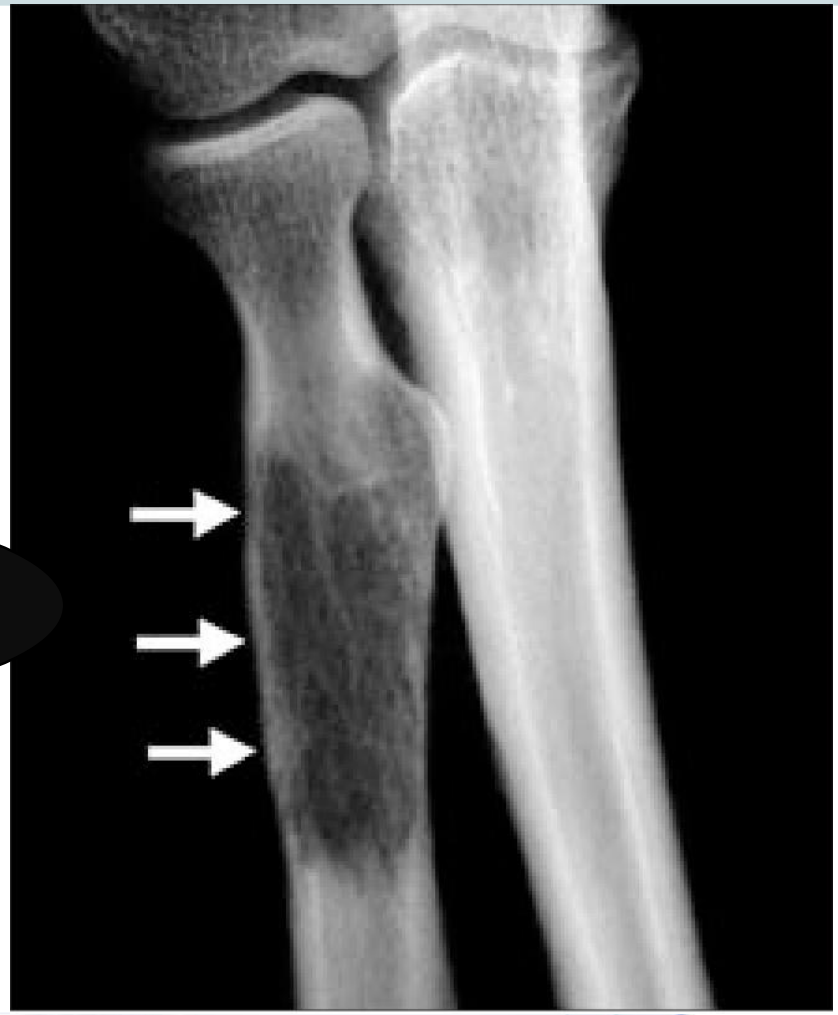
The most frequent lesions in clinical and experimental hypervitaminosis A occur in the bone, which is characterized by increased susceptibility to fractures.

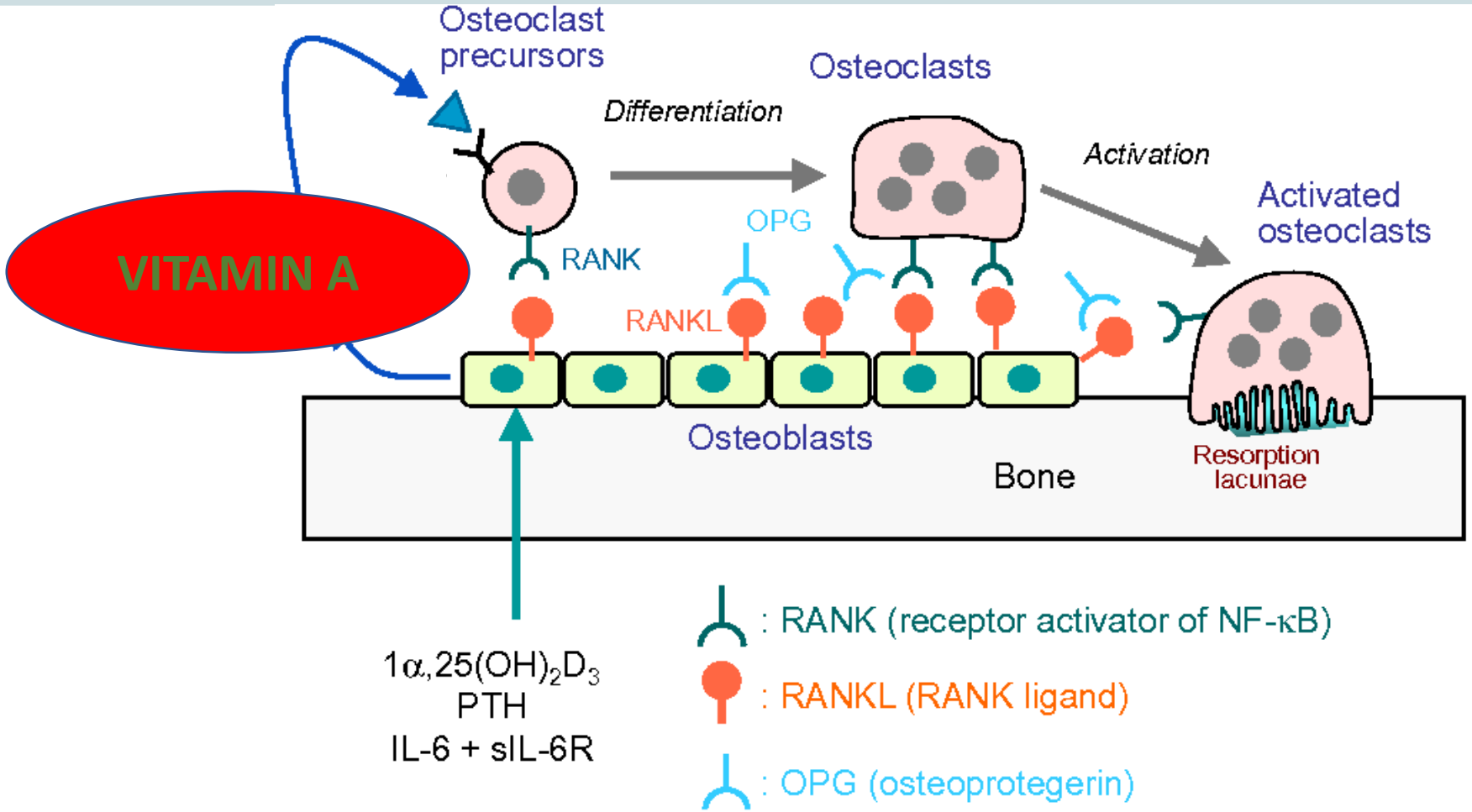
This is probably due to a direct action of vitamin A on the bone tissue leading to enhanced production of **osteoclasts** and increased **bone resorption**.

Alternatively, excess vitamin A may act on the parathyroid tissue, increasing the secretion of parathyroid hormone, perhaps through an interaction with the cell or secretion granule membrane.

OSTEOLYTIC EFFECT OF VITAMIN A

Vitamin A




Osteoclast precursors
Differentiation
Osteoclasts
Activation
Activated osteoclasts
VITAMIN A
RANK
OPG
RANKL
Osteoblasts
Bone
Resorption lacunae
1α,25(OH)2D3
PTH
IL-6 + sIL-6R
: RANK (receptor activator of NF-κB)
: RANKL (RANK ligand)
: OPG (osteoprotegerin)

Clin Nephrol

1979 Aug;12(2):63-8.

Serum vitamin A levels and associated abnormalities in patients on regular dialysis treatment

R Werb, W F Clark, R M Lindsay, E O Jones, A L Linton

Abstract

Serum Vitamin A was measured in 72 patients on RDT. Elevated serum Vitamin A levels (102.29 +/- 26.95 microgram/dl [3.57 +/- 0.94 mumoles/l]) were found in the dialysis population (normal 40.98 +/- 6.71 microgram/dl [1.43 +/- 0.23 mumoles/l]; P less than 0.0005).

Patients taking a VitaminA-containing multivitamin preparation had higher serum Vitamin A levels than those on a non-Vitamin A supplemented diet. **Positive correlations were found with serum levels of calcium, cholesterol and triglycerides.**

Patients receiving a Vitamin A supplement had **higher serum cholesterol levels** than non-supplemented patients.

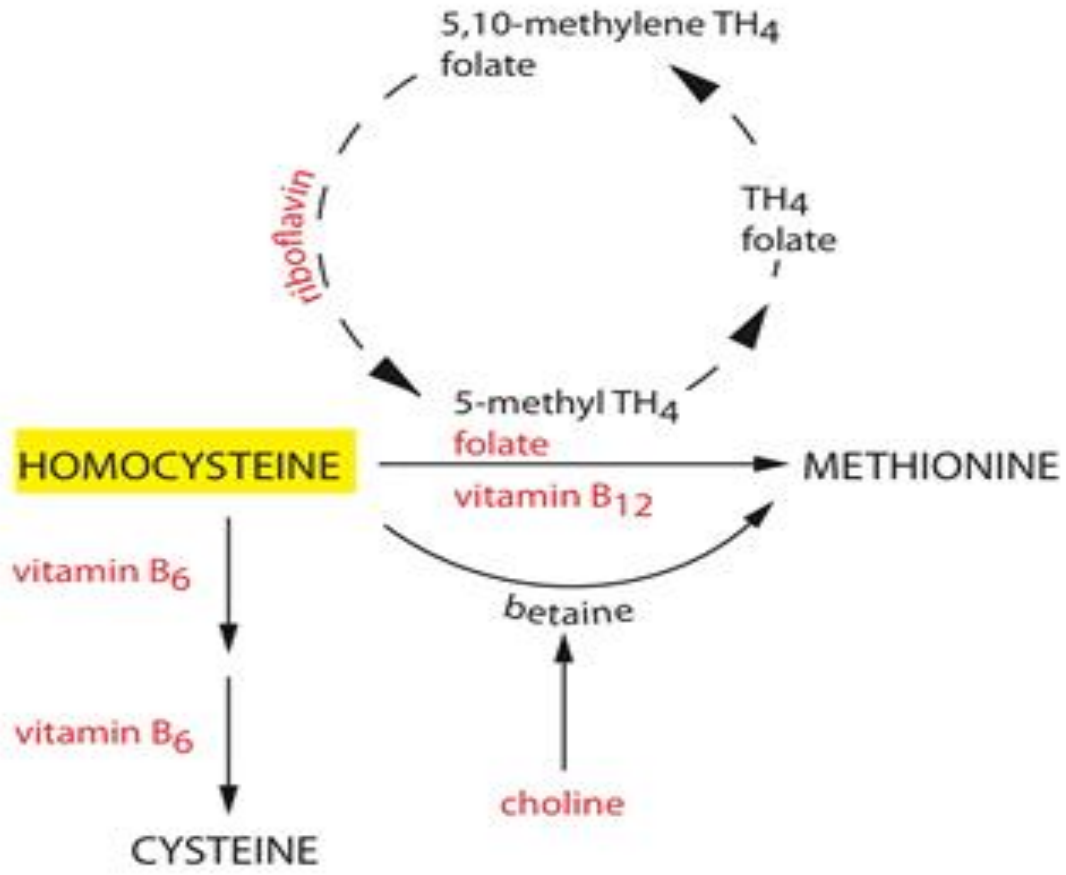
Vitamin A might be a factor in the high incidence of **cardiovascular disease** in RDT patients. We therefore advise discontinuing the long-term administration of Vitamin A-containing multivitamin supplements to patients on RDT.

Vitamin B

Homocysteine hypothesis

- ✓The “homocysteine hypothesis” arises from the observation that subjects with **very high** homocysteine blood levels due to congenital homocysteine metabolism impairment are more susceptible to develop a severe form of **progressing atherosclerosis.**
- ✓ Thus, over the years, research has been conducted into the possible link between an even moderate rise in homocysteine levels and cardiovascular risk and mortality, with conflicting results.

- ✓Homocysteine is a thiol-containing amino acid, not involved in protein synthesis, deriving from methionine metabolism.
- ✓ Plasma levels of homocysteine depend on several factors, such as genetic alteration of methionine metabolism enzymes , B12, vitamin B6 or folic acid.



Homocysteine can be found in reduced and oxidized form in the bloodstream: more than 90% of the total plasma homocysteine is oxidized and bound to proteins, while the remaining oxidized

homocysteine exists as a disulfide form. Only 2% of the total homocysteine in plasma is present as a free reduced form.

Normal homocysteine plasmatic level is <10 mmol/L, concentrations >10; however, levels<16 mmol/L are defined as mild hyperhomocysteinemia, while **severe hyperhomocysteinemia** is diagnosed when homocysteine **>100 mmol/L.**

Vitamin B & homocysteine

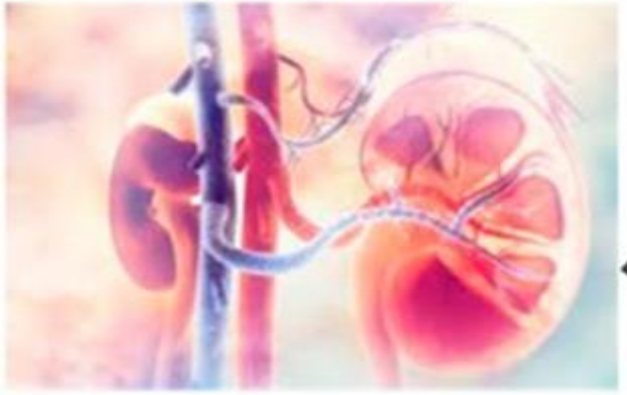
- ✓According to several observational studies there is a significant association between high concentrations of plasma total homocysteine and the risk of developing kidney damage such as diabetic nephropathy
- ✓ B-vitamin therapy (folic acid, vitamin B6, and vitamin B12) has been shown to lower the plasma concentration of homocysteine.

Hyperhomocysteinemia

⇧ Oxidative stress
⇧ Inflammatory status
⇧ Metalloproteinases
⇧ Collagen synthesis
⇧ Smooth muscle cell proliferation
⇧ Foam cells
⇩ NO

Folic acid deficiency

⇧ Oxidative stress
⇧ Superoxide generation
⇩ Myocardial function
⇩ NO
⇩ Endothelial NO synthase



Cardiovascular disease

Progression of Chronic Kidney Disease

- ✓Folic acid is derived from polyglutamates that are converted into monoglutamates in the bowel, and then transported across mucosal epithelia by a specific carrier.

The circulating form of folic acid is **5-methyltetrahydrofolate (5-MTHF).**

- ✓Vitamin B12, ingested with nutrients such as cobalamin, complexes with **salivary haptocorrin**, and is released abruptly from cobalamin by **pancreatic proteases** in the duodenum. Then, cobalamin, binds to an intrinsic factor secreted from the parietal cells of the **stomach**: when this complex arrives at the **distal ileum**, it is endocytosed from the enterocytes through cubilin. Then, cobalamin is carried into the plasma by a plasma transport protein named **transcobalamin** .
- ✓B12 is filtered by the glomerulus; however urine excretion is minimal due to reabsorption in the proximal tubule.

- ✓In target tissues, cobalamin is metabolized into two active forms: adenosylcobalamin in the mitochondria and methylcobalamin in the cytosol.
- ✓ Methylcobalamin is a methyl-transferring cofactor

  to the enzyme methionine synthase allowing homocysteine remethylation to methionine.

Metabolism of homocysteine includes two different pathways: **remethylation** and **transsulfuration**.

In the remethylation pathway, methionine is regenerated through a reaction catalyzed by the enzyme methionine synthase (MTS), requiring folate and vitamin B12 as cofactors.

Given that folate is not biologically active, it necessitates transformation into tetrahydrofolate that is then

converted into methylenetetrahydrofolate (MTHF) by the enzyme methylenetetrahydrofolate reductase(MTHFR).

Hyperhomocysteinemia in renal disease

Homocysteine is minimally eliminated by the kidney, since in physiological conditions, only non-protein bound homocysteine is subjected to glomerular filtration, and then for most part reabsorbed in the tubuli and oxidized to carbon dioxide and sulfate in the kidney cells .

Moreover, in the kidney, homocysteine is above all transsulfurated & remethylation and deficiency of this renal transsulfuration & remethylation contributes to the elevation of plasma homocysteine.

It has been hypothesized that hyperhomocysteinemia

in these patients may be induced by the abnormality of homocysteine metabolism in the kidneys rather than by reduced glomerular filtration rate.

Q J Med 2011; 104:171–172

doi:10.1093/qjmed/hcq120 Advance Access Publication 14 July 2010 Nephrotoxic effects of water-soluble B-vitamin therapy

in diabetic nephropathy?—How true can this be?

- ✓Andrew A. House, M.D., of the University of Western Ontario, and J. David Spence, M.D., of the Robarts Research Institute, London, Ontario, and colleagues conducted a study to examine whether B-vitamin therapy would slow the progression of diabetic nephropathy and prevent vascular events in **238 patients with type 1 or 2 diabetes**.
- ✓Patients received single tablet of B vitamins containing folic acid (2.5 mg/d), vitamin B6 (25 mg/d), and vitamin B12 (1 mg/d), or matching placebo.
- ✓The primary outcome was change in radionuclide glomerular filtration rate (GFR; a measure of kidney function) between baseline and 36 months. Other outcomes included dialysis and a composite of heart attack, stroke, revascularization and all-cause death. Plasma total homocysteine was measured. Participants were followed-up for an average of 31.9 months.

Patients with diabetic nephropathy (kidney disease caused by diabetes) who received high dose B-vitamin therapy experienced a more rapid decline in kidney function and had a higher rate of heart attack and stroke than patients who received placebo.

- ✓Also, participants randomized to **receive B vitamins** had a significantly greater number of cardiovascular and cerebrovascular events, with the **36-month risk of a composite outcome, including heart attack, stroke, revascularization, and all-cause mortality that was double in the B-vitamin group, compared to the placebo group**. There was no difference in requirement of dialysis.
- ✓"Given the recent large-scale clinical trials showing no treatment benefit, and our trial demonstrating harm, it would be prudent to discourage the use of high-dose B vitamins as a homocysteine-lowering strategy outside the framework of properly conducted clinical research," the authors conclude.

Folic Acid and Vitamin B12 Administration in CKD, Why Not?

- ✓Irene Capelli, Giuseppe Cianciolo, Lorenzo Gasperoni, Fulvia Zappulo, Francesco Tondolo,
- ✓Maria Cappuccilli and Gaetano La Manna *
- ✓Department of Experimental Diagnostic and Specialty Medicine (DIMES), Nephrology, Dialysis and Renal
- ✓Transplant Unit, S. Orsola Hospital, University of Bologna, 40138 Bologna, Italy; irene.capelli@gmail.com (I.C.);
- ✓giuseppe.cianciolo@aosp.bo.it (G.C.); lorenzo.gasperoni3@gmail.com (L.G.);
- ✓fulvia.zappulo@studio.unibo.it (F.Z.); francesco.tondolo@studio.unibo.it (F.T.); maria.cappuccilli@unibo.it (M.C.)
- ✓* Correspondence: gaetano.lamanna@unibo.it

- ✓Received: 29 January 2019; Accepted: 11 February 2019; Published: 13 February 2019

Folic acid metabolism is impaired in uremic patients. **Organic and inorganic anions**, whose clearance is reduced in CKD, inhibit the membrane transport of 5-MTHF, thus compromising the incorporation into nucleic acids and proteins. Data suggest that transport of folates is slower in uremia and this implicated that, even with normal plasmatic folate levels, the uptake rate of folates into tissues may be altered .

In fact, serum folate concentration does not represent a reliable measure of tissue folate stores, but rather reflects recent dietary intake of the vitamin. Erythrocyte folate concentration is a better indicator of whole folate status.

Although CKD patients display increased transcobalamin levels, they show an impaired vitamin tissue uptake of B12.

Moreover, in uremic patients a functional vitamin B12 deficiency can be observed because of increased transcobalamin losses in the urine and reduced absorption in the proximal tubule. This can lead to a “paradoxical” increase in cellular homocysteine levels despite normal total B12

On the other hand, potentially overdosage-related vitamin B12 toxicity could result exacerbated in individuals with CKD. Cyanocobalamin, the most commonly used form of B12 supplementation therapy, is indeed metabolized to active methylcobalamin, releasing small amounts of cyanide whose clearance is reduced in CKD .

Under normal conditions, methylcobalamin is required to remove cyanide from the circulation through conversion to cyanocobalamin. However, in CKD patients, the reduced cyanide clearance prevents conversion of cyanocobalamin to the active form and therefore supplementation is less effective.

homocysteine & cardiovascular events in CKD

For CKD and ESRD patients, in spite of the increased homocysteine levels (average homocysteine level in the general population about 10–15 mmol/L versus 25–35 mmol/L in uremic patients), the role of homocysteine as a cardiovascular and mortality risk factor is still uncertain and many retrospective and interventional studies resulted in conflicting evidences.

The prospective studies included in the meta-analysis showed that in unsupplemented patients with ESRD, an increase of 5 mmol/L in homocysteine concentration is associated with an increase of 7% in the risk of total mortality and an increase of 9% in the risk of cardiovascular events.

Conversely, in a prospective cohort of 341 hemodialysis patients, we previously failed to demonstrate a relationship between baseline homocysteine as well as MTHFR polymorphisms and mortality.

Reverse Epidemiology

An inverse correlation between homocysteine levels and cardiovascular outcomes in **and in hemodialysis patients has also been documented, configuring the phenomenon known as“reverse epidemiology” that also involves other cardiovascular risk factors, including Body Mass Index(BMI), serum cholesterol and blood pressure .**

Specifically, two studies showed that patients with Very low homocysteine plasma levels had worse outcomes, as confirmed by a higher incidence of hospitalization and mortality.

These data call into question the reliability of homocysteine as a marker of cardiovascular risk and mortality in patients with CKD and ESRD, raising the suspicion that other mechanisms beyond elevated homocysteine levels might be implicated. Given that DNA methyltransferases are among the main targets of hyperhomocysteinemia, it has been hypothesized that epigenetic alterations could playa role in hyperhomocysteinemia-mediated tissue damage.

Vitamin c

POSITIVE EFFECT OF VIT C

- ✓Ingestion of vitamin C is generally regarded as harmless. Vitamin C serves to protect host cells from oxidative damage during the inflammatory response through its role as an antioxidant ,it preserves other endogenous antioxidants, including lipid soluble vitamin E and glutathione, and it has been shown to contribute to bactericidal activity via augmentation of T-cell and neutrophil function .
- ✓As plasma vitamin C is quickly depleted during severe inflammatory states, vitamin C has emerged as a possible adjuvant therapy in sepsis

HYPEROXALURIA

Vitamin C is a precursor of oxalate, liable to **produce hyperoxaluria** .

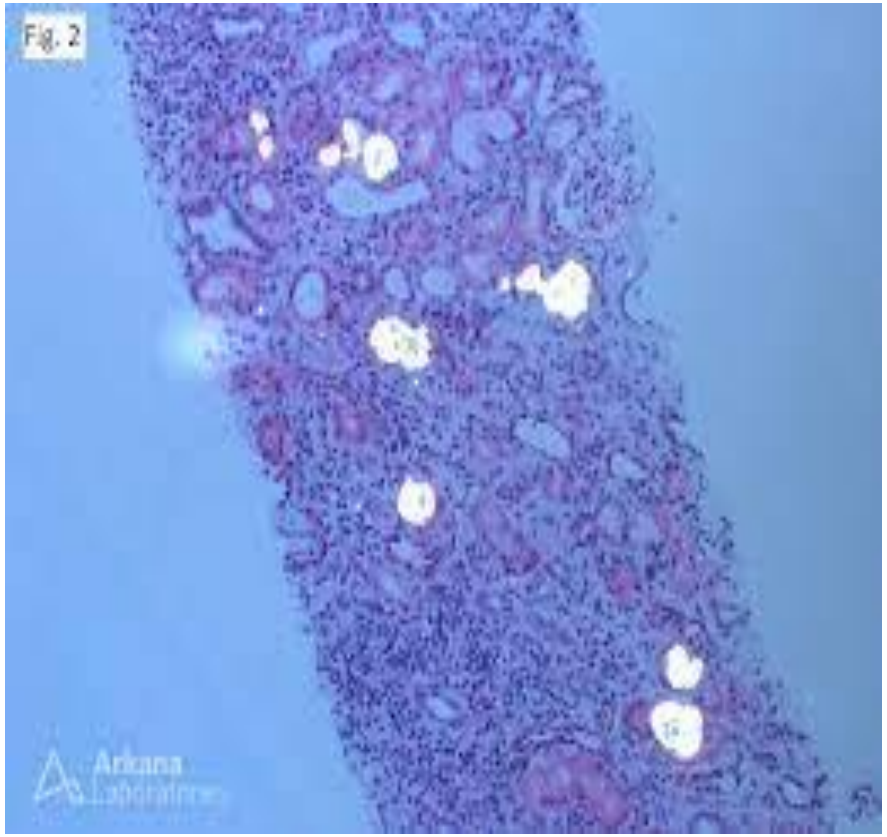
Oxalate nephropathy is an infrequent condition and is characterized by oxalate deposition in the renal tubules, in some cases resulting in acute kidney injury.

It can be caused by overproduction of oxalate in genetic disorders and, more frequently, as a secondary phenomenon provoked by ingestion of oxalate or substances that can be transformed into oxalate in the patient.

It can also **increase oxalate absorption**, further accentuating the hyperoxaluria & is a risk factors predispose to nephrolithiasis and progressive renal failure.

characteristic finding on kidney biopsy

presence of acute tubular injury associated with polarizable crystals in the tubular lumen and epithelial cytoplasm.



BMC Nephrol

2021 Nov 20;22(1):387. doi: 10.1186/s12882-021-02599-1.

High dose intravenous vitamin C treatment in Sepsis: associations with acute kidney injury and mortality

Thomas R McCune, Angela J Toepp, Brynn E Sheehan, Muhammad Shaheer K Sherani, Stephen T Petr, Sunita

- ✓Methods: Electronic medical records of 1390 patients n a retrospective **cohort** study from an academic hospital who were categorized as Treatment (received at least one dose of 1.5 g IV vitamin C, n = 212) or Comparison (received no, or less than **1.5 g IV vitamin C**, n = 1178) were reviewed. Propensity score matching was conducted to balance a number of covariates between groups. Multivariate logistic regressions were conducted predicting AKI and in-hospital mortality among the full sample and a sub-sample of patients seen in the ICU.

- ✓Results: Data revealed that vitamin C therapy was associated with increases in AKI (OR = 2.07 95% CI [1.46-2.93]) and in-hospital mortality (OR = 1.67 95% CI [1.003-2.78]) after adjusting for demographic and clinical covariates. When stratified to examine ICU patients, **vitamin C therapy remained a significant risk factor of AKI** (OR = 1.61 95% CI [1.09-2.39]) and provided no protective benefit against mortality (OR = 0.79 95% CI [0.48-1.31]).

BMC Nephrol

2018 Oct 12;19(1):265. doi: 10.1186/s12882-018-1060-9.

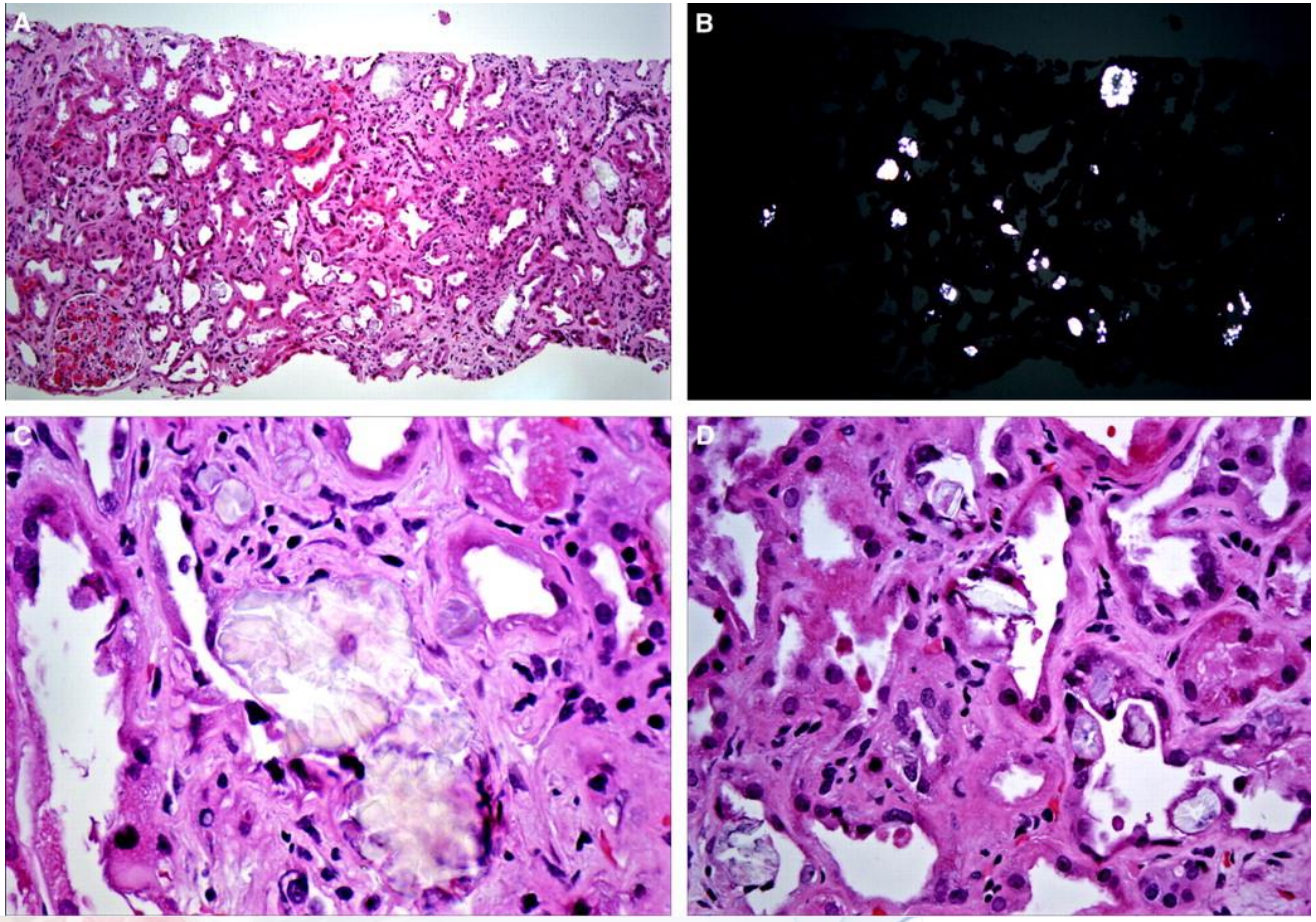
Vitamin C-induced oxalate nephropathy in a renal transplant patient related to excessive ingestion of cashew pseudofruit (Anacardium occidentale L.): a case report

Miguel Moyses-Neto, Bruno Rafael Santos Brito, Dyego José de Araújo Brito, Noelia Dias Carneiro Barros, Márcio Dantas, Natalino Salgado-Filho, Roberto Silva Costa, Gyl Eanes Barros Silva

Case presentation:

We present a case of acute oxalate nephropathy in a 59-year-old black male with type 2 diabetes mellitus, who received a kidney transplant 11 years prior. He ingested a large amount of cashew pseudofruit ("cashew apple") during 1 month and developed acute kidney injury. His previous blood creatinine was 2.0 mg/dL, which increased to 7.2 mg/d; he required hemodialysis. He was subsequently discharged without need for dialysis; 3 months later his blood creatinine stabilized at 3.6 mg/dL.

Kidney biopsy showing extensive birefringent calcium oxalate crystal deposition and epithelial degenerative changes. Polarized microscopy (hematoxylin and eosin) in a background of interstitial fibrosis, tubular atrophy, glomerulosclerosis, and hyaline arteriosclerosis.



Vitamin C Nephrotoxicity in a COVID-19 Patient: A Case Report

Noémie Lemee, Paul Chamley, Alexis Francois, Thomas Guincestre, Marion Duval, Aude Promerat, Cécile Lemoine

Nephrology Dialysis Transplantation, Volume 37, Issue Supplement_3, May 2022, gfac066.019, https://doi.org/10.1093/ndt/gfac066.019

case

- ✓A 73-year-old Caucasian woman admitted for hyperthermia and digestive disorders. She had recently started a first-line chemotherapy for multiple myeloma with partial response. She also displayed preexisting stage 4 CKD (eGFR 18.50 mL/min/1.73 m² using CKD-EPI) of unknown aetiology.
- ✓She also received high doses **(15 g/24 h) of vitamin C** for three consecutive days.
- ✓**The rationale for vitamin C use in COVID-19 is based on in vitro studies showing its antioxidant, anti-inflammatory, anticoagulant and immune modulatory properties.**
- ✓Histology revealed hundreds of intratubular calcium oxalate crystals, with severe and diffuse acute tubular necrosis and interstitial edema. There was no amyloidosis, no sign of active glomerular disease and no interstitial fibrosis. Immunofluorescence (IgA, IgG, IgM, C1Q, C3, kappa and lambda) was negative. We concluded to oxalate nephropathy.

Vitamin C-induced hyperoxaluria causing reversible tubulointerstitial nephritis and chronic renal failure: a case report

Shradha Rathi, William Kern & Kai Lau

Journal of Medical Case Reports volume 1, Article number: 155 (2007) Cite this article

Case

A 73-year-old man with both risk factors was hospitalized with serum creatinine of 8.4 mg/dL (versus 1.2 mg/dL four months earlier) (normal 0.6–1.3 mg/dL). Given his oxalate-rich diet, chronic diarrhea, and daily 680 mg vitamin C and furosemide, we postulated Ca oxalate-induced nephropathy, a diagnosis confirmed by documenting hyperoxaluria, and finding of diffuse intraluminal crystals and extensive interstitial fibrosis on biopsy. He was hemodialysed 6 times to remove excess oxalate. Two weeks off vitamin C, his creatinine spontaneously fell to 3.1 mg/dL. Three months later, on low oxalate diet and 100 mg vitamin B6, urine oxalate to creatinine ratio decreased from 0.084 to 0.02 (normal < 0.035), while creatinine fell and stayed at 1.8 mg/dL.

Vitamin D

- ✓Vitamin D toxicity is a known cause of hypercalcemia and renal failure.
- ✓ The daily requirement of vitamin D is about 200–600 IU and the skin can only produce around 10,000 IU of vitamin D after total body exposure to UV light.

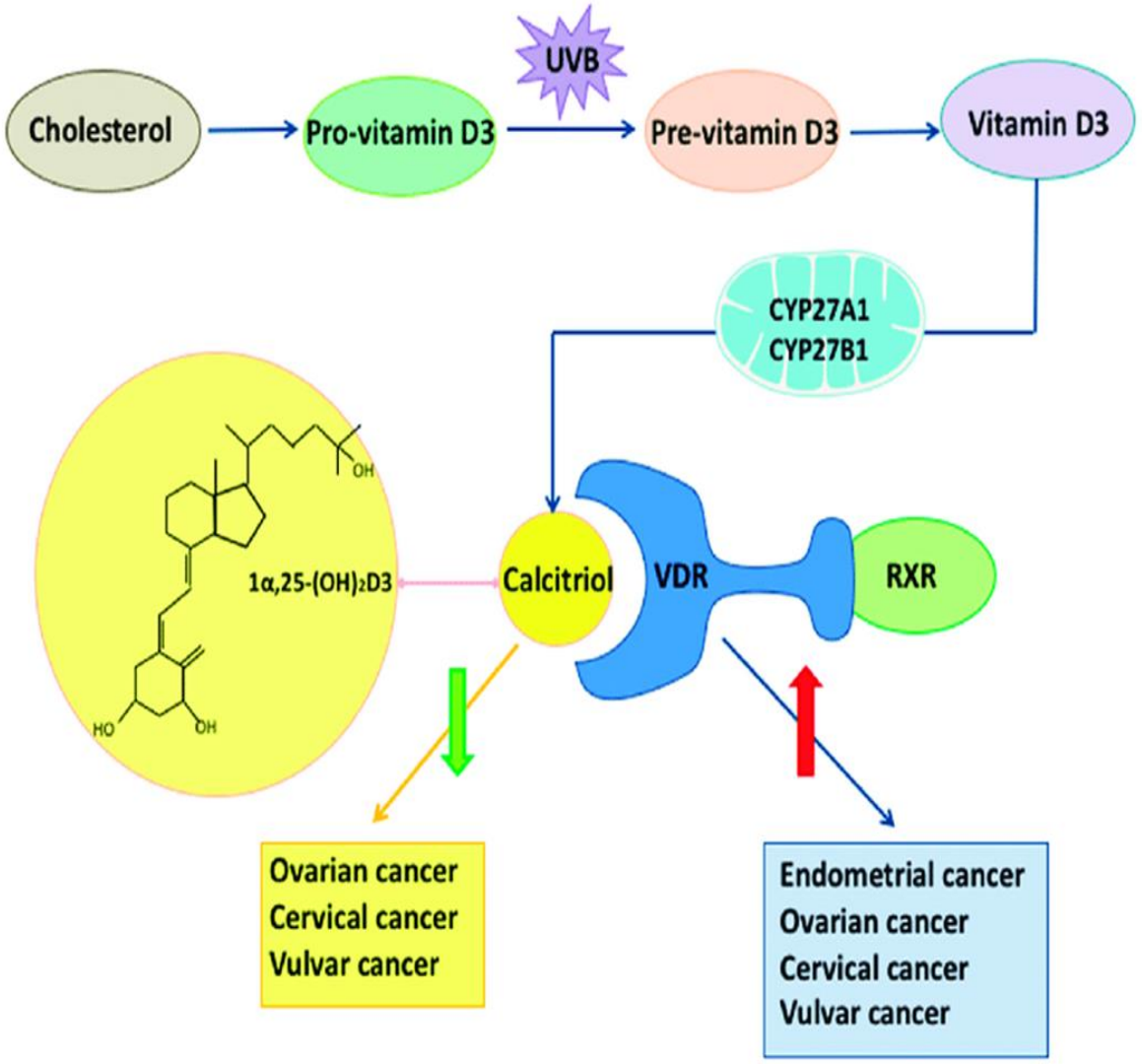
Although vitamin D has a wide therapeutic index, its toxicity is well known and cases of

- ✓accidental ingestion
- ✓ self medication
- ✓Malpractice

have been reported

Mechanism of vitamin D toxicity

- ✓its widespread availability in various **over-the-counter formulations** may pose a substantial risk to uninformed patients.
- ✓ After consumption, vitamin D is carried to the liver where it undergoes hydroxylation and is activated by either microsomal CYP2R1 or mitochondrial CYP27A1 to 25-hydroxyvitamin D3. The resulting 25-hydroxyvitamin D3 binds to the vitamin D binding protein and is carried to the kidneys for further 1α-hydroxylation by CYP27B1 to produce 1,25 dihydroxyvitamin D3.

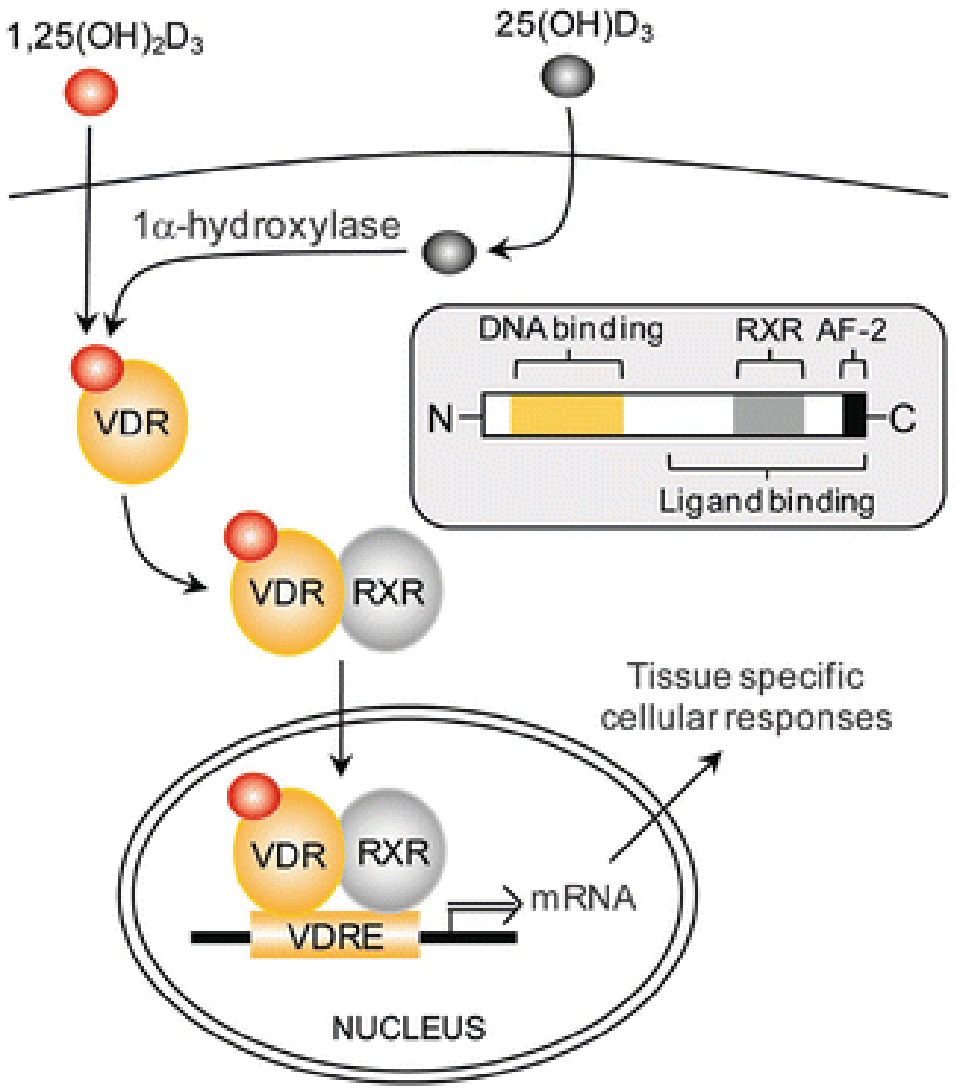


Mechanism of vitamin D toxicity

1,25 dihydroxyvitamin D3 is transported to target cells and enters the nucleus of the vitamin D receptor, leading to an upregulation in gene expression.

Although it is transported by vitamin D binding protein, 1,25 dihydroxyvitamin D3 has a lower affinity to binding relative to 25-hydroxyvitamin D3 and its metabolites.

A leading hypothesis suggests that an oversaturation of the vitamin D binding protein causes an increase in free active Vitamin D (1,25 dihydroxyvitamin D3), resulting in hypercalcemia.



Mechanism of vitamin D toxicity

- ✓**CYP24A1** plays an important role in the deactivation of 1,25 dihydroxyvitamin D3 to **calcitroic acid.**
- ✓ CYP24A1 also breaks down precursor 25-hydroxyvitamin D3 to 24,25-dihydroxyvitamin D3.
- ✓Loss-of-function mutations in CYP24A1 have been associated with hypercalcemia because of increased vitamin D sensitivity.

Vitamin D intoxication can be

- ✓accidental :

  due to self medication

  after the topical application of vitamin D ointment

  induced by dietary or OTC supplements

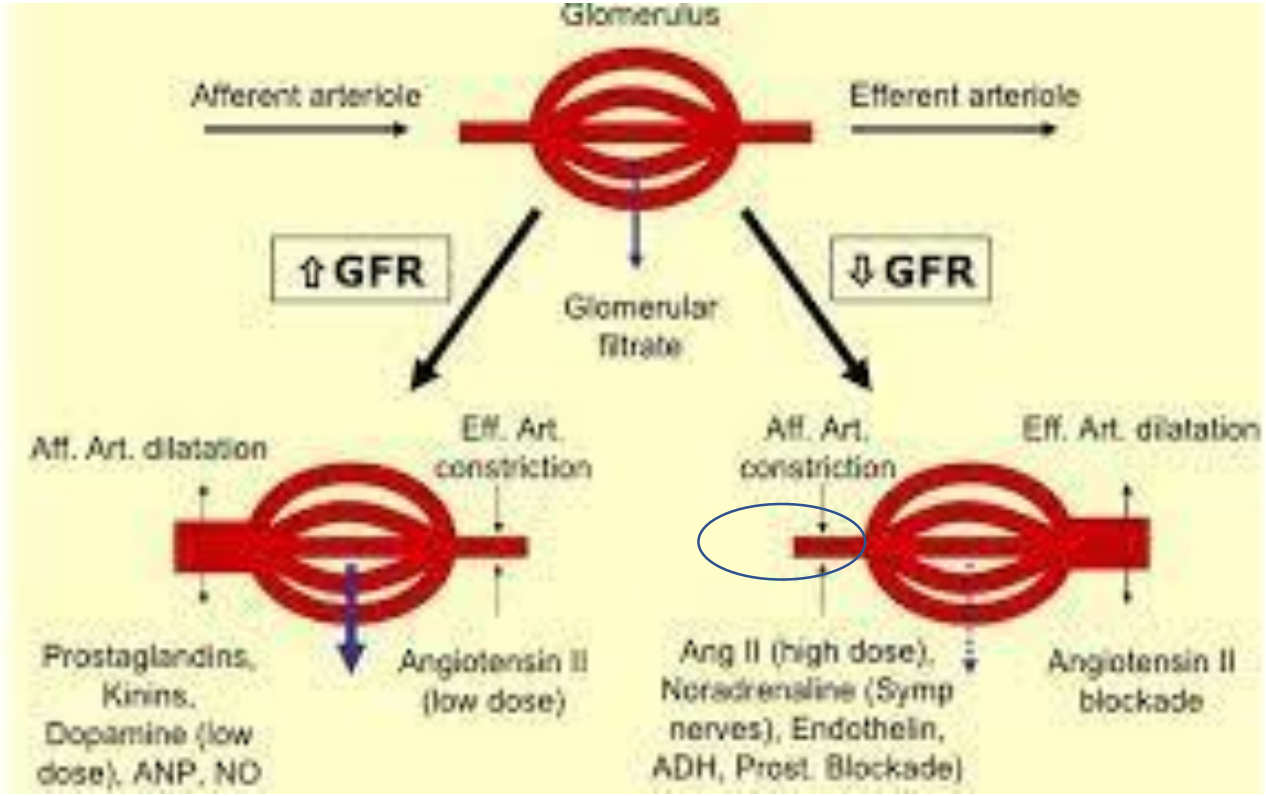
- ✓ or iatrogenic in some unusual cases
- ✓ The clinical manifestations of this intoxication are **kidney disorders (65.0%), renal insufficiency (51.0%)**, gastrointestinal tract disorders (23.0%), and **arterial hypertension (52.0%)**

- ✓In terms of renal involvement, hypercalcemia can cause kidney injury both **acutely** and **chronically**.
- ✓ Hypercalcemia can cause acute kidney injury primarily by 2 mechanisms:

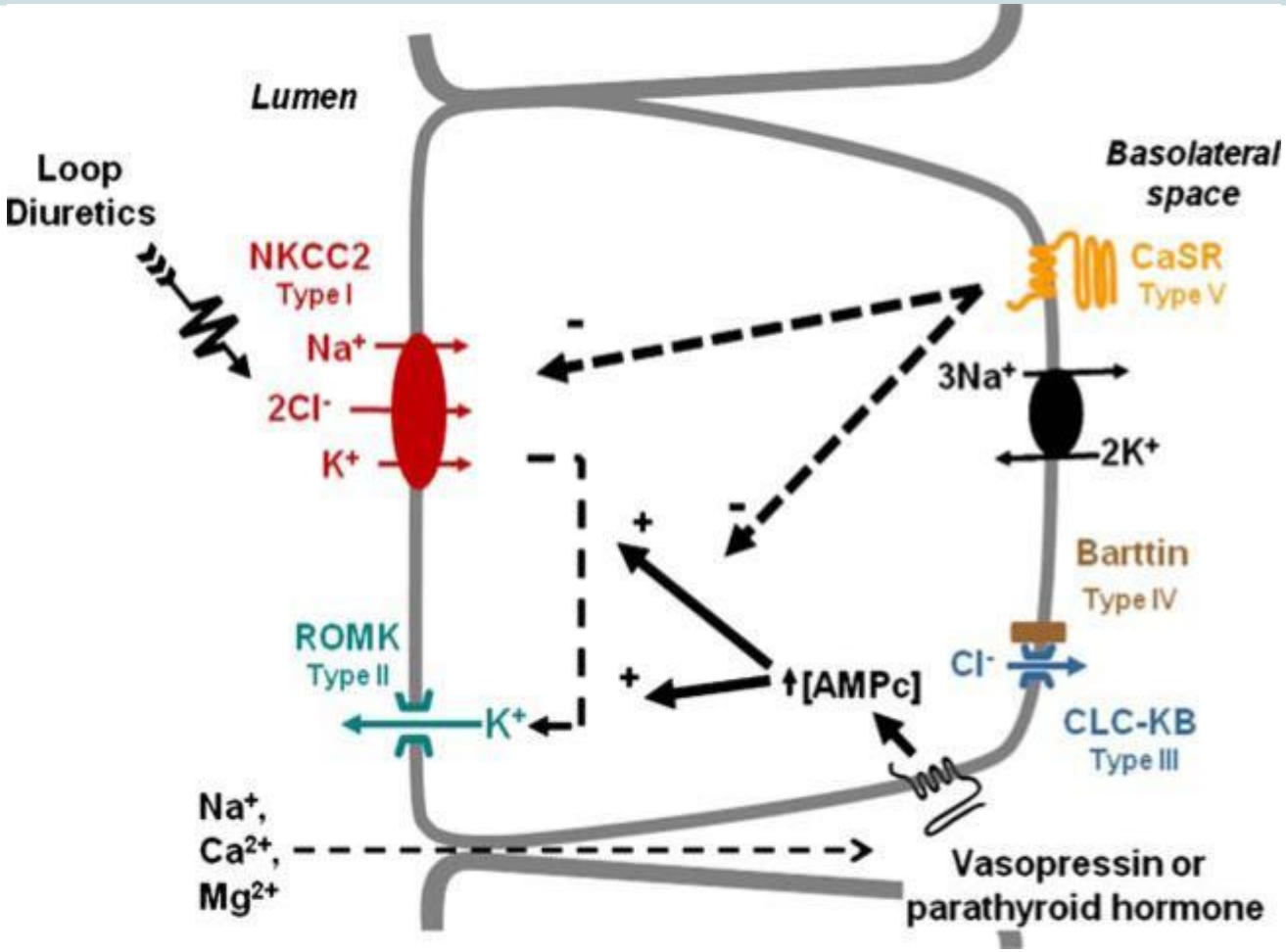
afferent arteriolar constriction

intravascular volume depletion from a diuretic effect through activation of calcium-sensing receptor at the sodium–chloride cotransporter in the loop of Henle.

Afferent Arteriolar Constriction



Intravascular volume depletion from a diuretic effect through activation of calcium-sensing receptor at the sodium–chloride cotransporter in the loop of Henle.



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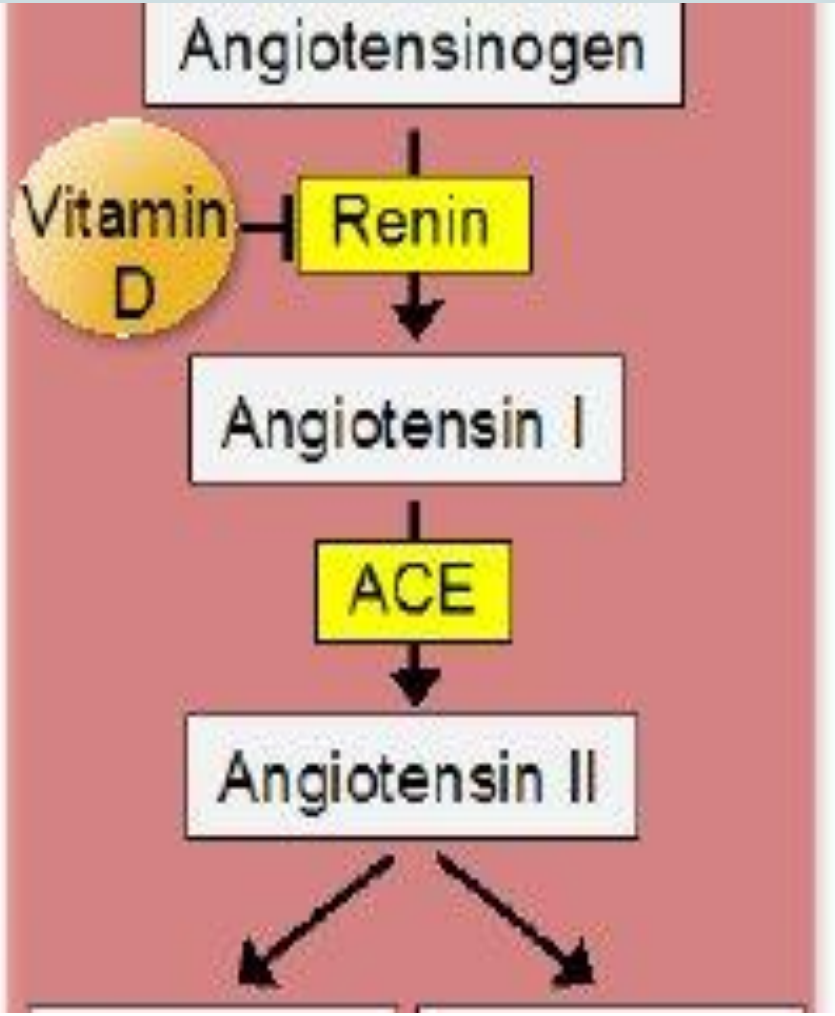
Vitamin D and Acute Kidney Injury: A Two-Way Causality Relation and a Predictive, Prognostic, and Therapeutic Role of Vitamin D

Spyridon Graidis, Theodosios S. Papavramidis, and Maria Papaioannou

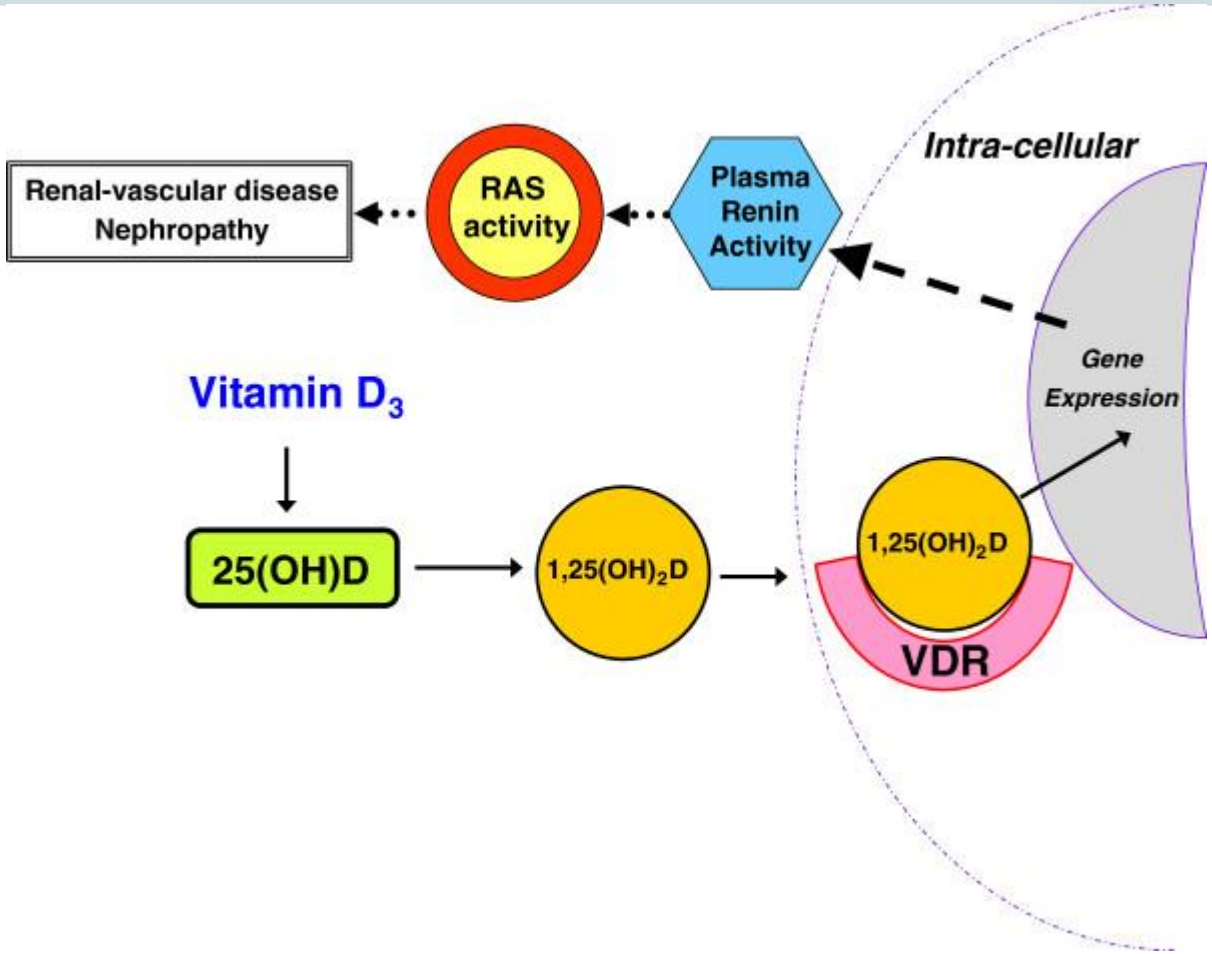
- ✓Methods: A systematic review had been conducted to identify the pathogenetic relation of VitD and AKI and the potential role of VitD as a biomarker and therapeutic–renoprotective factor.
- ✓Results: From 792 articles, 74 articles were identified that fulfilled the inclusion criteria. Based on these articles, it has been found that not only can **VitD disorders (VitD deficiency or toxicity) cause AKI** but, also, AKI can lead to great disruption in the metabolism of VitD. Moreover, it has been found that **VitD serves as a novel biomarker for prediction of the risk of developing AKI and for the prognosis of AKI's severity.** Finally, animal models showed that VitD can both ameliorate AKI and prevent its onset, suggesting its renoprotective effect.

VitD Deficiency Induces AKI

- ✓VitD depletion, VDR knock-out, or disruption of VitD synthesis contributes to AKI development by leading **to upregulation of RAAS** and to **elevated mRNA expression of renal-vascular renin.**
- ✓ Due to obstruction and increased levels of **extracellular matrix proteins** (such as **collagen I and fibronectin**) and **proinflammatory and profibrogenic factors** [such as **TGF-β**, **connective tissue growth factor**, and monocyte chemoattractant protein-1 **(MCP-1)],** the renal injury becomes more severe.

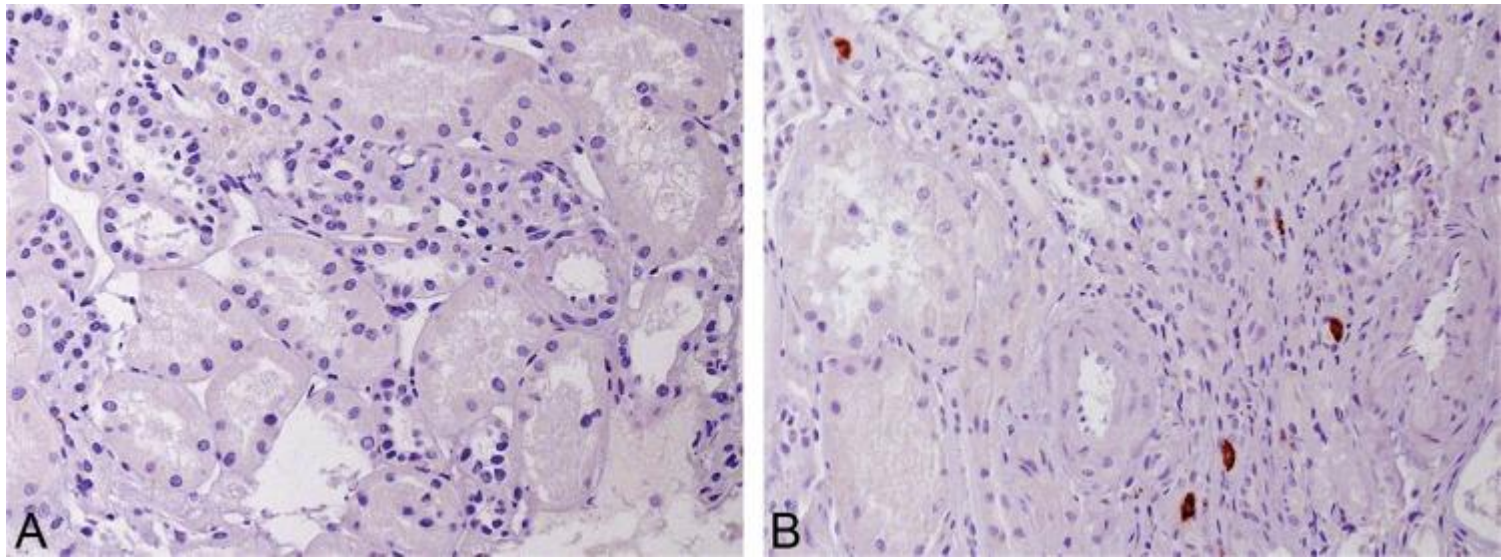


elevated mRNA expression of renal-vascular renin.

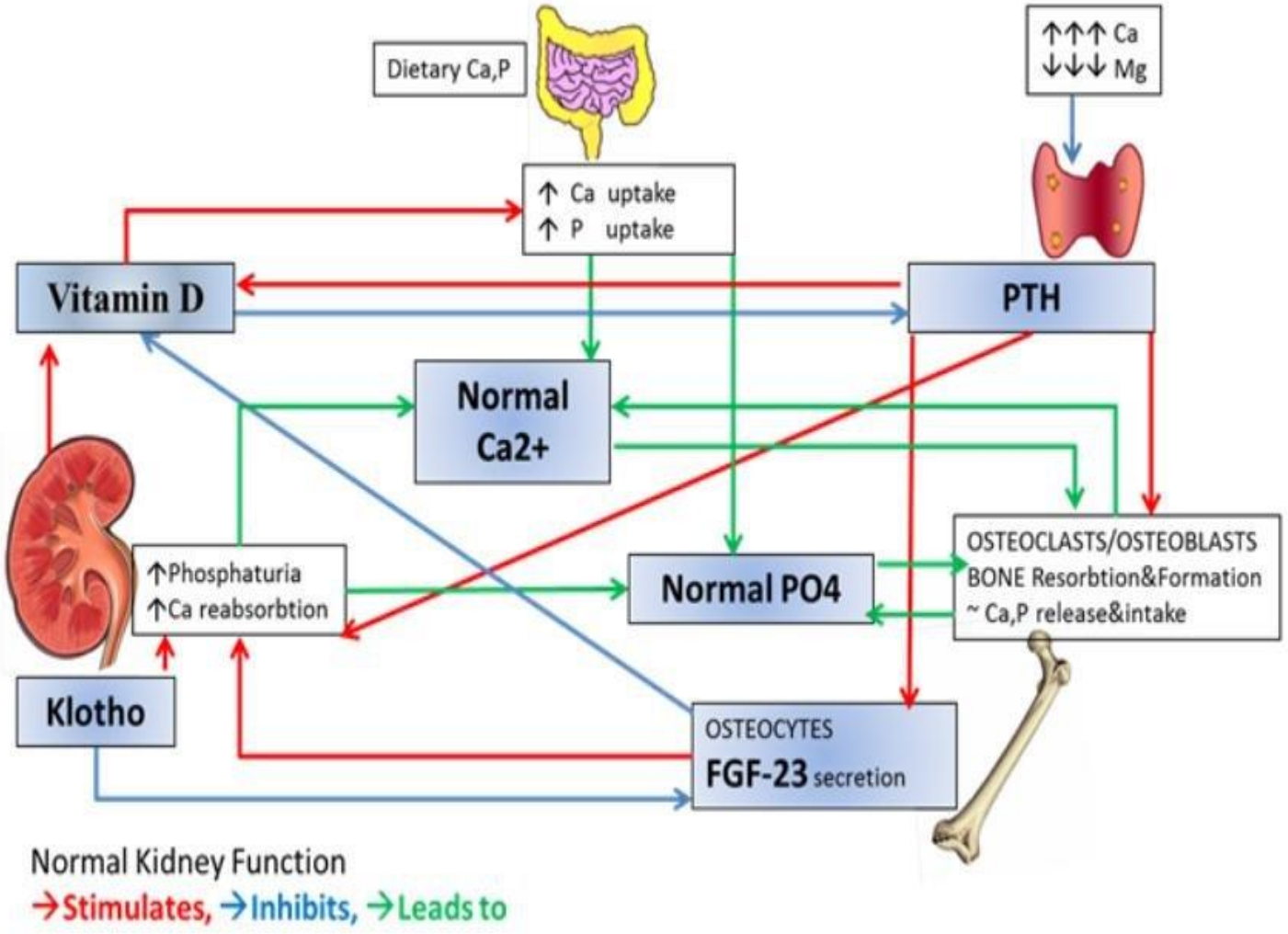


PRESENTATION & RENAL Bx

- ✓**Proteinuria**
- ✓ **podocytes damage**
- ✓ **mesangial dilation**
- ✓ **macrophage infiltration**



Moreover, VitD deficiency can exacerbate **pre-existing AKI [ischemia/reperfusion injury (IRI) induced AKI]** by deteriorating the renal vascular condition and it can accelerate the AKI-to-CKD progression, via both an increased **TGF-β1 signaling** and a **decreased VDR and Klotho.**



Vitamin E

Vitamin E deficiency

is rarely seen in humans and is characterized by a **sensory ataxia**.

It can arise due to illnesses that impair generalized fat absorption (such as **chronic cholestasis or abetalipoproteinemia**) or in the rare hereditary condition, **familial isolated vitamin E (FIVE) deficiency**, due to mutations in the gene that codes for **α-tocopherol transferase** which exports vitamin E from the liver to the circulation. Whether patients with a chronic and severe vitamin E deficiency are also renally impaired is not yet known.

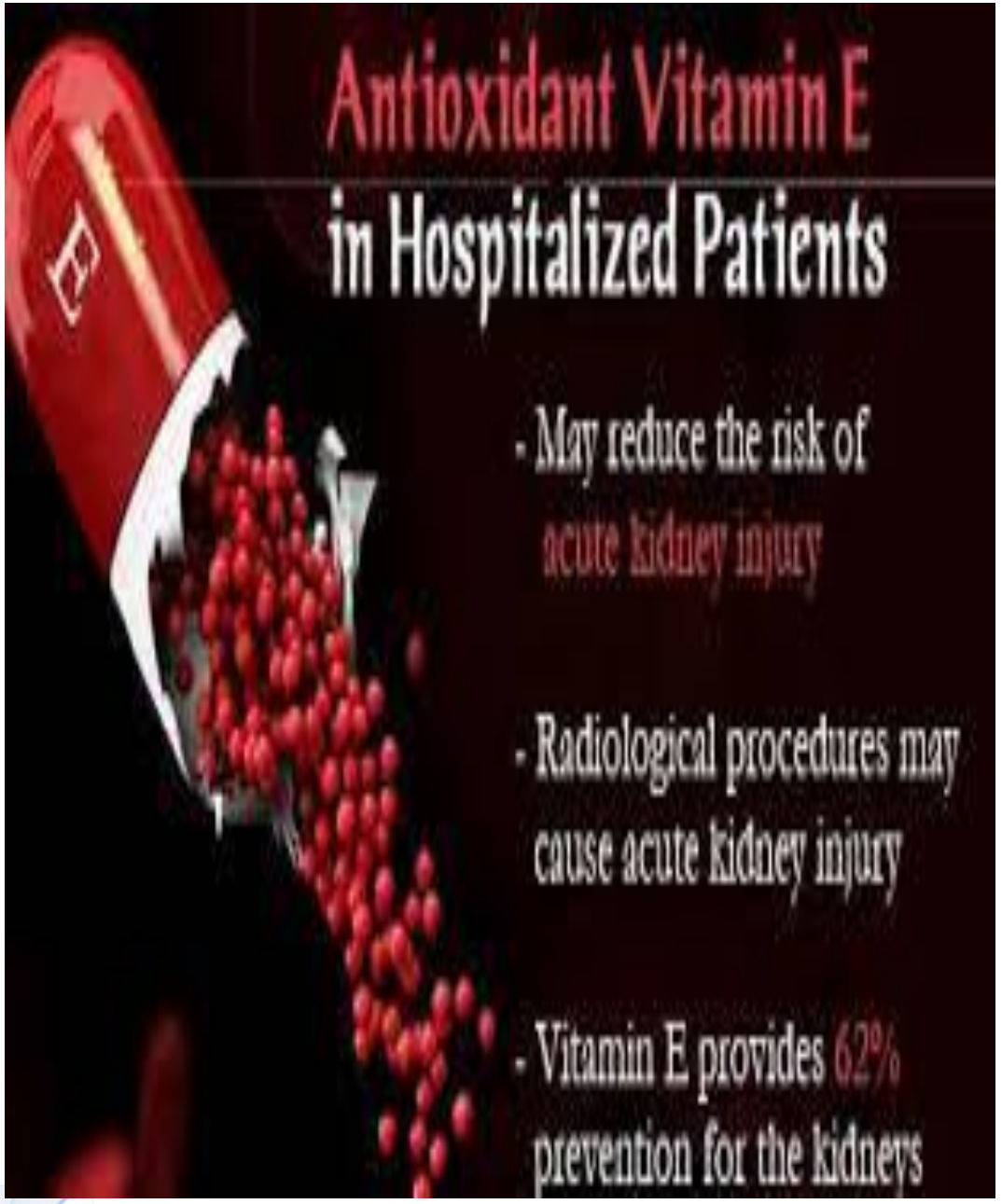
Vitamin E toxicity

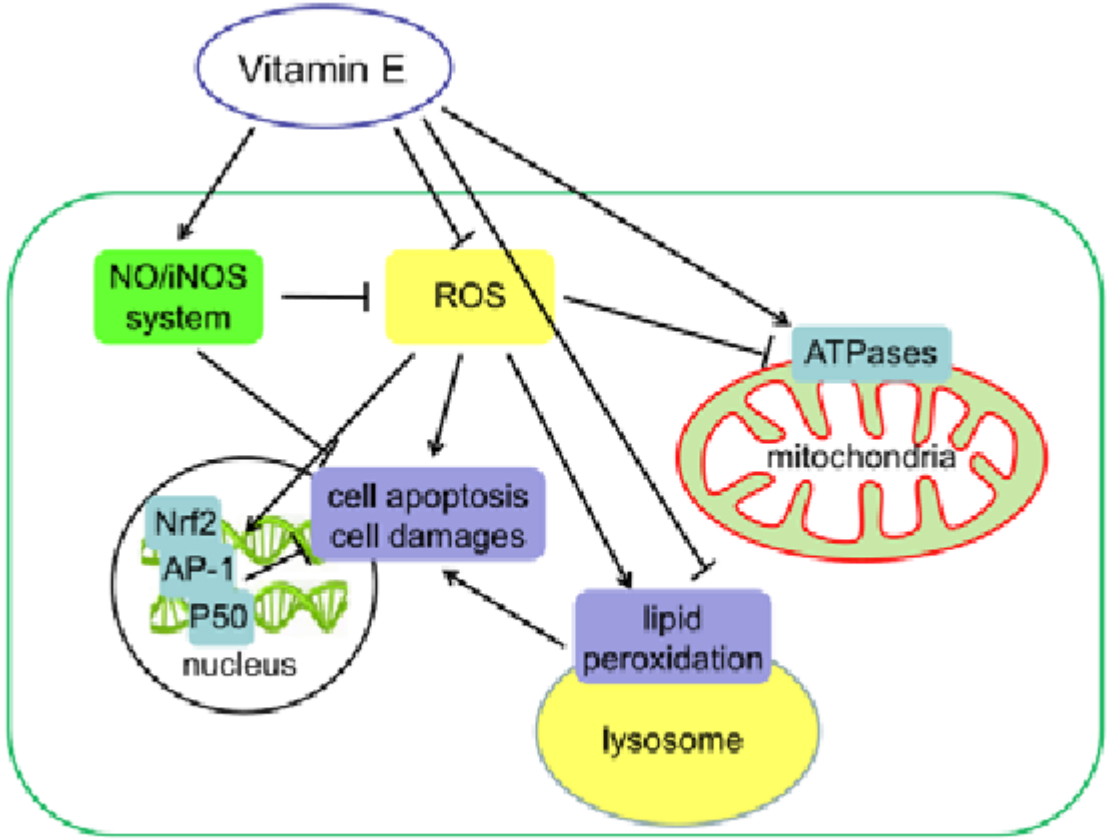
Vitamin E is one of the *least toxic* of the vitamins.

Daily doses as high as 400 IU can be considered harmless.

Large oral doses as great as 3200 IU have not been found to have consistent ill effects.

- ✓Preservation of glomerular membrane integrity is crucial to renal function and biological membranes are protected from oxidative deterioration by the lipophilic antioxidant vitamin E, principally in the second form **(α-tocopherol)**.





E based therapy against AKI. Mechanisms of vitamin E bas

- ✓Vitamin E also physically stabilizes membrane permeability and fluidity.
- ✓ Further extended antioxidant functions include preservation of membranes from harmful endogeneous lipid-degrading enzymes, promotion of neutral endothelial vasoactivity, reduction of neutrophil chemotaxis and tissue infiltration and the inhibition of platelet aggregation
- ✓ Vitamin E therefore has potent anti-inflammatory and anticoagulant properties. Additionally, it can prevent apoptosis due to oxidative stress.
- ✓It is required for the detoxification of oxidizing nitrogen oxides such as peroxynitrite, derived from the reaction between nitric oxide with superoxide radical. Nitric oxide is a powerful vasodilator and is involved in chronic renal failure patients with septic shock.

Vitamin E is effective in:

- ✓INFLAMMATORY KIDNEY DISEASE
- ✓RHABDOMYOLYSIS
- ✓CISPLATIN NEPHROTOXICITY
- ✓NEPHROTOXINS
- ✓DIABETIC NEPHROPATHY
- ✓FOCAL SEGMENTAL GLOMERULOSCLEROSIS
- ✓AGEING KIDNEYS

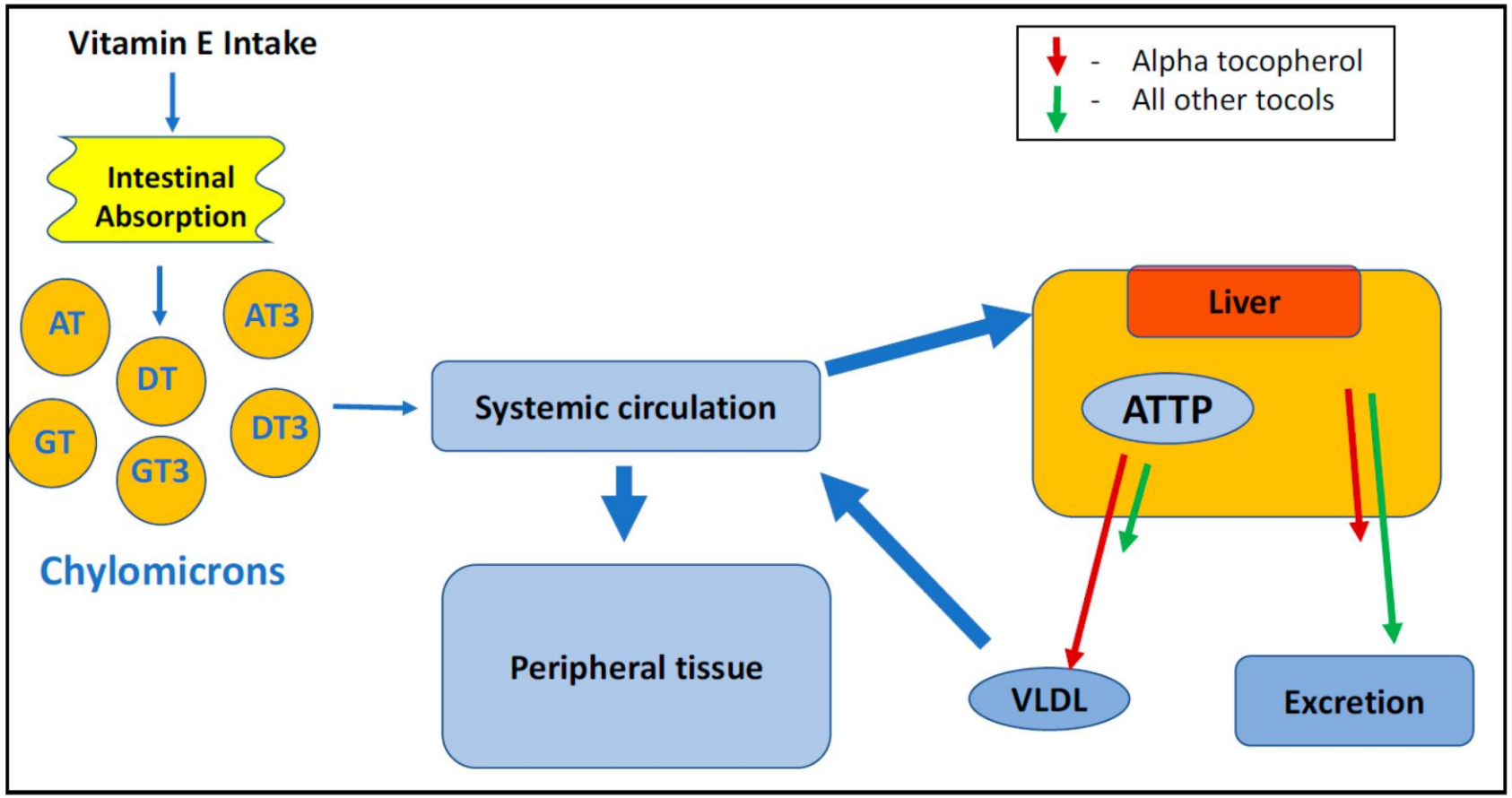
EFFECTIVE DOSAGE OF VITAMIN E IN RENAL FAILURE:

- ✓the **recommended daily intake for vitamin E is 8 mg (12 IU) for women and 10 mg (15 IU) for men** (1 mg = 1.5 IU), based on minimum levels required to prevent deficiency symptoms.
- ✓Plasma pool-turnover is rapid (1.4 ± 0.6 pools/day) and the normal circulating plasma range is from 11.5 to 35.0 μM. Large oral doses (1500–3200 IU/day) appear to be harmless, with minor and well-tolerated gastrointestinal side effects, although circulating levels can only be increased by two to four times the normal amount.

EFFECTIVE DOSAGE OF VITAMIN E IN RENAL FAILURE:

- ✓The optimal dose for vitamin E that may be helpful in **slowing renal failure in humans** may lie between **300 to 700 IU/day.** (This is taken to be the safe **'therapeutic range',** i.e. the levels of the vitamin thought to be necessary to prevent long-term degenerative disease caused by oxidative stress, but below the threshold level for appearance of side effects.

Vitamin E EXCRETION



Vitamin E Toxicity

By Larry E. Johnson, MD, PhD, University of Arkansas for Medical Sciences
Last full review/revision Nov 2020| Content last modified Sep 2022

Many adults take relatively large amounts of vitamin E (alpha-tocopherol 400 to 800 mg/day) for months to years without any apparent harm. Occasionally, muscle weakness, fatigue, nausea, and diarrhea occur. The most significant risk is **bleeding**. However, bleeding is uncommon unless the dose is **≥ 1000 mg/day or the patient takes oral coumarin or warfarin**.

Thus, the upper limit for adults aged ≥ 19 years is 1000 mg for any form of tocopherol.

Analyses of previous studies report that high supplemental vitamin E intake may increase the risk of hemorrhagic stroke and premature death.


Thanks
for your
attention