The Pathophysiology of Vascular Calcification

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DISCLOSURES

- None

Presentation Overview:

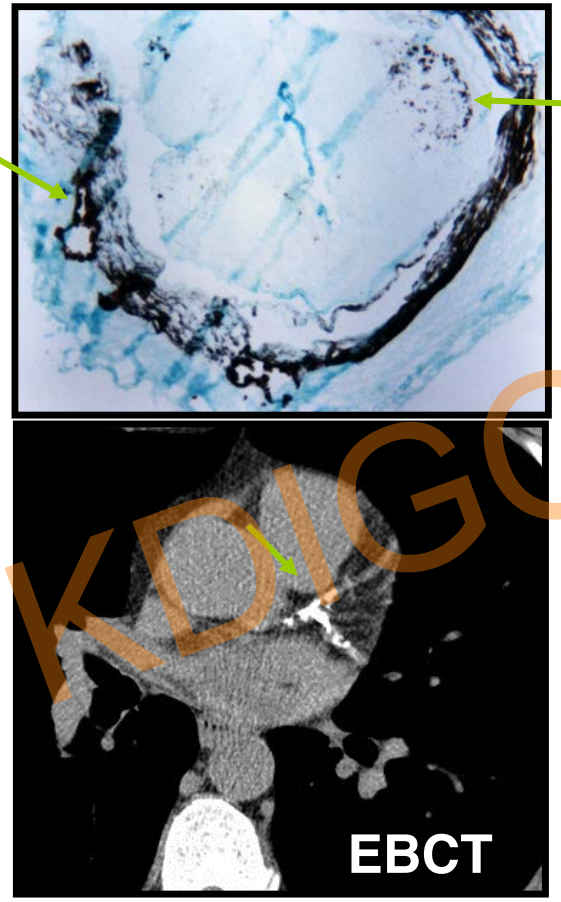
- Vascular smooth muscle cell-mediated calcification
  - VSMC phenotypes
  - Setting in which it occurs
- Processes that promote or drive vascular calcification
  - Hyperphosphatemia, hypercalcemia
  - Loss of inhibitory mechanisms
  - Oxidative stress
- How CKD specifically leads to vascular calcification
- Are patterns of coronary and/or peripheral calcifications – in a clinical and/or pathophysiological way - different in CKD-patients?

Vascular calcification occurs at two sites

MEDIAL

Diabetes
Renal Disease
Ageing

Stiffness



INTIMAL

Atherosclerosis

Plaque Rupture

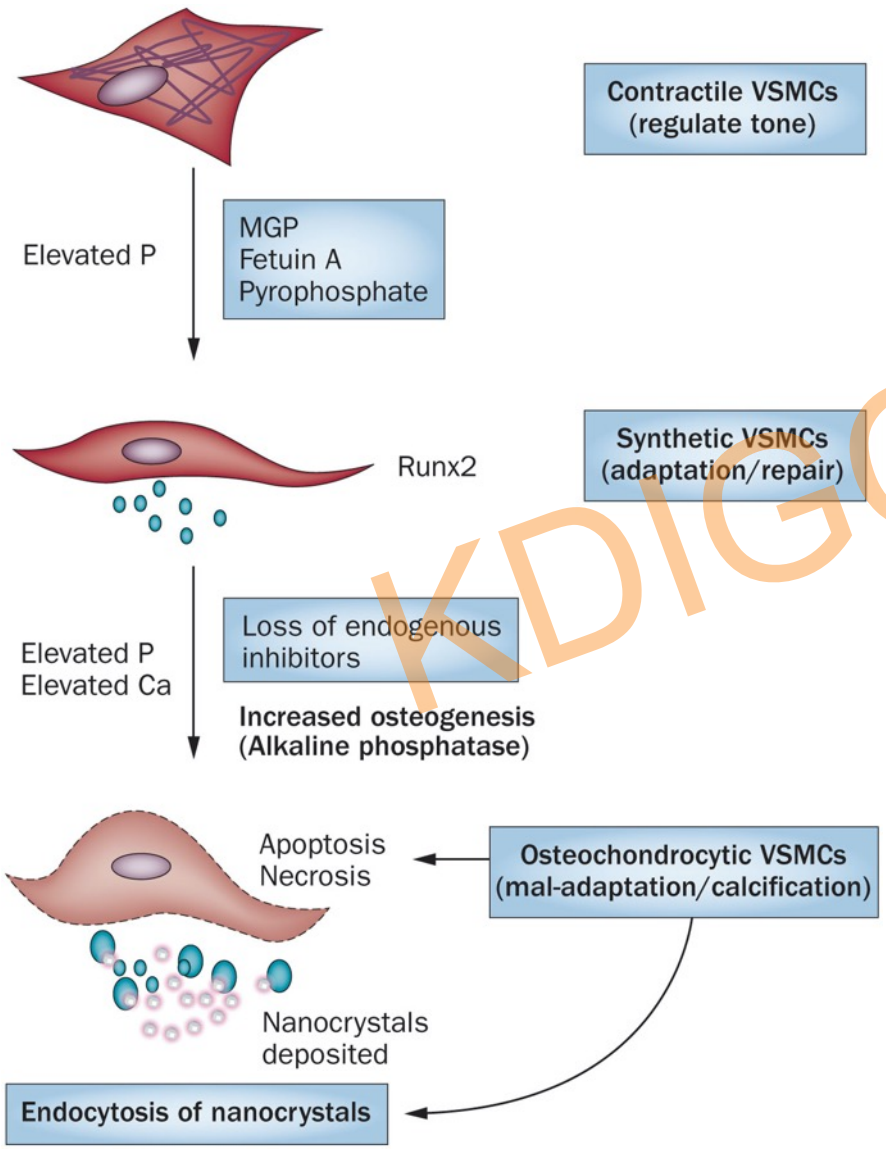
- **Major cause of cardiovascular mortality in CKD**
- **Increased risk of myocardial infarction and all cause mortality**
- **Surgical complications and amputations**
- **Valve calcification**

Vascular Calcification is a Cell-Mediated Process similar to bone calcification

Mechanisms of Vascular Smooth Muscle Cell Calcification

CKD
Diabetes
Ageing

ROS?



DAMAGE/STRESS

↓

LOSS OF INHIBITORS

↓

OSTEOGENIC DIFFERENTIATION

↓

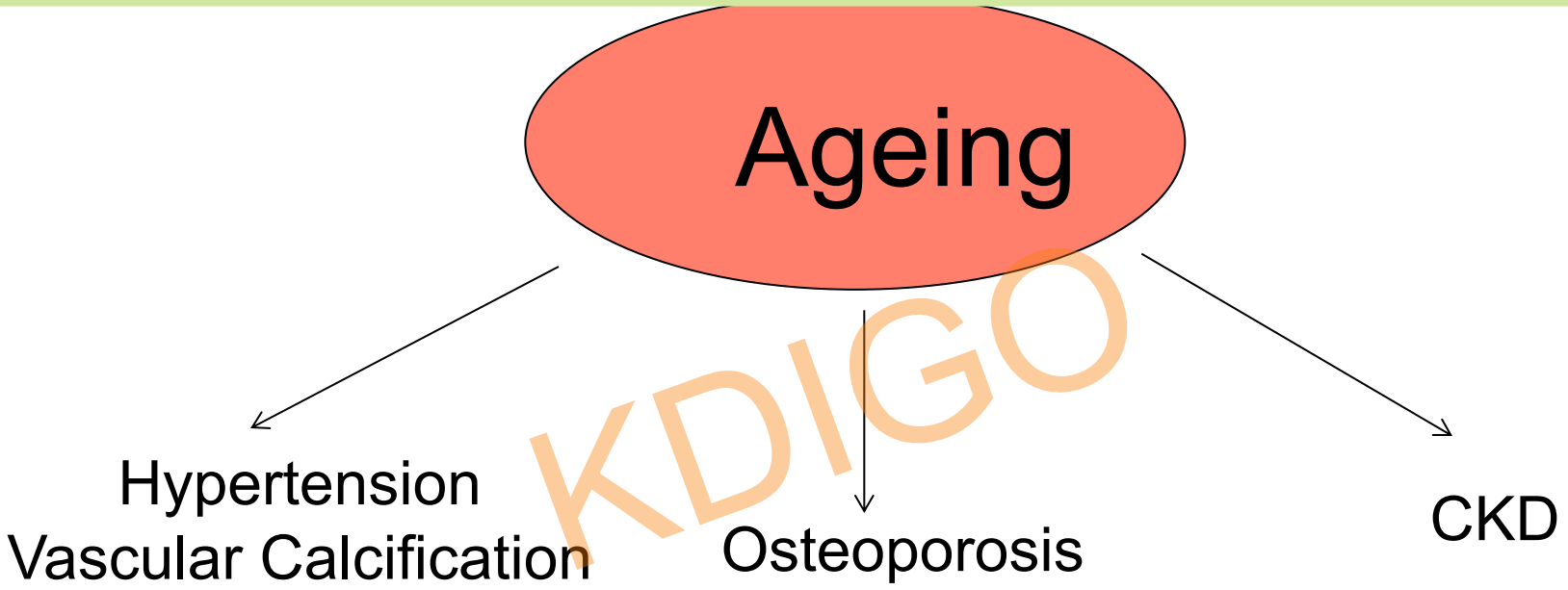
CELL DEATH/VESICLE RELEASE

↓

MINERALIZATION

Shanahan, C. M. (2013)

Ageing is the Strongest Risk Factor for Defects in Kidney-Bone-Vascular Axis Tissues

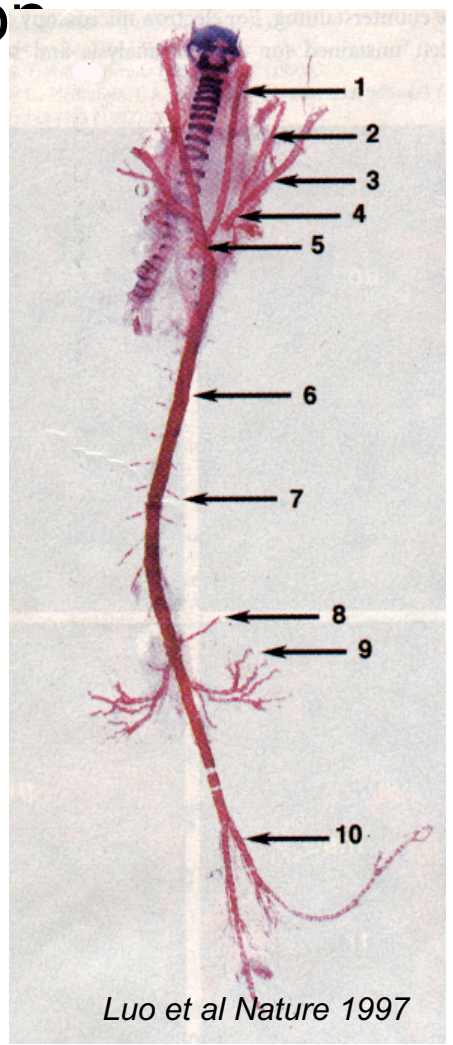


- Elevated Phosphate/FGF23/Klotho
- Low Vitamin D
- DNA damage
- Oxidative Stress
- Systemic Inflammation

Inhibitors Prevent Vascular Calcification

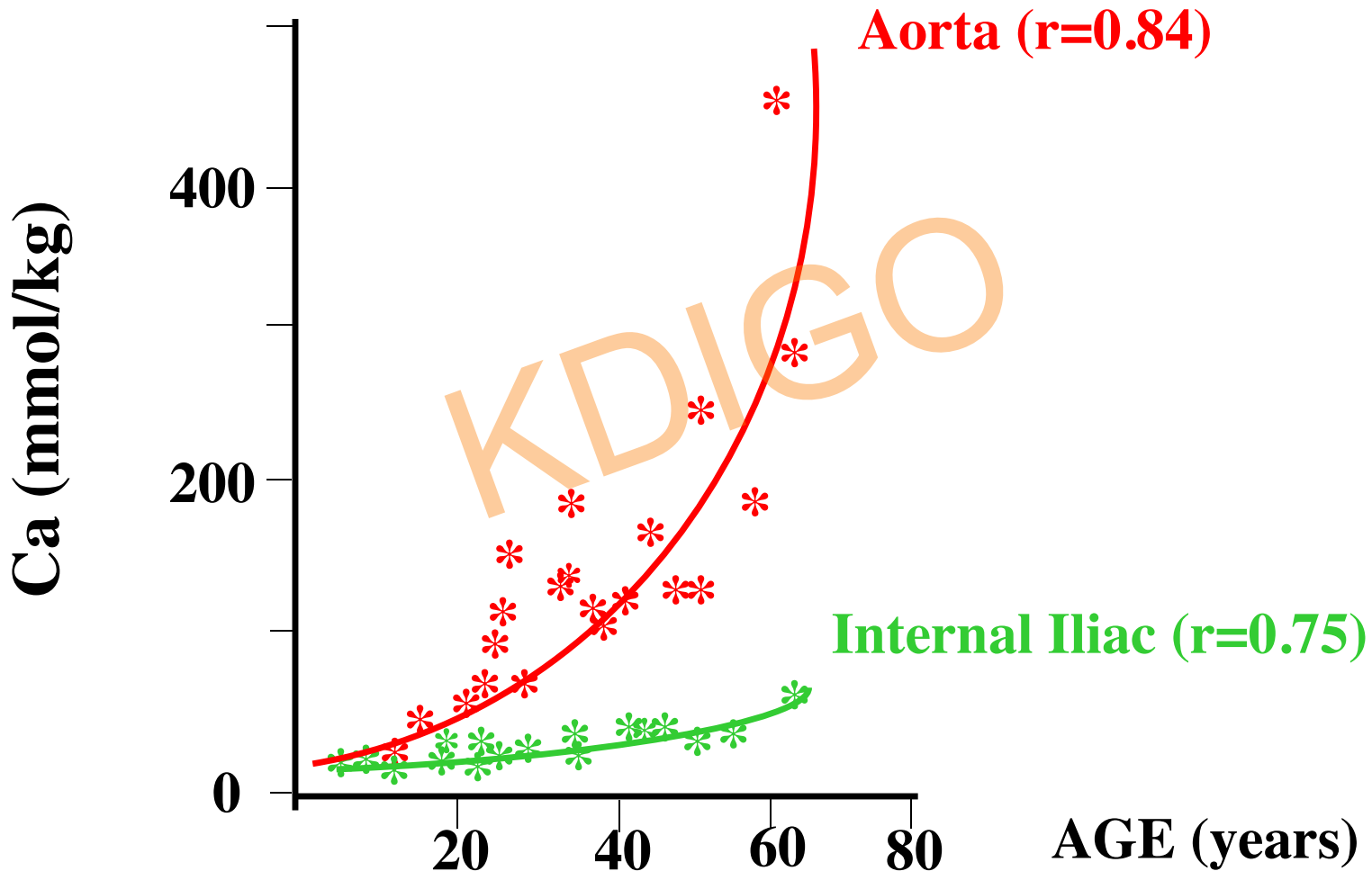
Mouse gene knockouts develop vascular calcification and bone defects (eg. osteoporosis).

- MGP (matrix Gla protein)
- Fetuin**
- Osteoprotegerin
- Klotho/ FGF23** - Phosphate and Vit D metabolism – premature ageing
- Pyrophosphate metabolism (ENPP1)
- carbonic anhydrase
- Smad 6



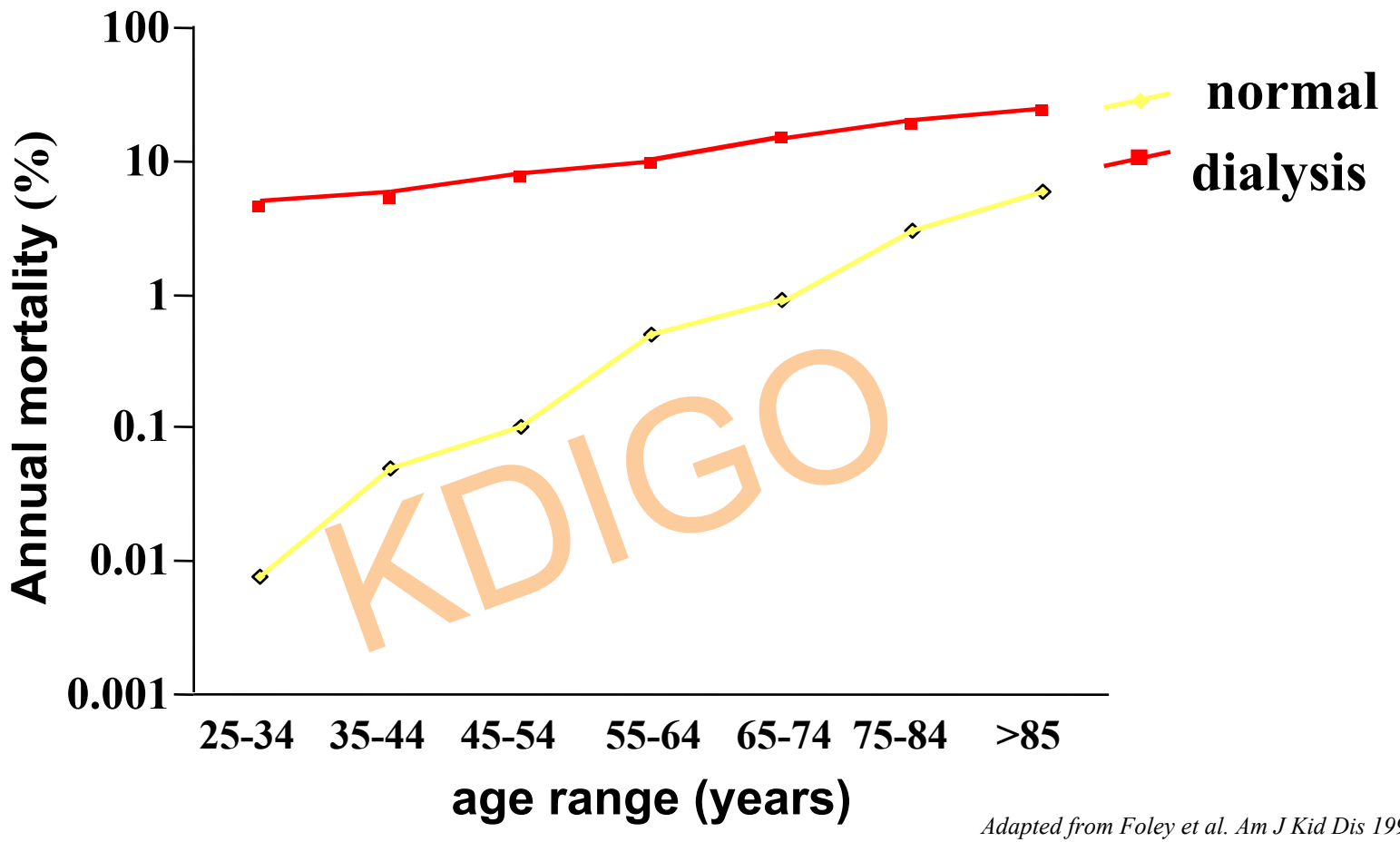
Luo et al Nature 1997

Incidence of Vascular Calcification with Age



Ibels et al. Am J Med 1979

Cardiovascular mortality in CKD patients

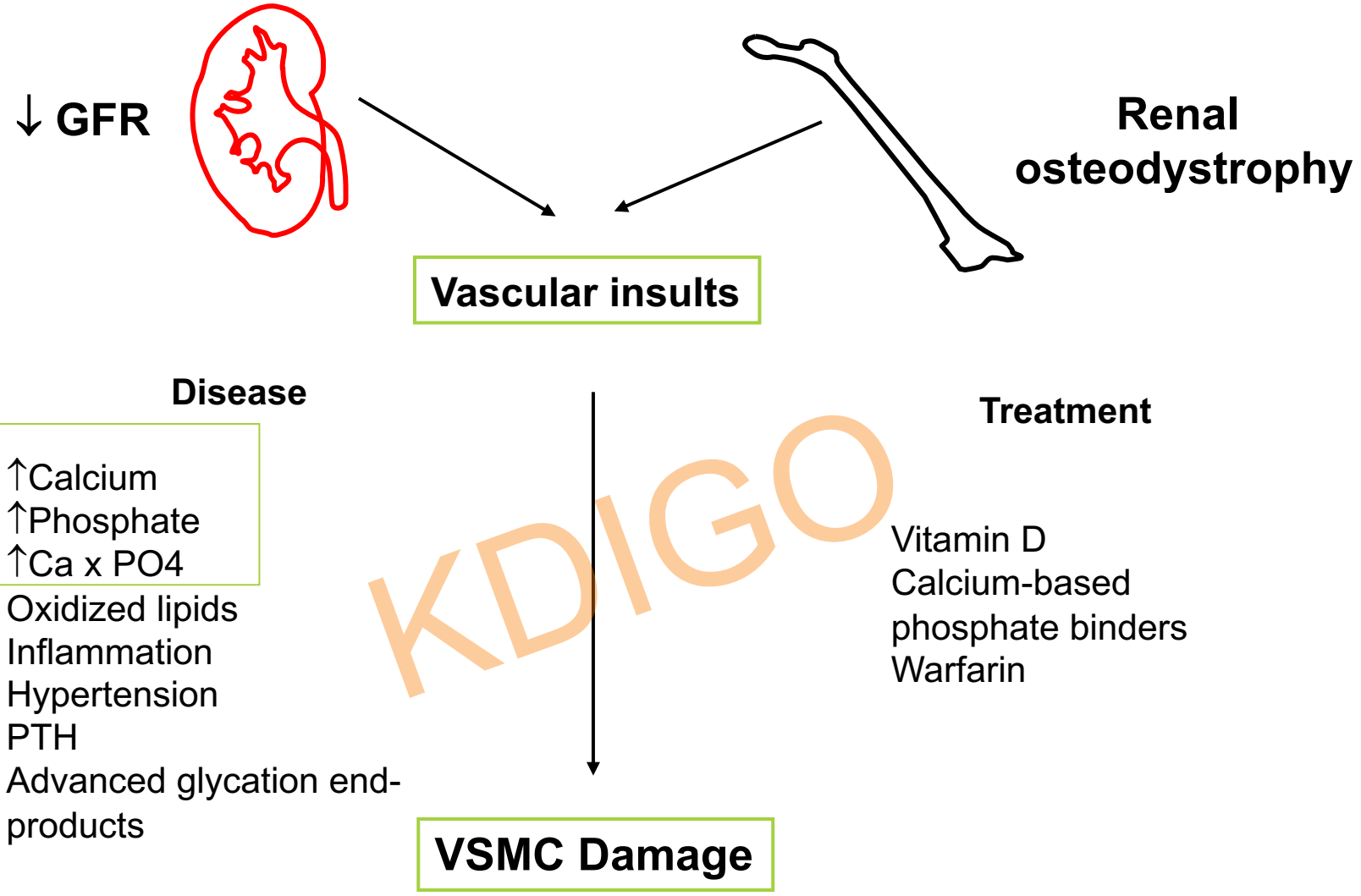


Adapted from Foley et al. Am J Kid Dis 1998

Adolescents and young adult with CKD:

- structural and functional abnormalities in the large vessels
- present even in the second decade of life
- linked to disorders in mineral metabolism

Goodman, NEJM, 2000; Litwin, JASN, 2005; Mitsnefes, JASN 2005; Goldsmith, NDT, 2006



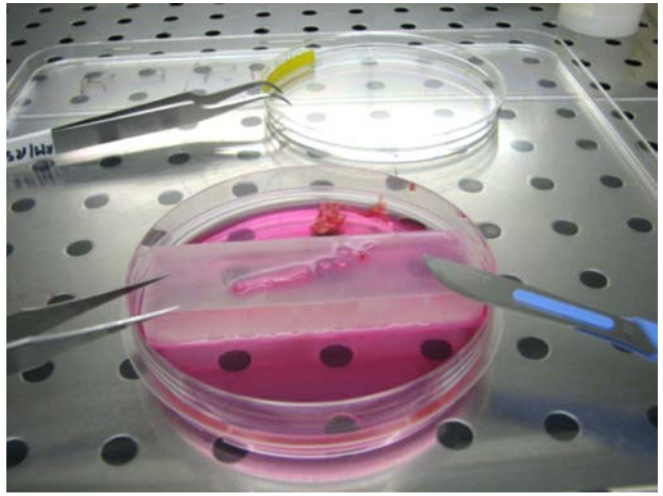
- Time on dialysis
- Pre-existing vascular calcification (once present rapidly progresses)

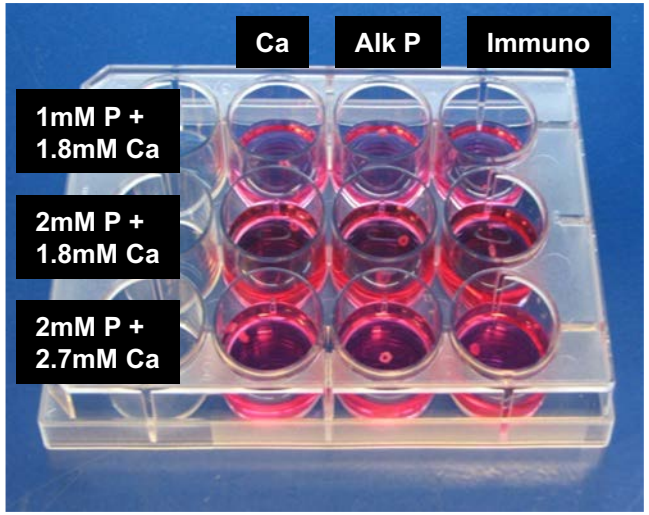
Vessel Rings from Children *in vivo* and *ex vivo*

Studied vessels from children on dialysis who develop rapid medial vascular calcification

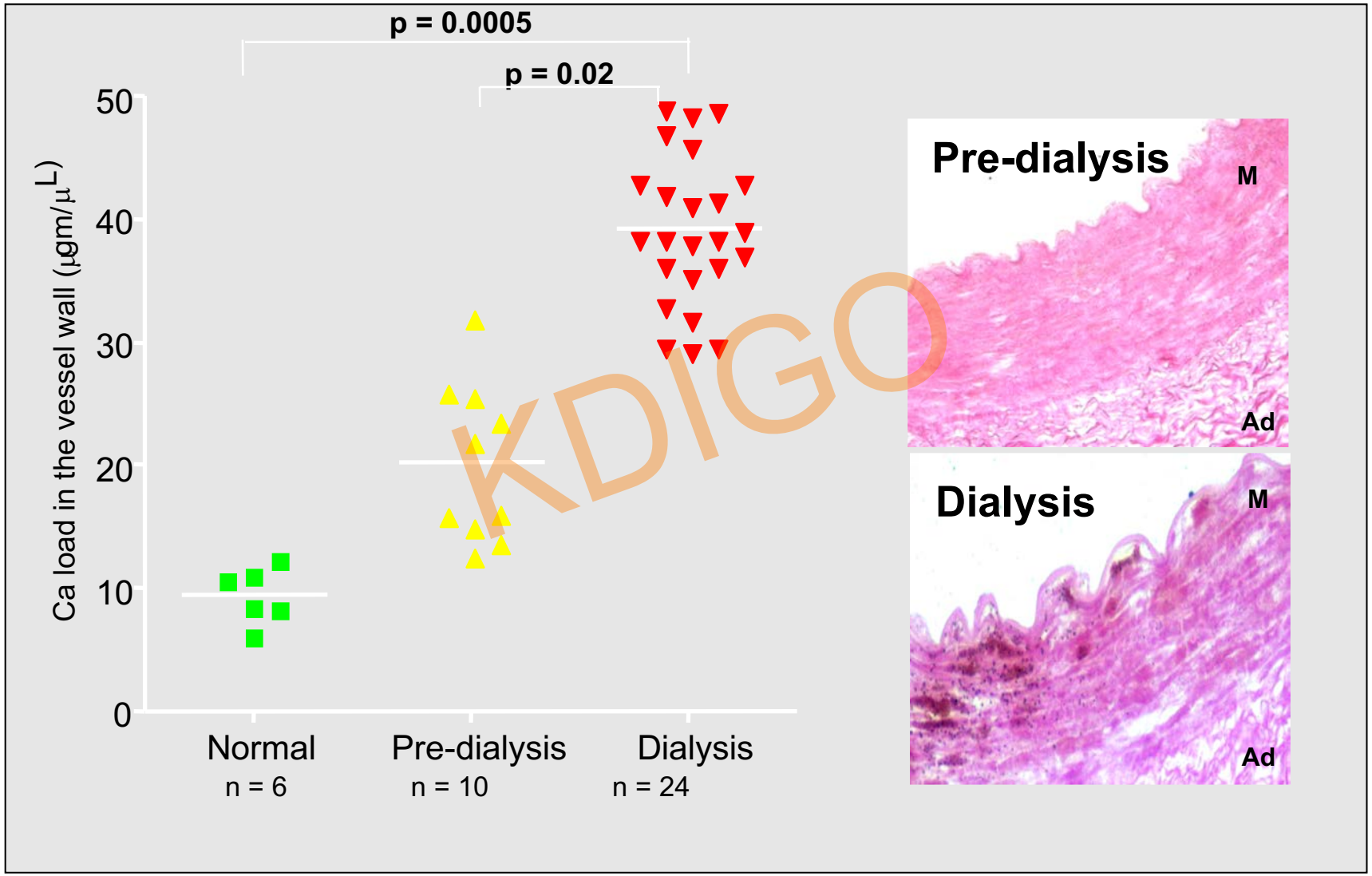
- pristine vessels -no atherosclerosis
- Intact - vascular matrix structure maintained

Measured:	CALCIUM LOAD VESSEL HISTOLOGY
Correlated with :	VASCULAR MEASURES BIOCHEMICAL DATA



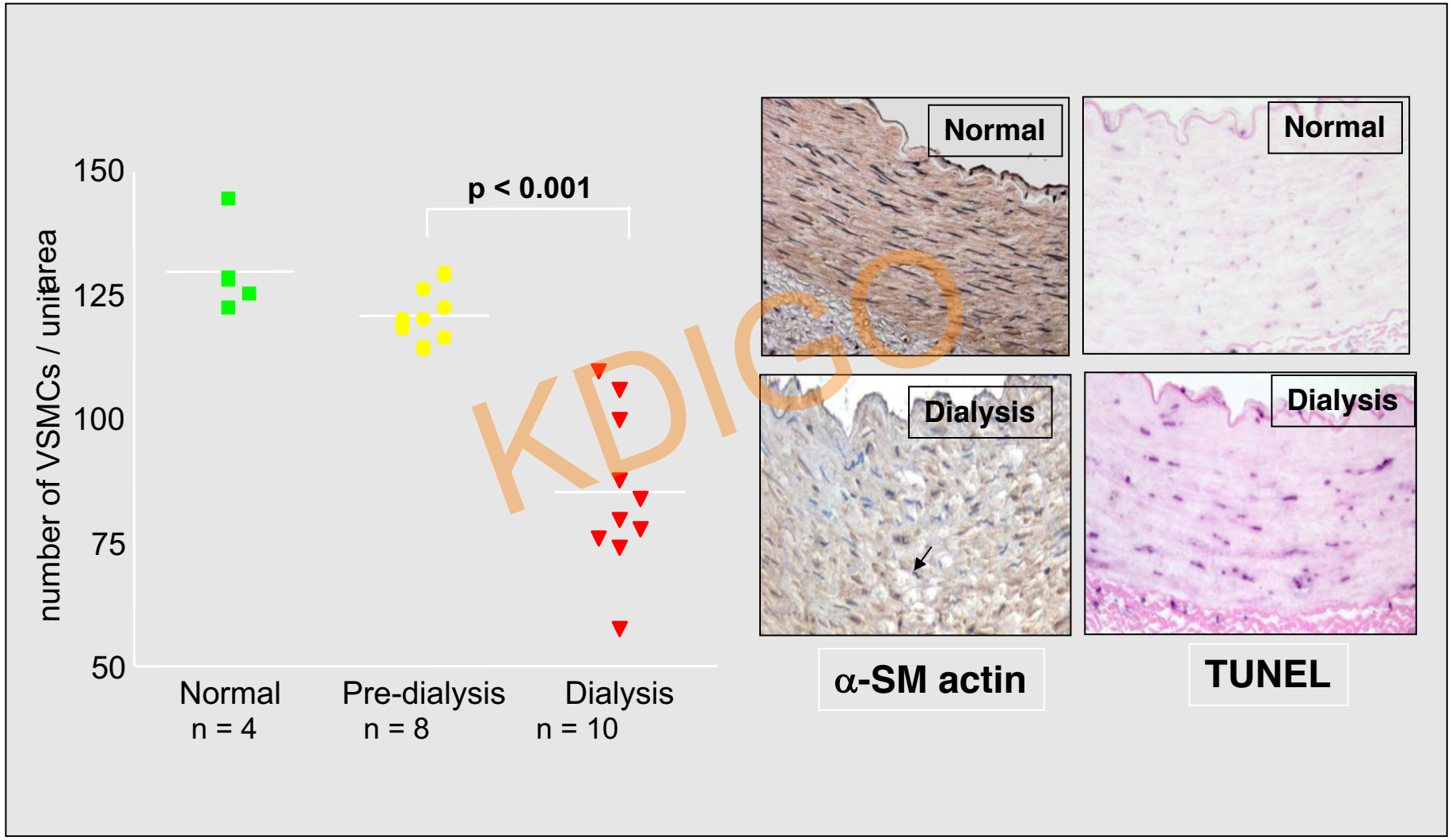


Children on Dialysis develop rapid medial calcification

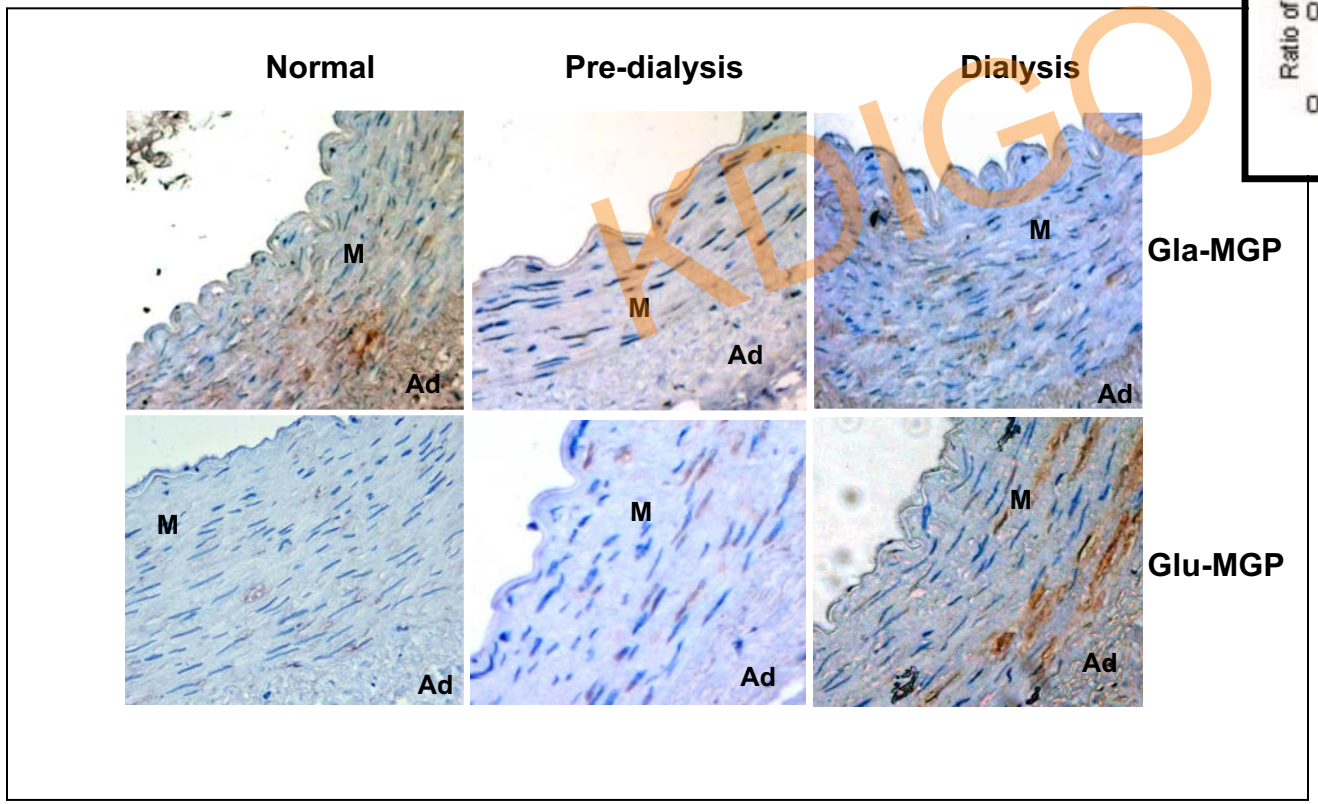


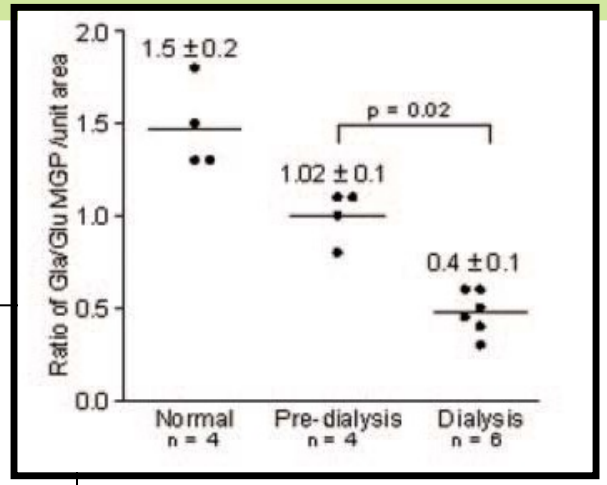
High Circulating Phosphate Levels, Transient Hypercalcemia?

Calcification correlates with VSMC loss via apoptosis

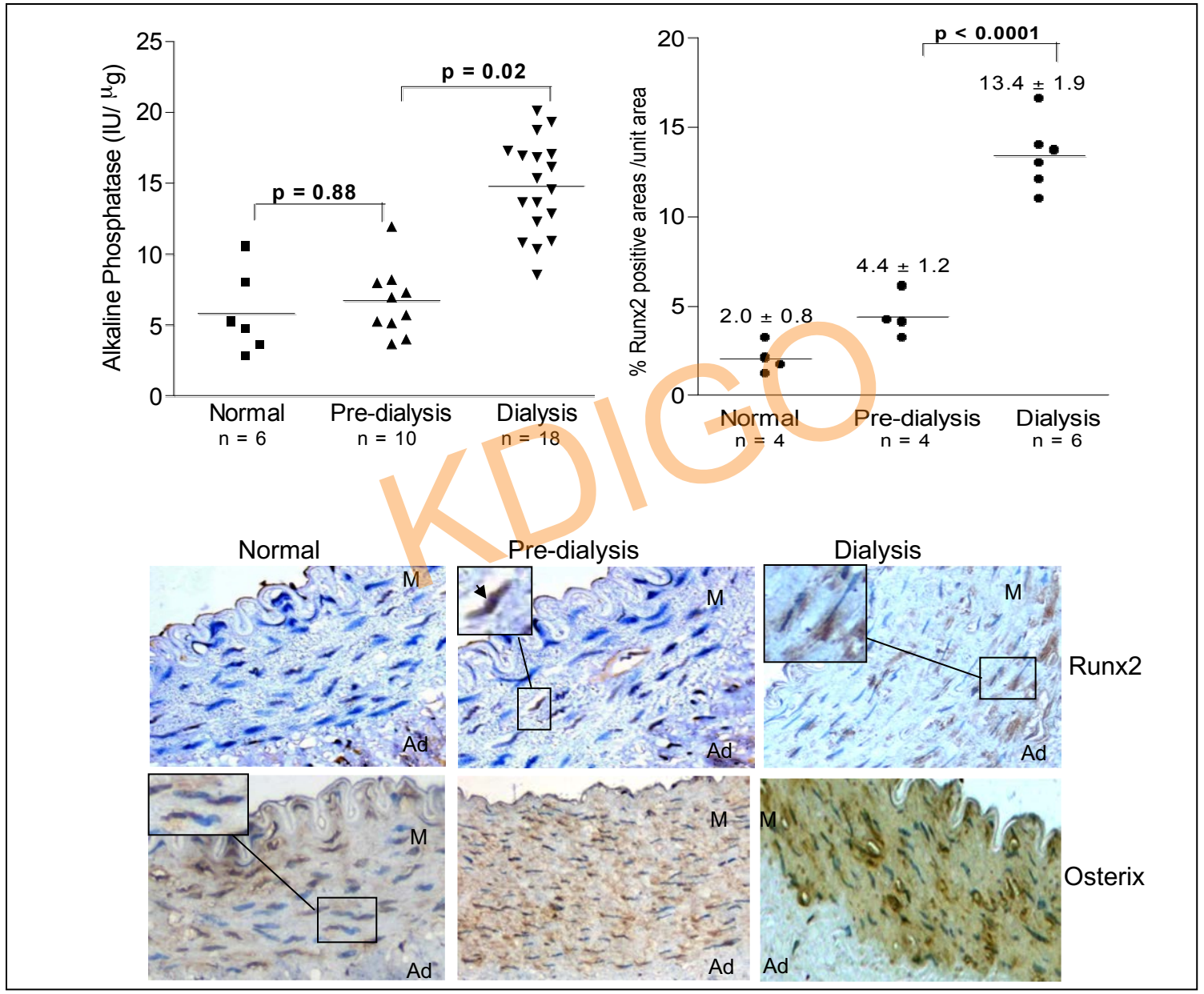


Loss of Calcification Inhibitors
Non-functional Glu-MGP predominates in Dialysis vessels



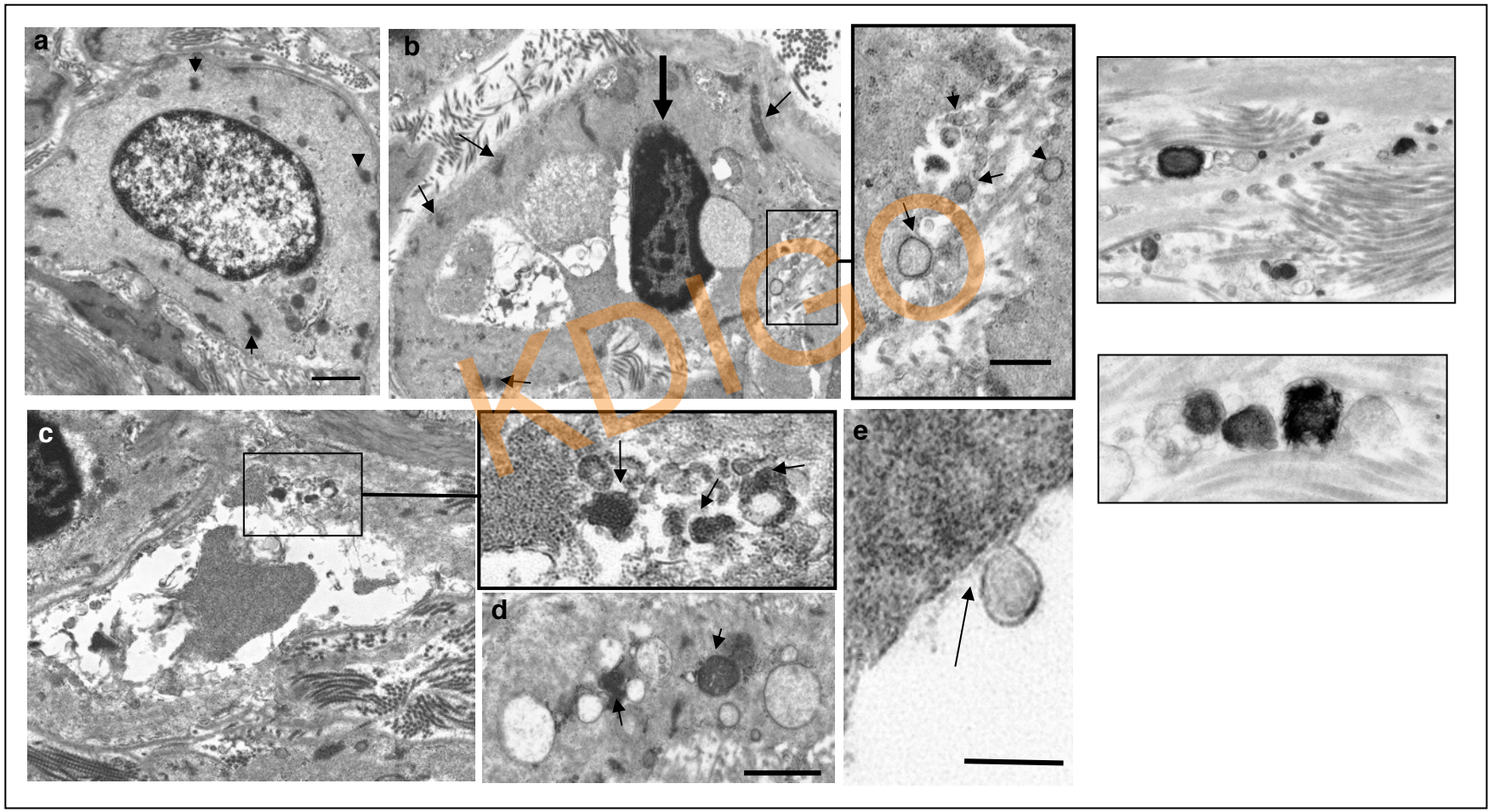


Dialysis vessels show increased osteogenic differentiation



(Shroff et al 2008,Circulation)

Ca load is associated with increased vesicle deposition by VSMCs



(Shroff et al 2008, *Circulation*)

Is there Evidence that the VSMCs from Children on Dialysis are Prematurely Aged?

ENVIRONMENTAL TOXINS

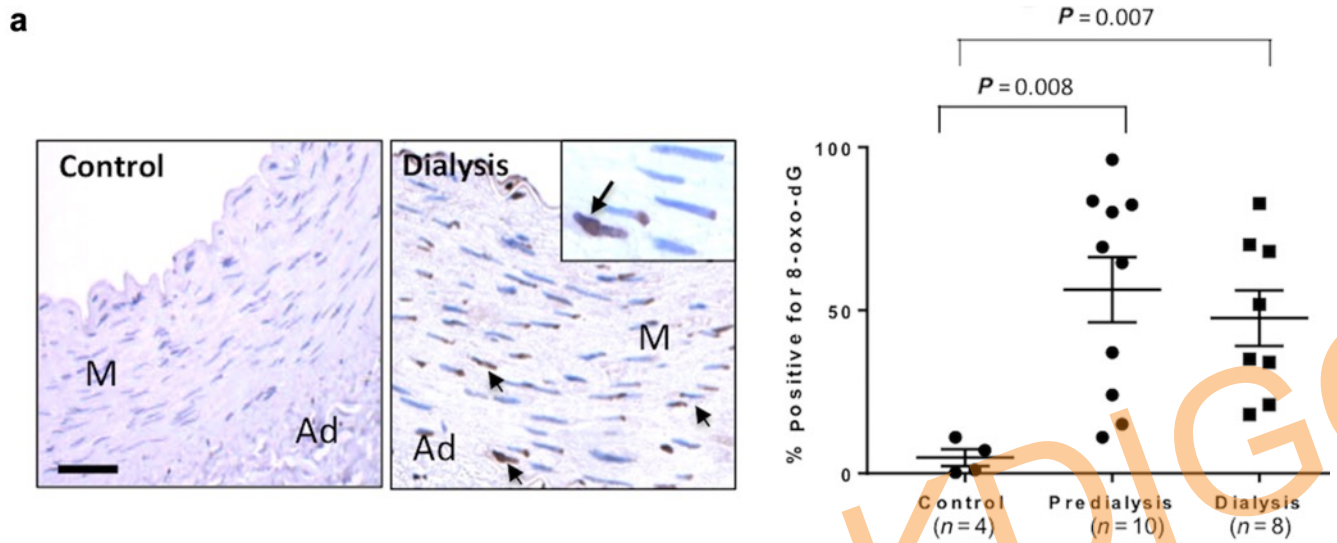
↓

DNA DAMAGE

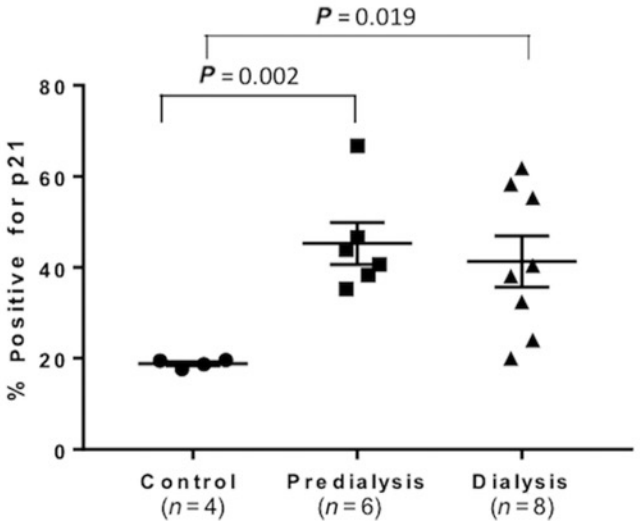
↓

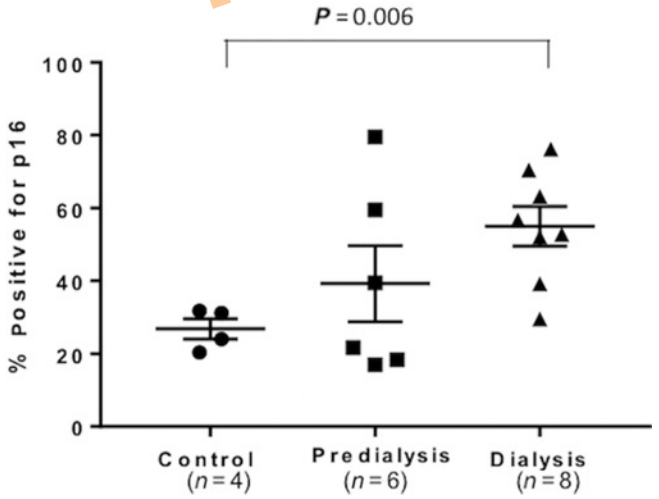
SENESCENCE
and
CELL DEATH

Vessels from Children on dialysis have increased senescence markers and oxidative DNA damage



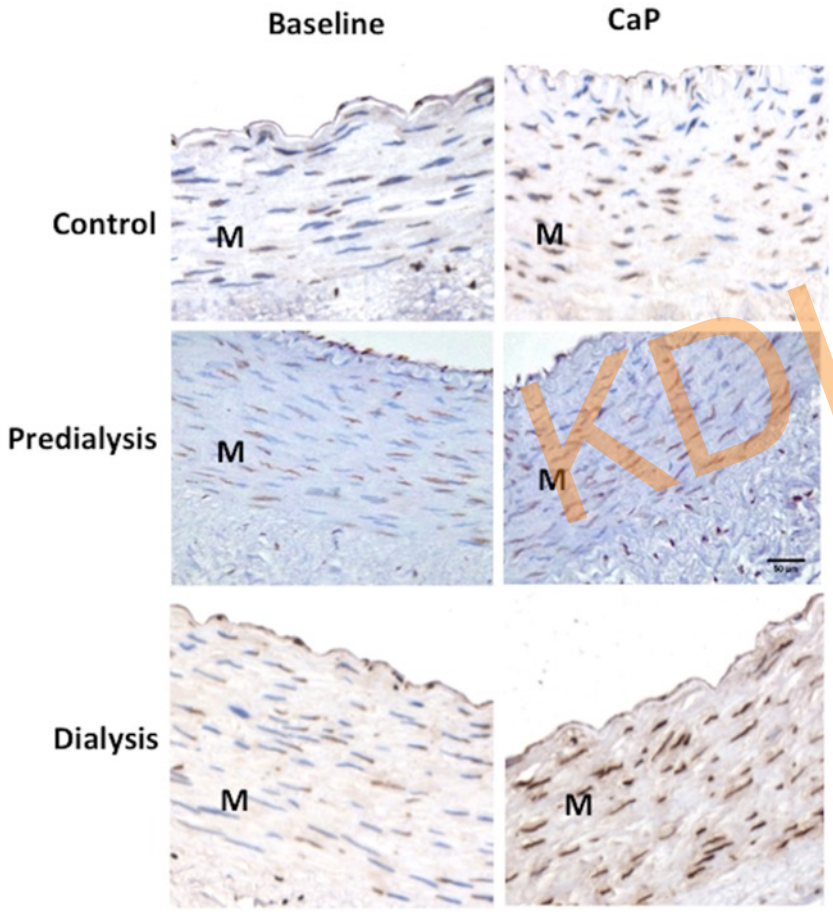
Oxidative DNA damage increases predialysis

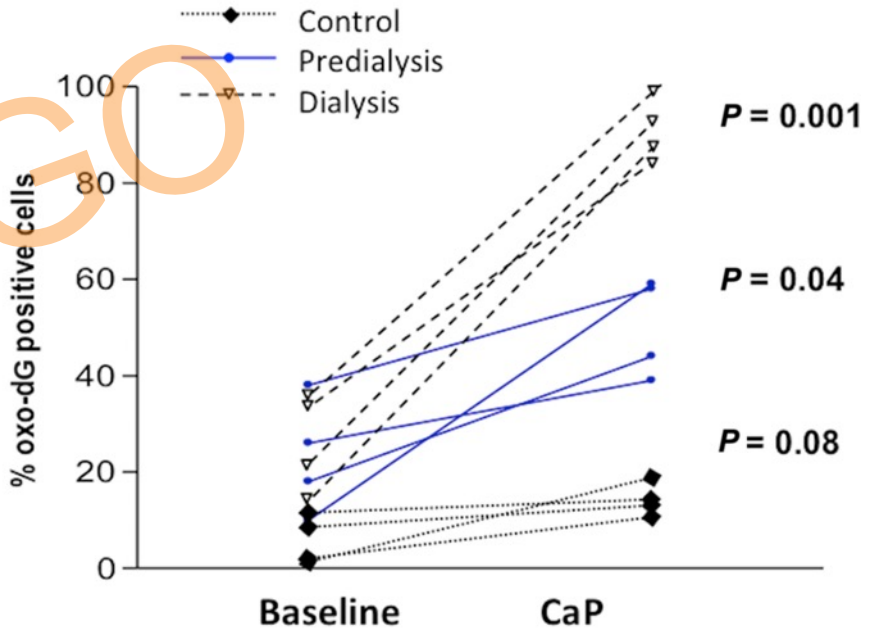




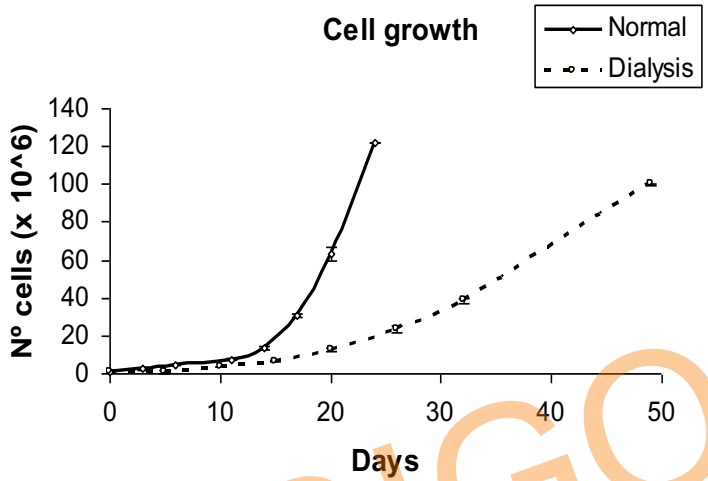
p16 is increased in Dialysis

Calcium and Phosphate Drive Oxidative DNA damage in Dialysis Vessels



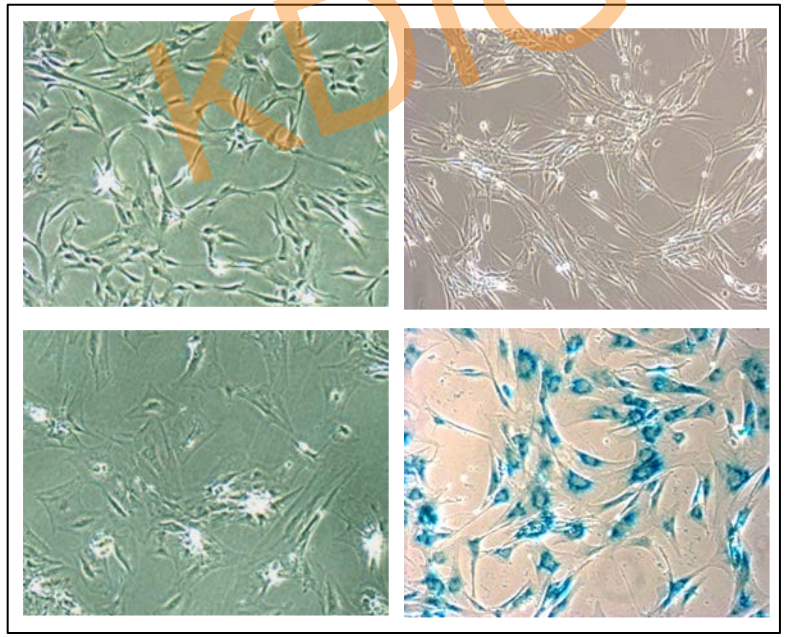


VSMCs from children on dialysis senesce early in culture



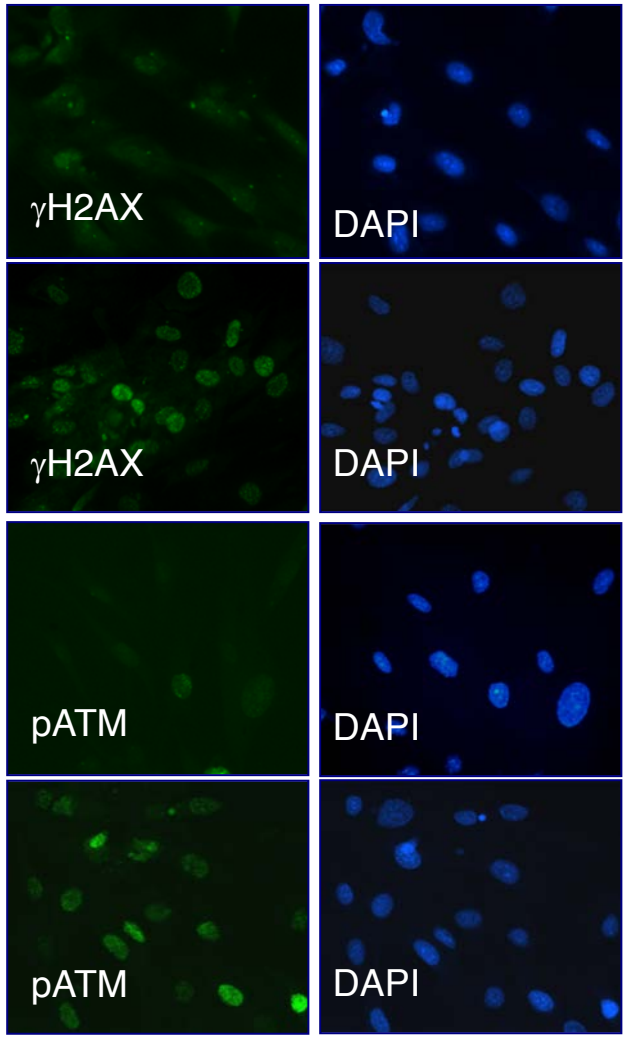
Normal P6

Dialysis P7



SAβG = senescence associated β-galactosidase

Calcium and Phosphate Induce DNA damage

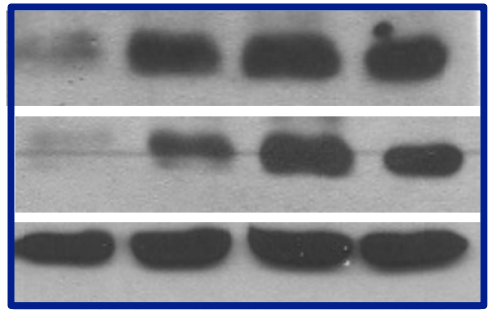


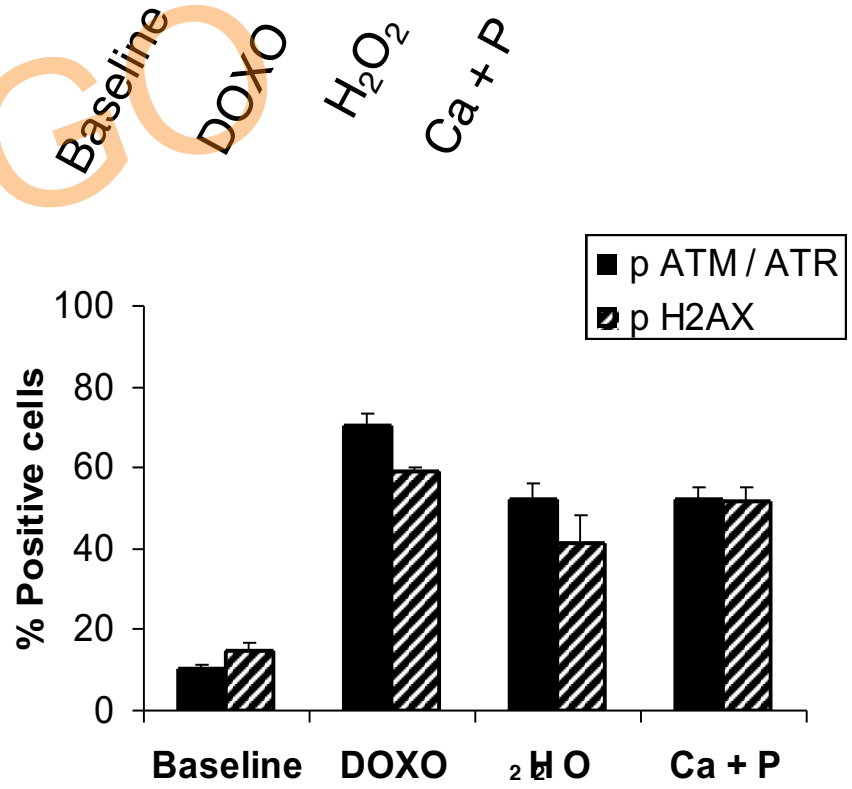
No treatment

Ca + P

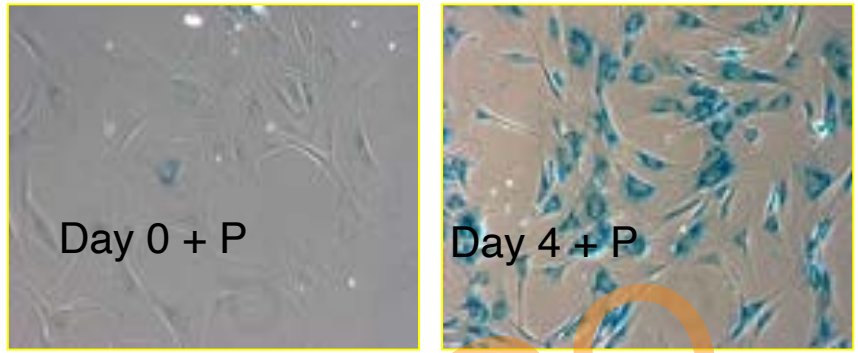
No treatment

Ca + P

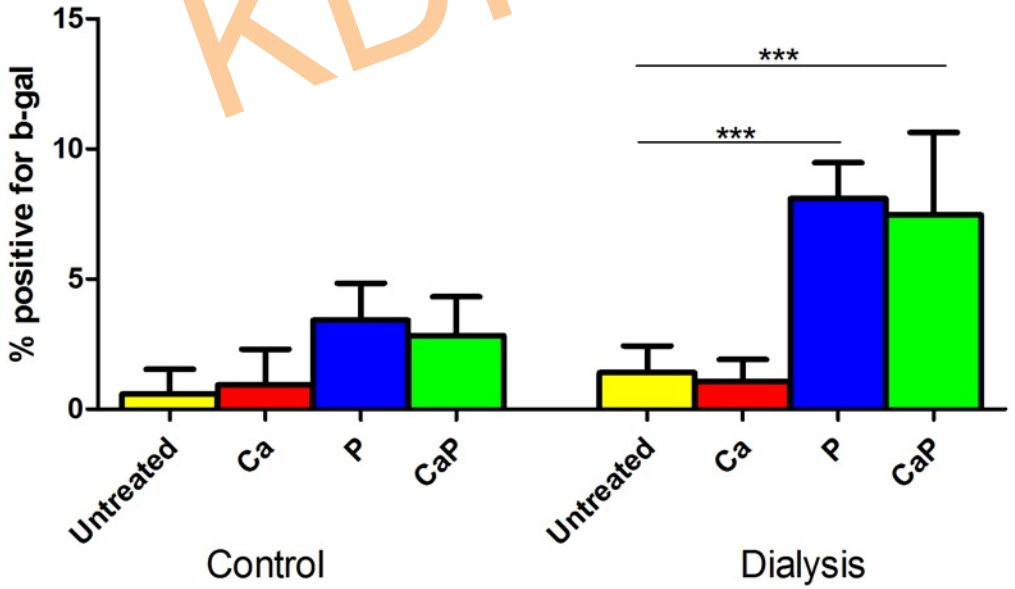




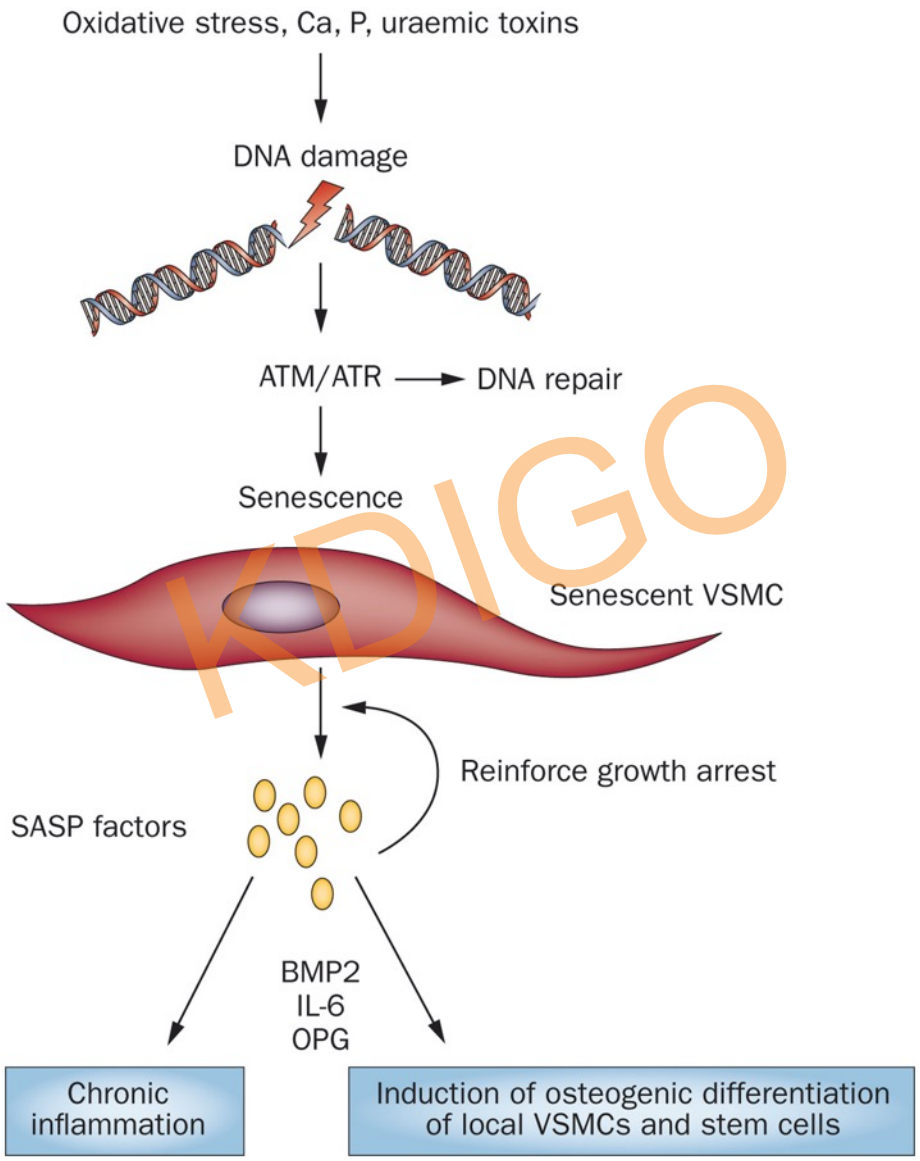
Phosphate treatment promotes VSMC senescence



SAβG

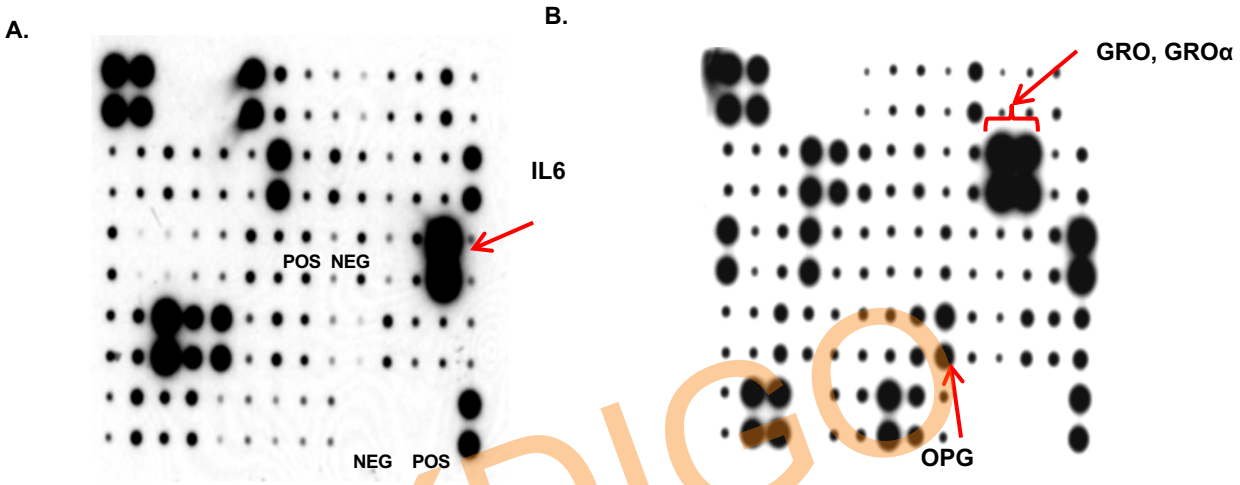


Senescence Associated Secretory Phenotype (SASP)



Shanahan, C. M. (2013)

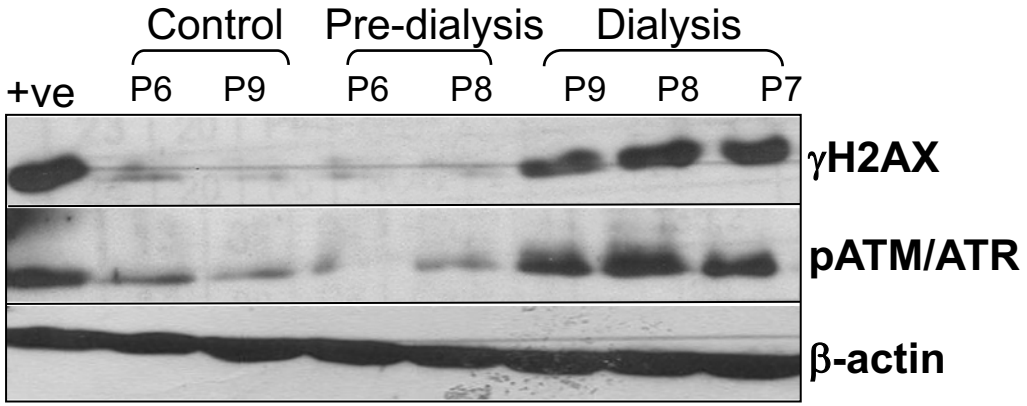
Array analysis shows VSMCs secrete pro-osteogenic cytokines in response to prelamin A accumulation

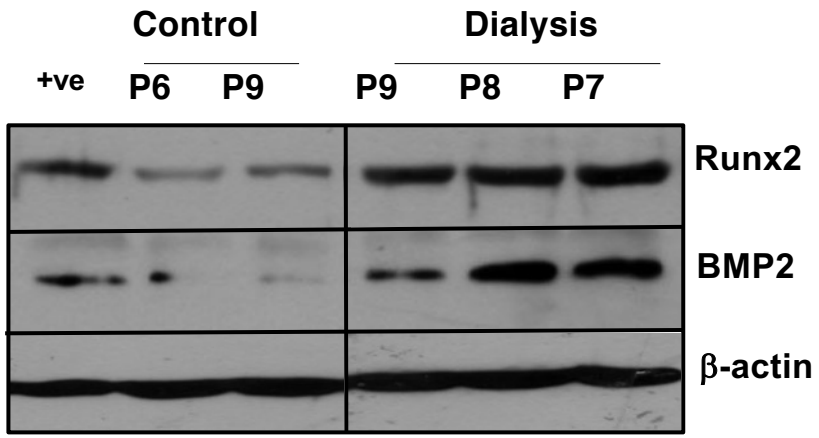


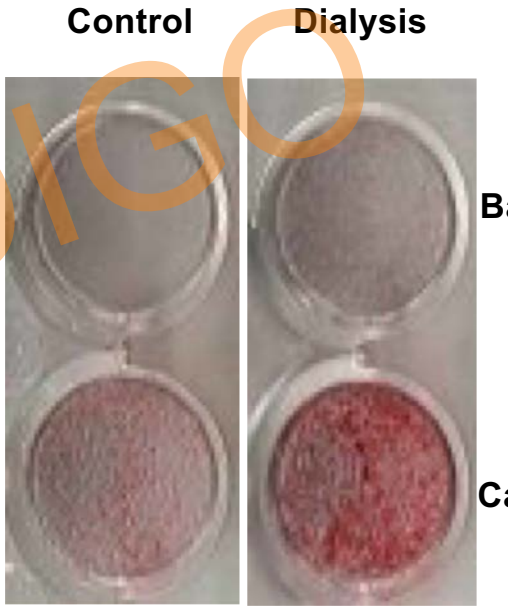
	SASP factors
Interleukins and chemokines	IL6, IL8, GRO, GROα, MCP-1, -2, -3, ENA78, GCP-2
Growth factors and regulators	Angiogenin, IGFBP-4, -6, VEGF, BMP2
Proteases	TIMP-1, -2
Soluble or shed receptors or ligands	OPG, Fas, uPAR, ICAM-1

Drugs that block the DDR reduce secretion of SASP factors and calcification.

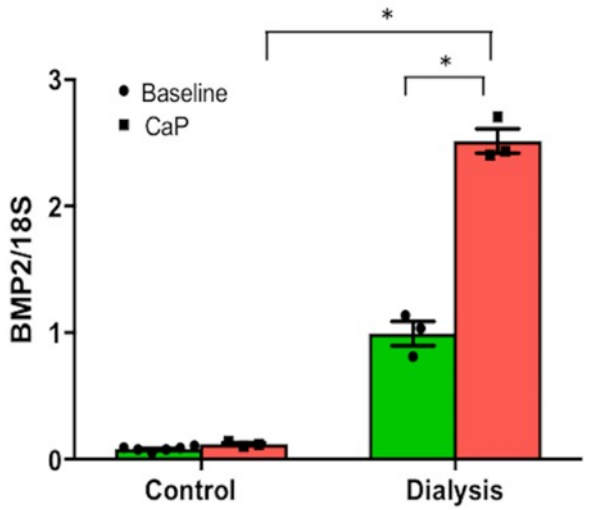
VSMCs from children on dialysis have increased levels of DNA damage and osteogenic differentiation *in vitro*







Elevated BMP2

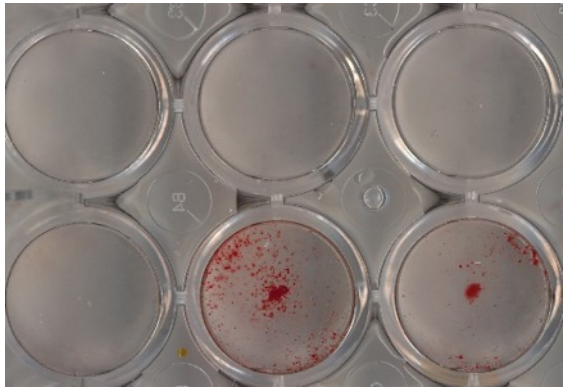


Pilar Sanchis et al, KI 2019

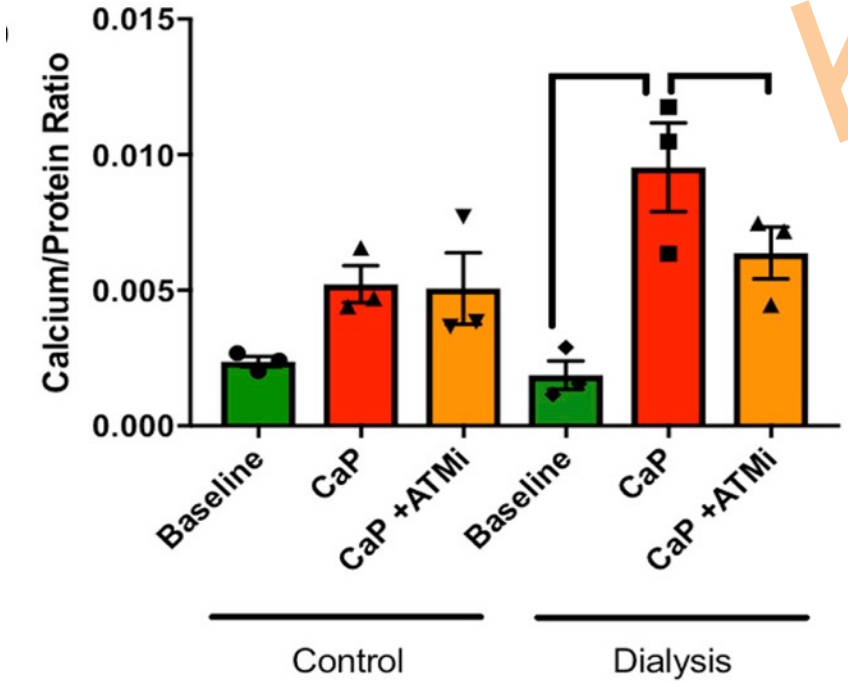
ATM inhibition blocks calcification and Inflammation in VSMCs from Children on Dialysis

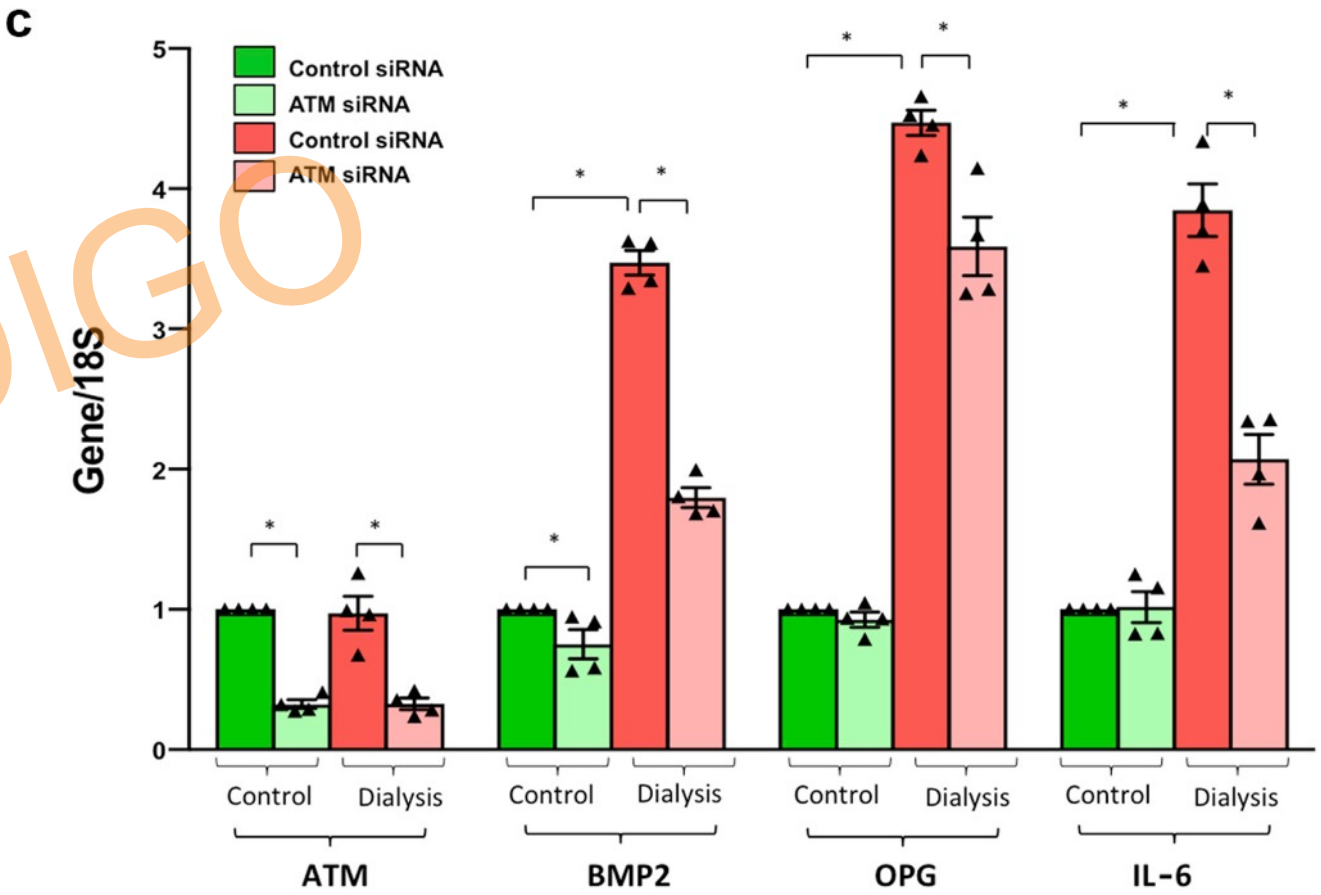
Control

Dialysis

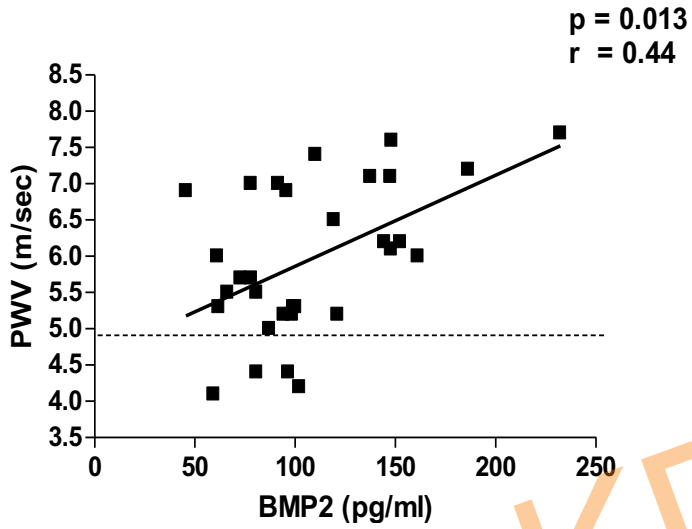


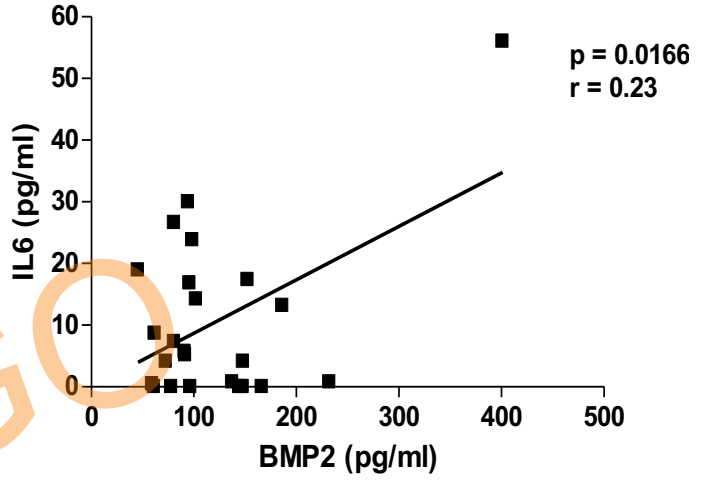
Baseline Ca/P Ca/P + iATM

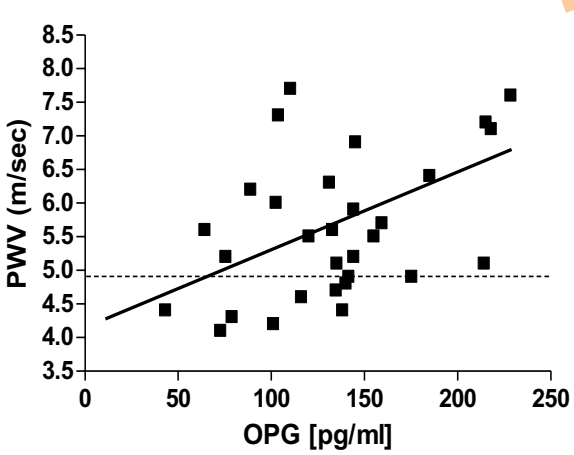


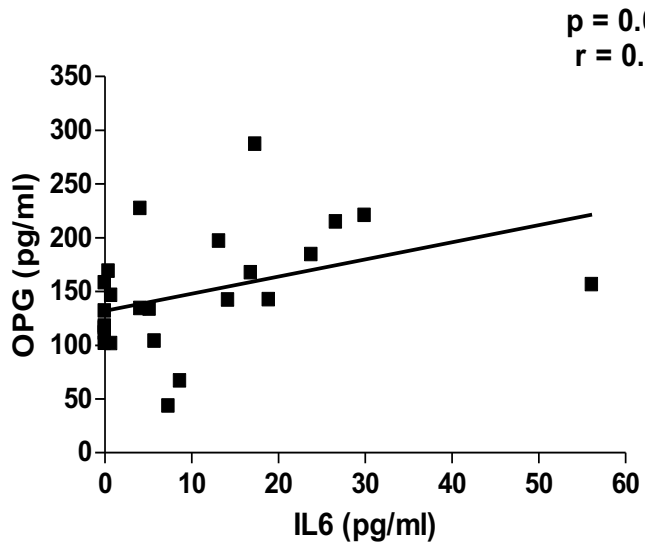


BMP2, IL6 and OPG are elevated in children on dialysis and correlate with vascular stiffness



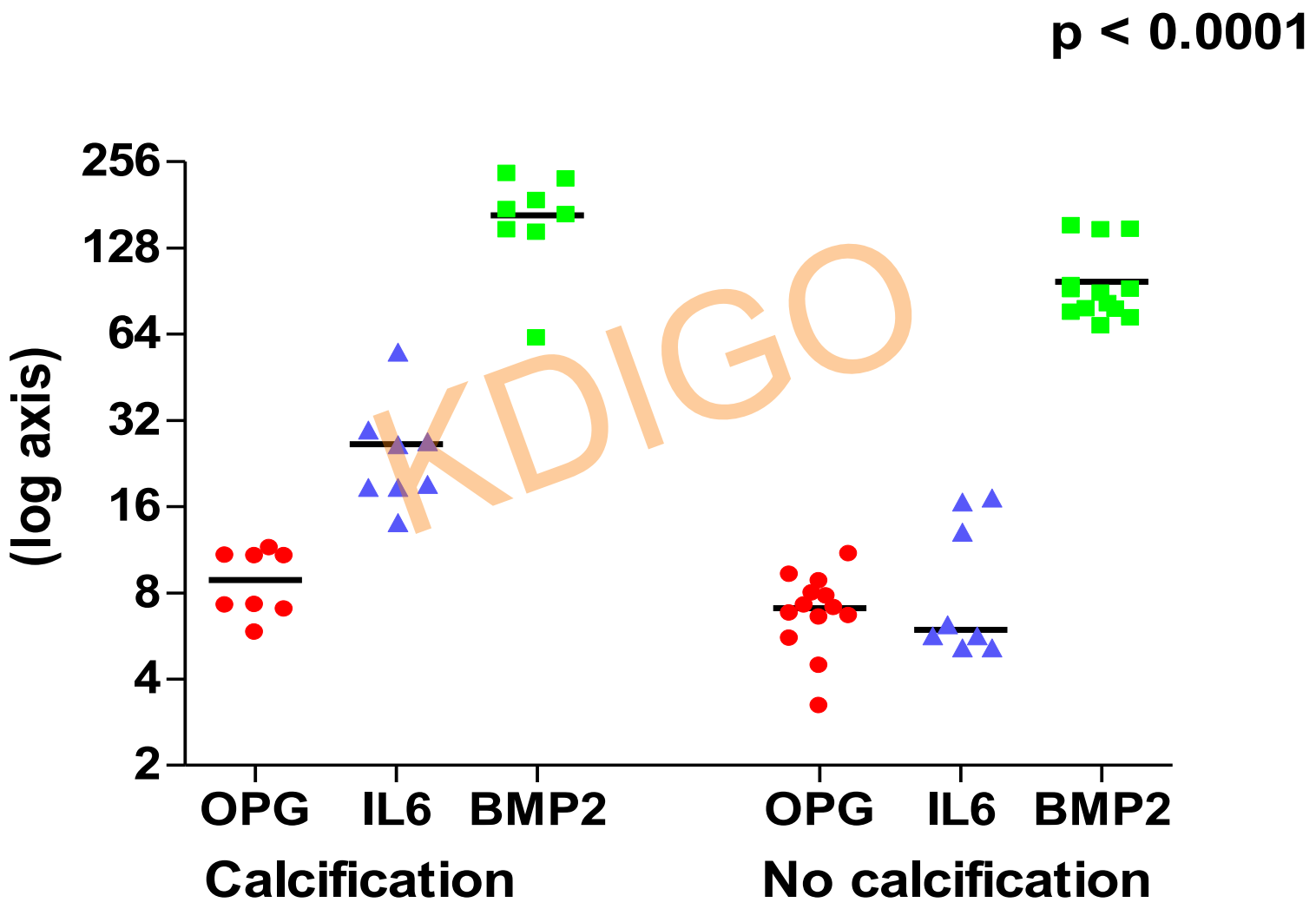




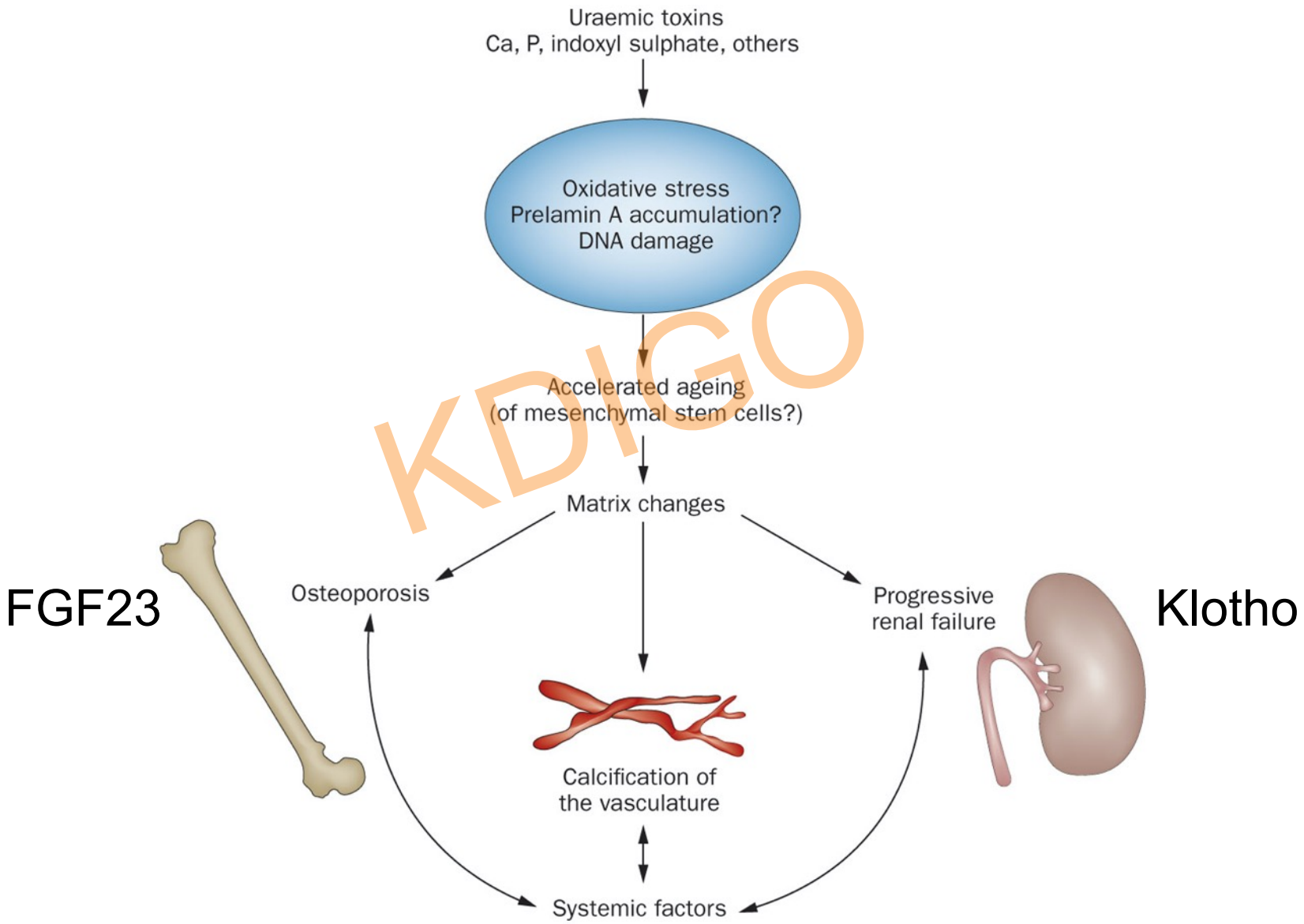


N=49

Circulating cytokines were significantly increased in children with calcification



Tissue ageing is driven by DNA damage and inflammatory mediators released from senescent tissues



Increased DNA Damage and Senescence in AAA

Journal of Vascular Research

Research Paper

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Progressive Development of Aberrant Smooth Muscle Cell Phenotype in Abdominal Aortic Aneurysm Disease

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[a]Leeds Institute of Cardiovascular and Metabolic Medicine (LICAMM), [b]Institute of Medical and Biological Engineering, School of Mechanical Engineering, and [c]Multidisciplinary Cardiovascular Research Centre (MCRC), University of Leeds, and [d]Leeds Vascular Institute, Leeds General Infirmary, Leeds, [e]Faculty of Life Sciences, University of Bradford, Bradford, and [f]Royal London Hospital, London, UK

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Age-Associated Sirtuin 1 Reduction in Vascular Smooth Muscle Links Vascular Senescence and Inflammation to Abdominal Aortic Aneurysm

Hou-Zao Chen*, **Fang Wang***, **Peng Gao***, **Jian-Fei Pei***, **Yue Liu**, **Ting-Ting Xu**, **Xiaoqiang Tang**, **Wen-Yan Fu**, **Jie Lu**, **Yun-Fei Yan**, **Xiao-Man Wang**, **Lei Han**, **Zhu-Qin Zhang**, **Ran Zhang**, **Ming-Hui Zou**, and **De-Pei Liu**

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Atherosclerosis

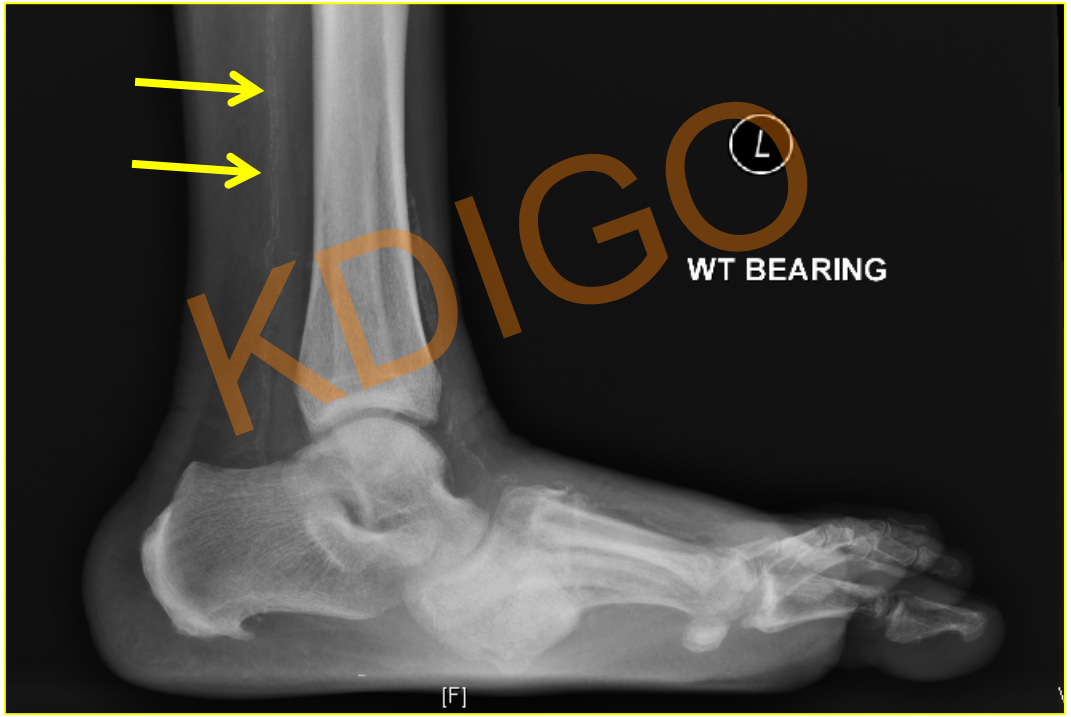
journal homepage: www.elsevier.com/locate/atherosclerosis

Association of relative telomere length with cardiovascular disease in a large chronic kidney disease cohort: The GCKD study

Julia Raschenberger [a, 1], Barbara Kollerits [a, 1], Stephanie Titze [b], Anna Köttgen [c], Barbara Bärthlein [d], Arif B. Ekici [e], Lukas Forer [a], Sebastian Schönherr [a], Hansi Weissensteiner [a], Margot Haun [a], Christoph Wanner [f], Kai-Uwe Eckardt [b], Florian Kronenberg [a, *], for the GCKD study Investigators

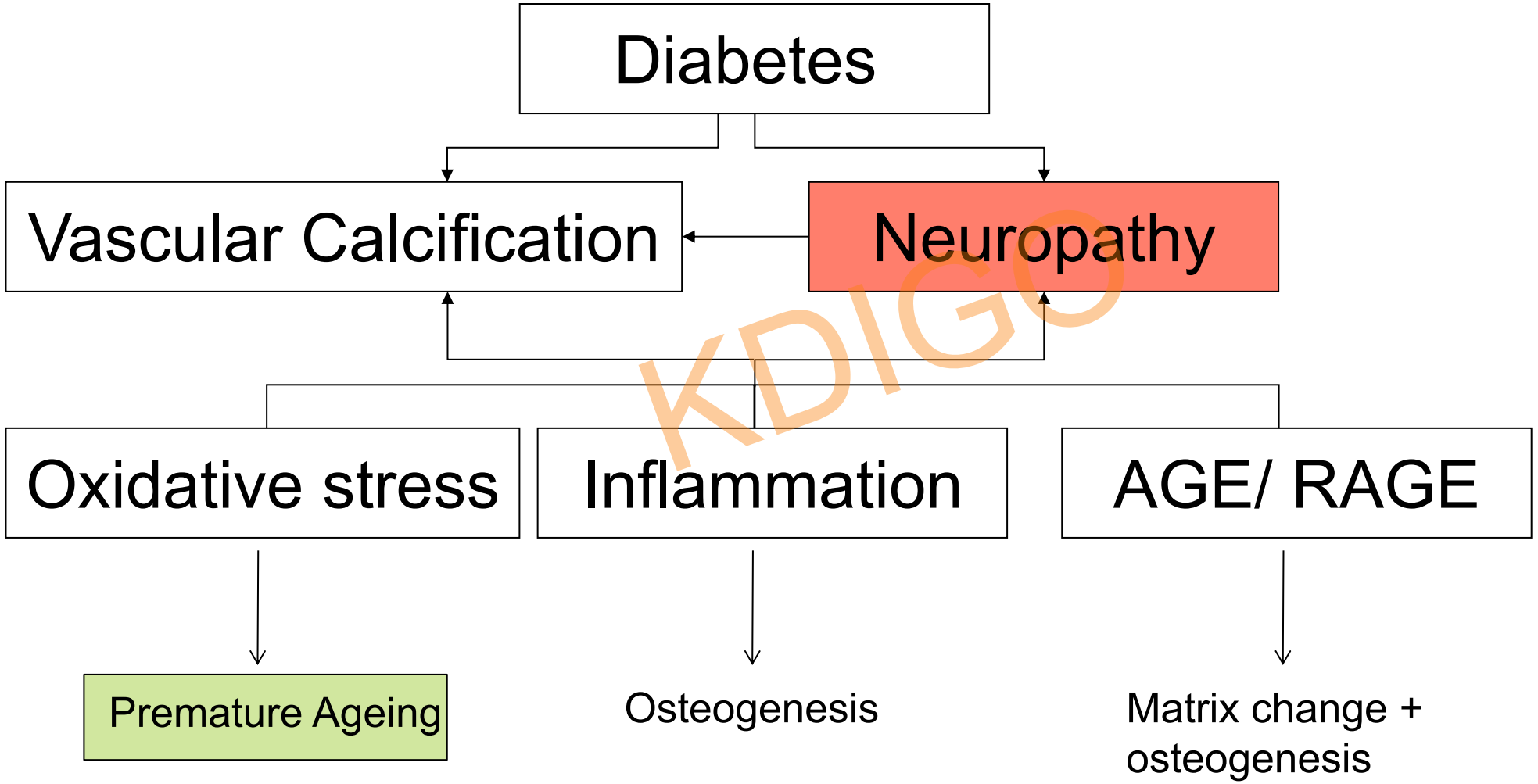
Diabetes is Associated with a high Prevalence of Vascular Calcification in Peripheral Arteries

Peripheral Artery Calcification in Diabetes



Associated with increased CV mortality, amputation and ulcers, surgical complications

Mechanisms of Calcification in Diabetes/Charcot Foot



Neuropathy as a Novel Cause of Vascular Calcification in the Extremities

TABLE 11—*Prevalence of neuropathy, proliferative retinopathy, and proteinuria in patients with calcification compared with patients without calcification, and significances of differences*

	Neuropathy		Proliferative retinopathy		Proteinuria	
	Present	Absent	Present	Absent	Present	Absent
Patients with calcification	16	4	9	11	10	10
Patients without calcification	4	16	1	19	3	17
Significance of difference*	$p<0.001$		$p<0.02$		$p<0.05$	

*χ^2 test with Yates's correction.

Diabetologia (1983) 24: 347–350

Diabetologia

Mönckeberg's Sclerosis After Sympathetic Denervation in Diabetic and Non-diabetic Subjects

F.-D. Goebel and H. S. Füessl

Medizinische Poliklinik, University of Munich, FRG

Edmonds, ME et al 1982

Mechanisms Unknown:

Loss of Trophic Factors?

Calcium Metabolism?

KDIGO

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