

Roles of Fetuin-A in Hypertension

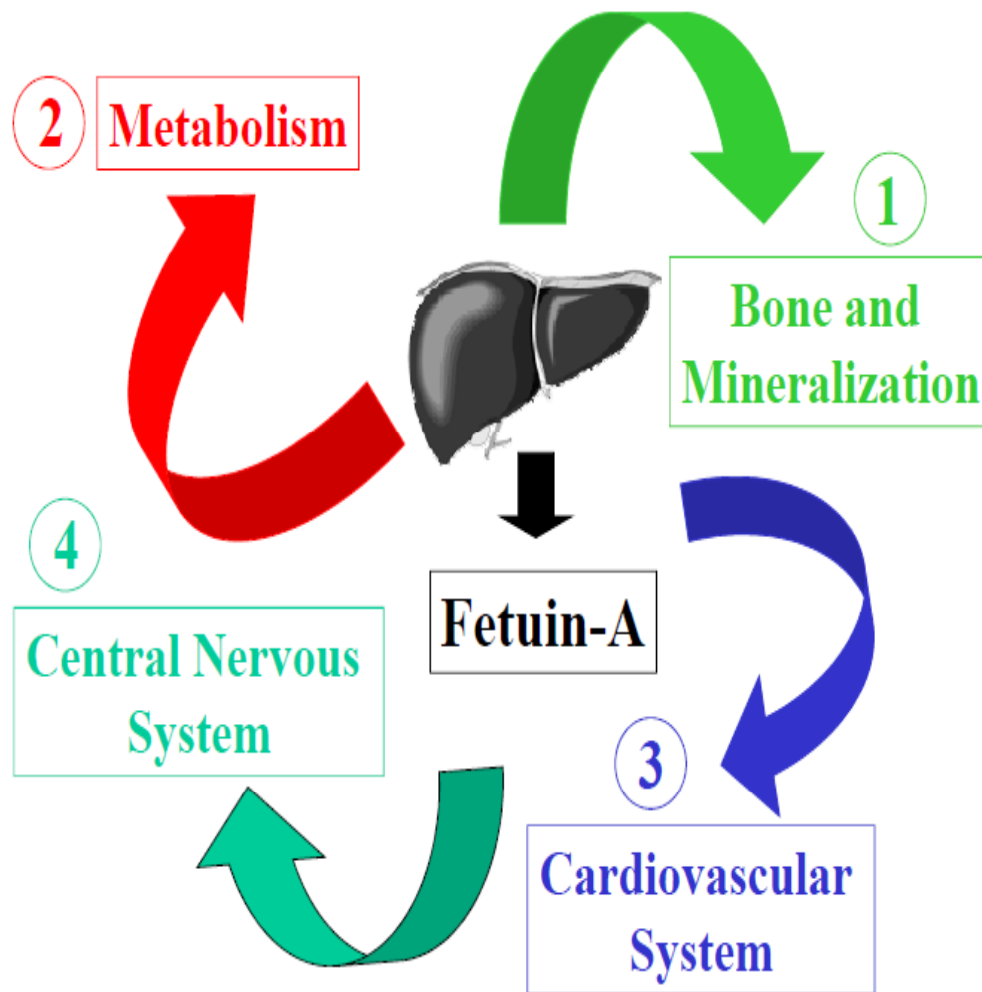
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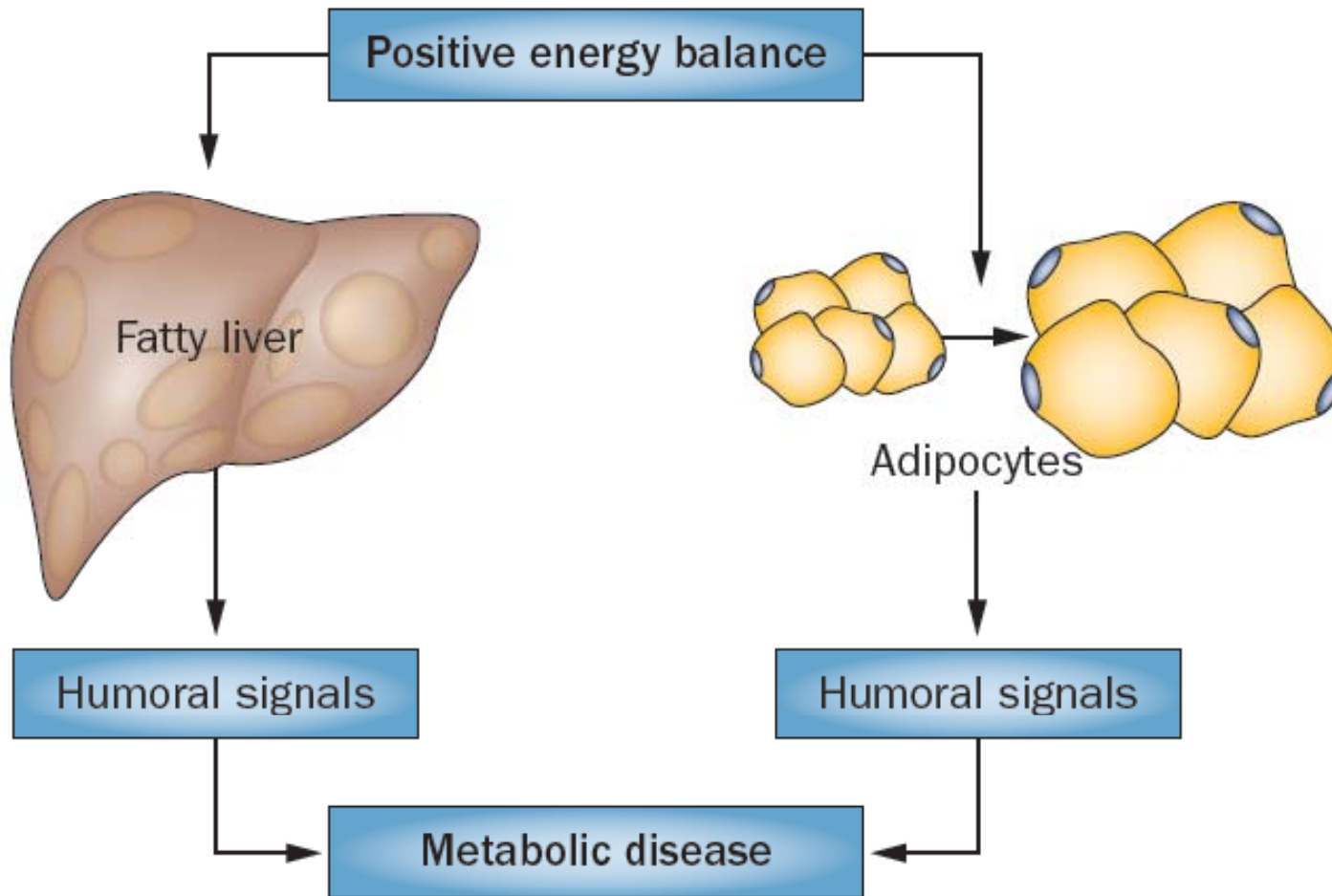
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Fetuin-A (Alpha-2-HS-glycoprotein)



- **Multi-functional protein secreted by liver**
- **Involves in a variety of physiological and pathological conditions**
 - ✓ **Bone metabolism**
 - ✓ **Insulin resistance**
 - ✓ **Inflammation**
 - ✓ **Vascular calcification**
 - ✓ **Neurodegenerative diseases**

Roles of liver and adipose tissue in metabolic diseases



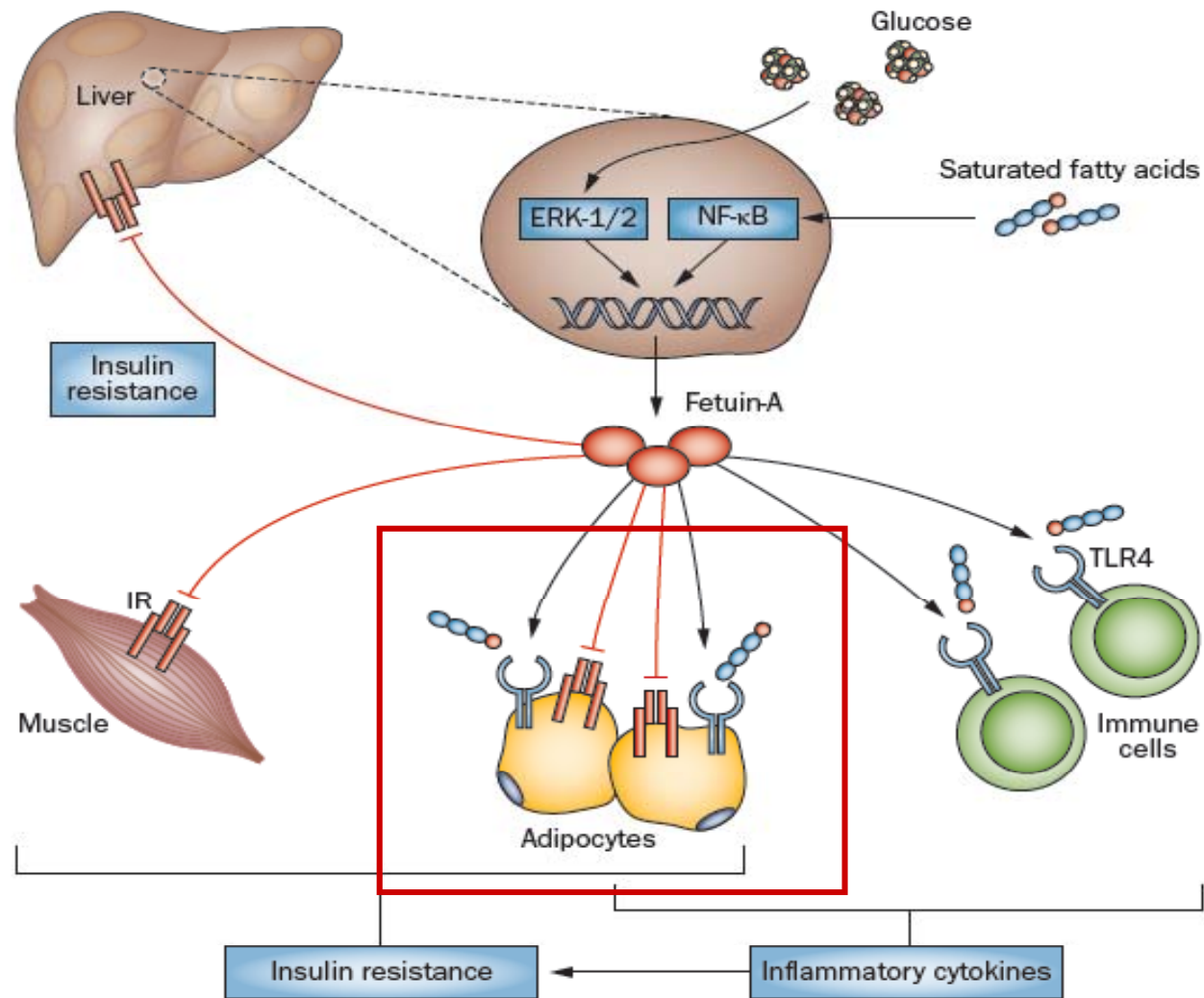
Nature 2013; 9: 144

Functions of key hepatokines in metabolism

Hepatokine	Effects	
	<i>In vitro</i> or in animal models	In humans
Angiopoietin-related protein 6	Energy expenditure ↑ Obesity ↓ NAFLD ↓ Insulin resistance ↓	Insulin resistance ↑
Fetuin-A	Obesity –/↑ Insulin resistance ↑ Subclinical inflammation ↑	Obesity – NAFLD ↑ Insulin resistance ↑ Subclinical inflammation ↑ T2DM ↑ CVD ↑
FGF-21	Energy expenditure ↑ Insulin resistance ↓ β-cell survival ↑	Obesity ↑ NAFLD ↑ Insulin resistance ↑
IGFs and IGFBPs	Insulin resistance –/↑/↓	Insulin resistance ↑/↓
Selenoprotein P	Insulin resistance ↑	Insulin resistance ↑ Subclinical inflammation ↑
Sex hormone-binding globulin	Sex hormone bioavailability ↑ Sex hormone signalling ↑	Obesity ↓ NAFLD ↓ Insulin resistance ↓ Subclinical inflammation ↓ T2DM ↓ CVD ↓

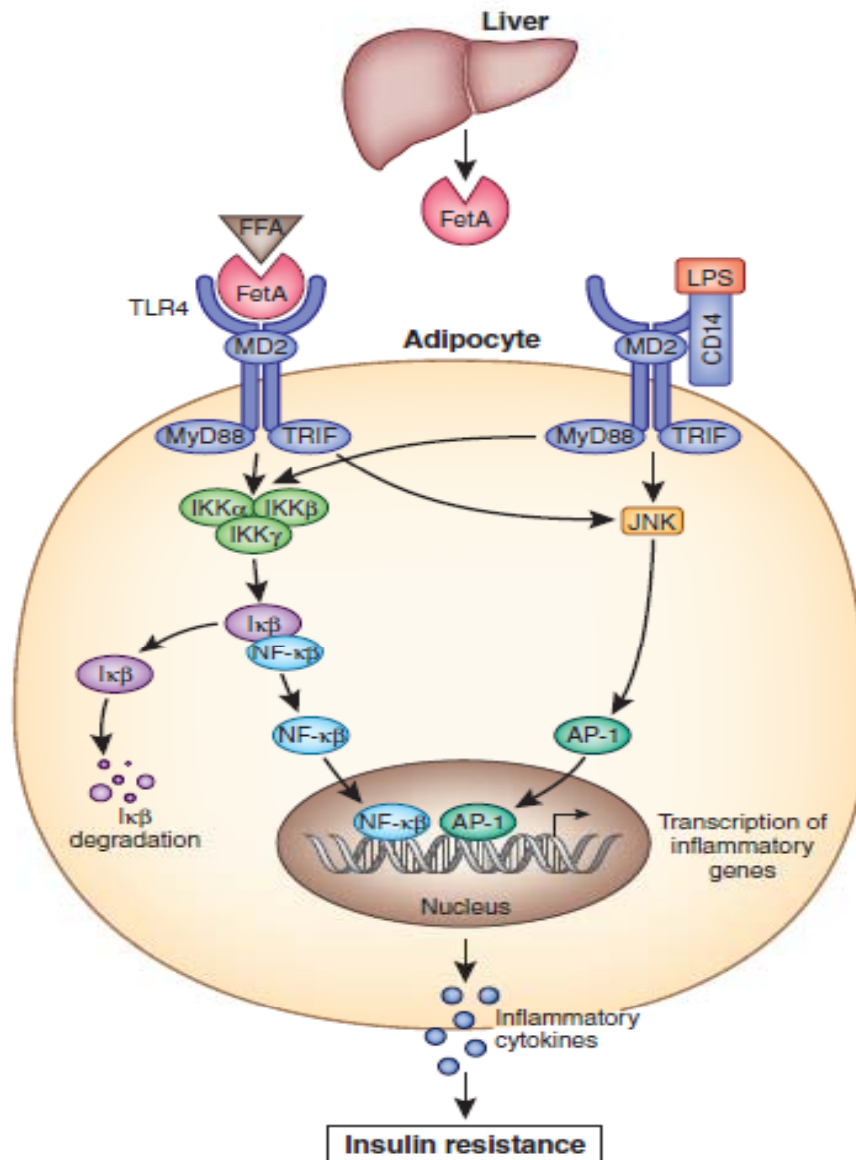
Nature 2013; 9: 144

Causes and consequences of increased production of fetuin-A



Nature 2013; 9: 144

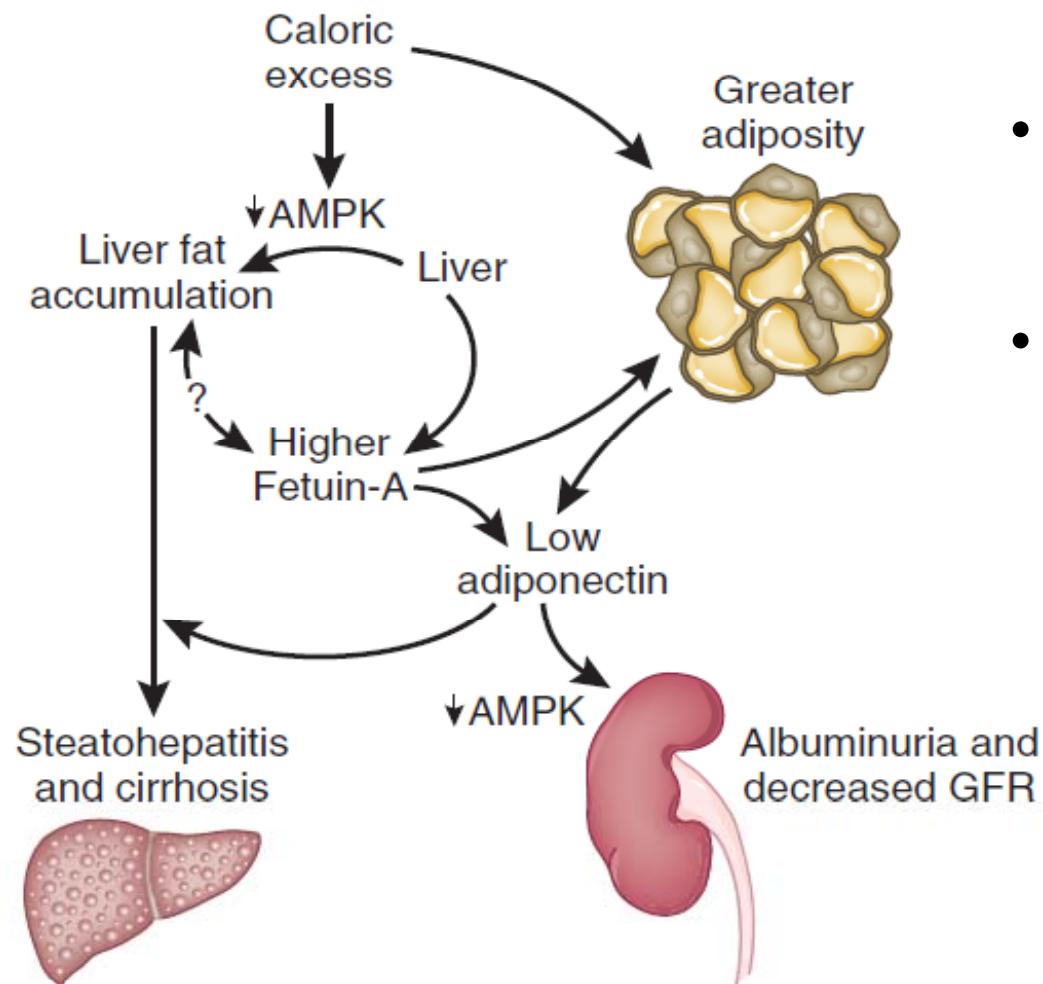
Fetuin-A and inflammation



Fetuin-A functions as an adaptor between FFAs and TLR4 signaling in lipid-induced inflammation.

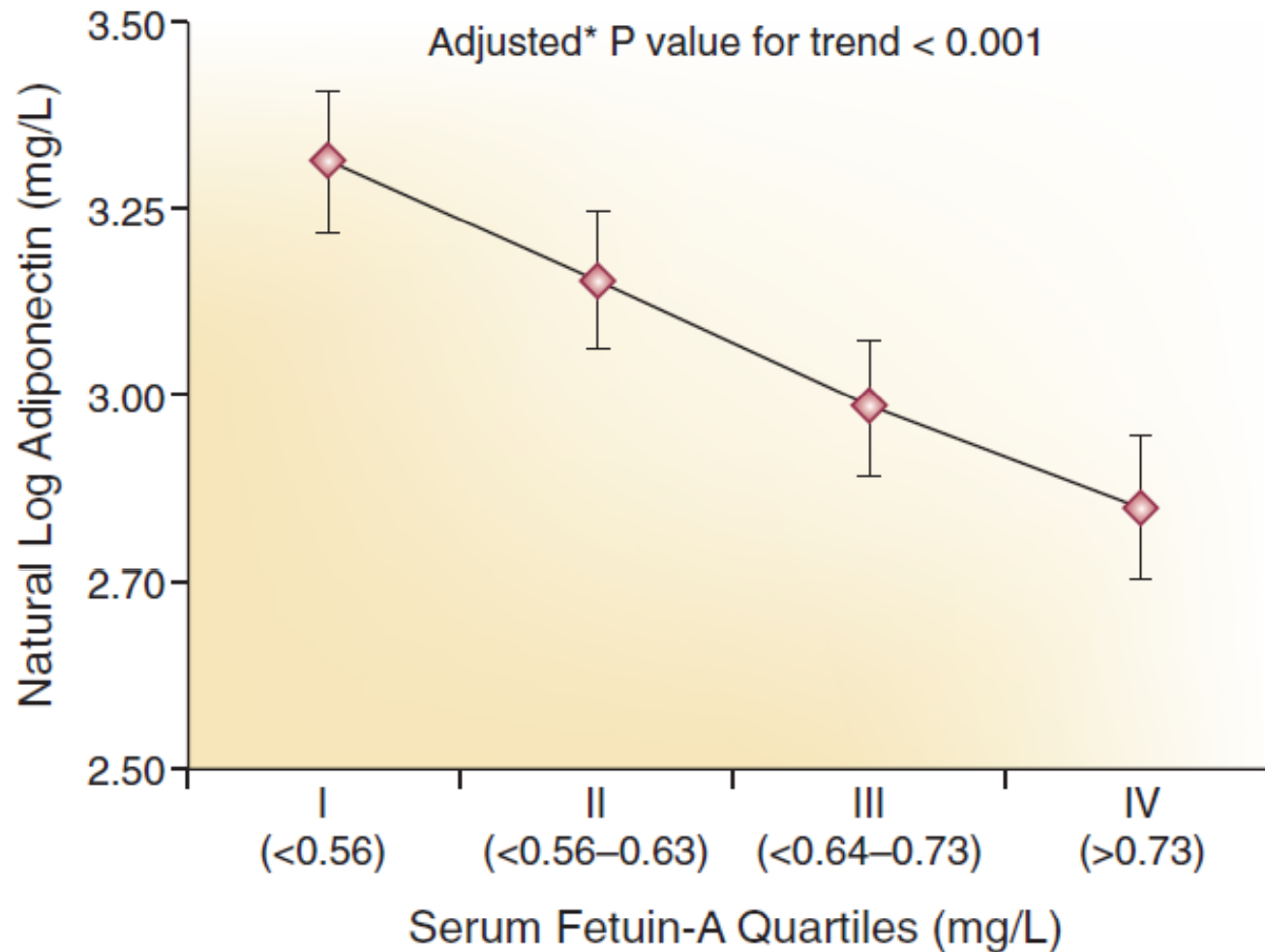
Nature Med 2012; 18: 1182

Relationship between fetuin-A and adiponectin

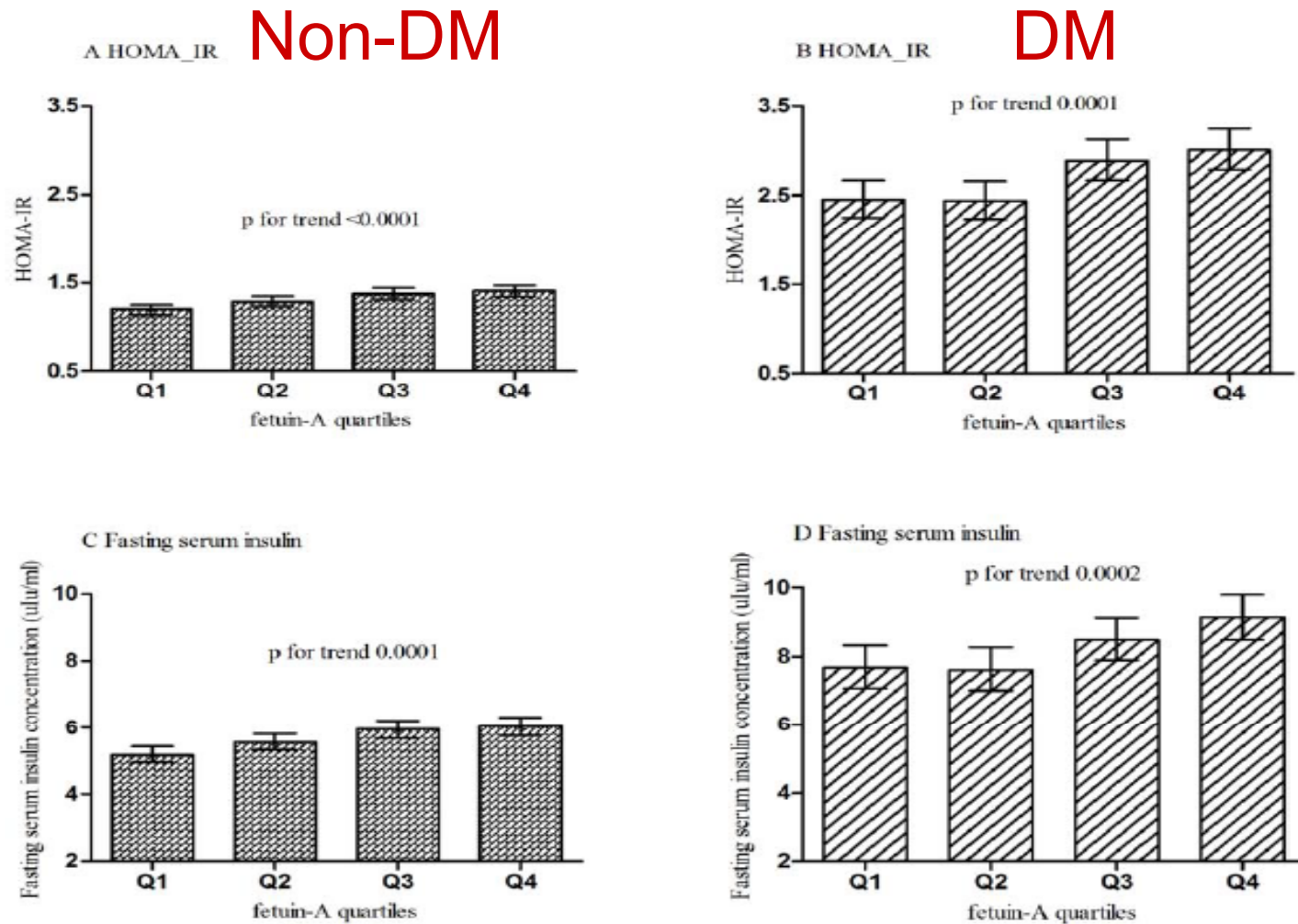


- Fetuin-A can directly suppress adiponectin transcription
- Lower adiponectin reduces AMPK, which promotes steatohepatitis in the liver and foot process effacement in the kidney leading to albuminuria

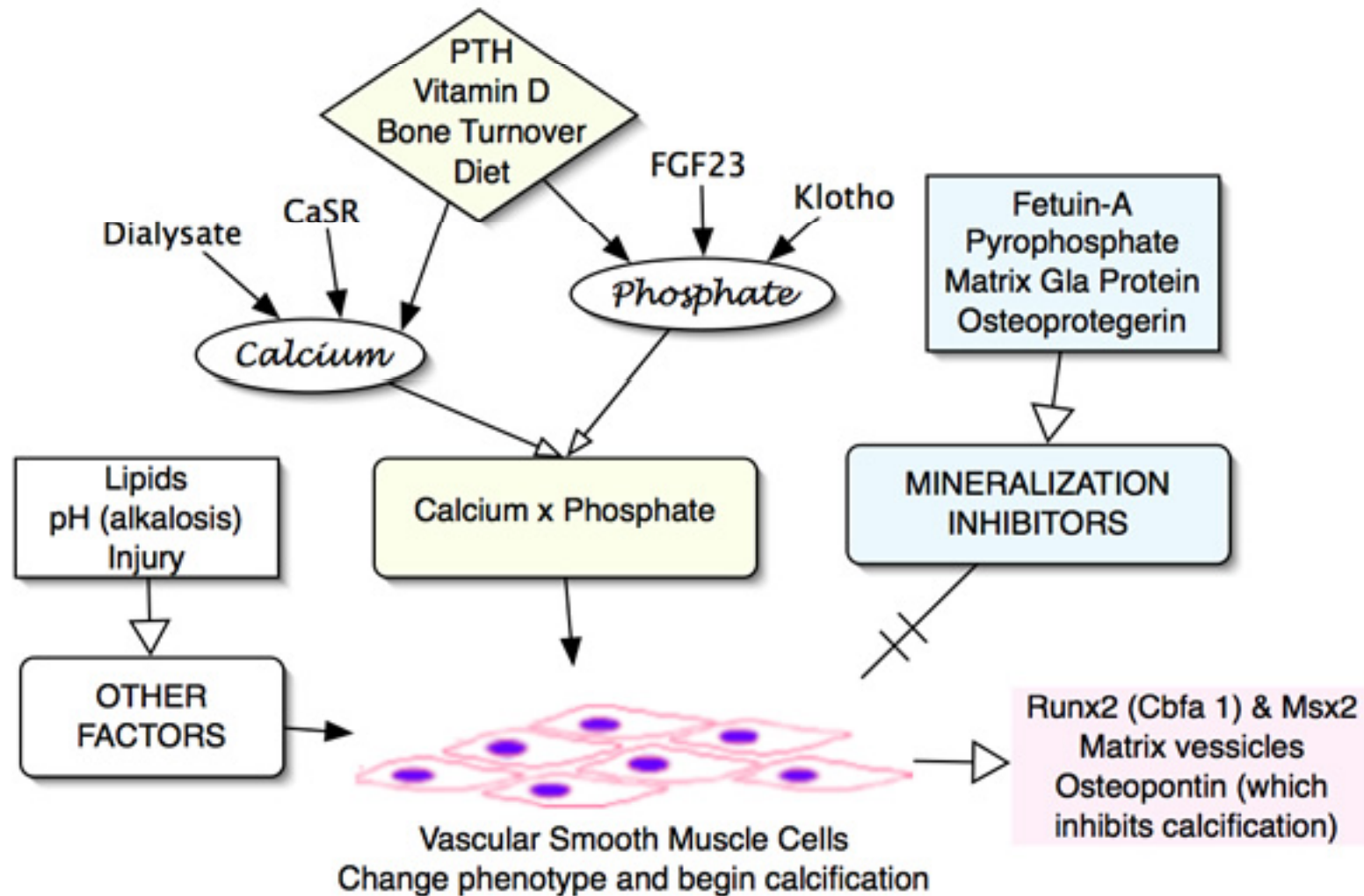
Serum fetuin-A is inversely correlated with adiponectin levels



Serum fetuin-A levels in Chinese adults

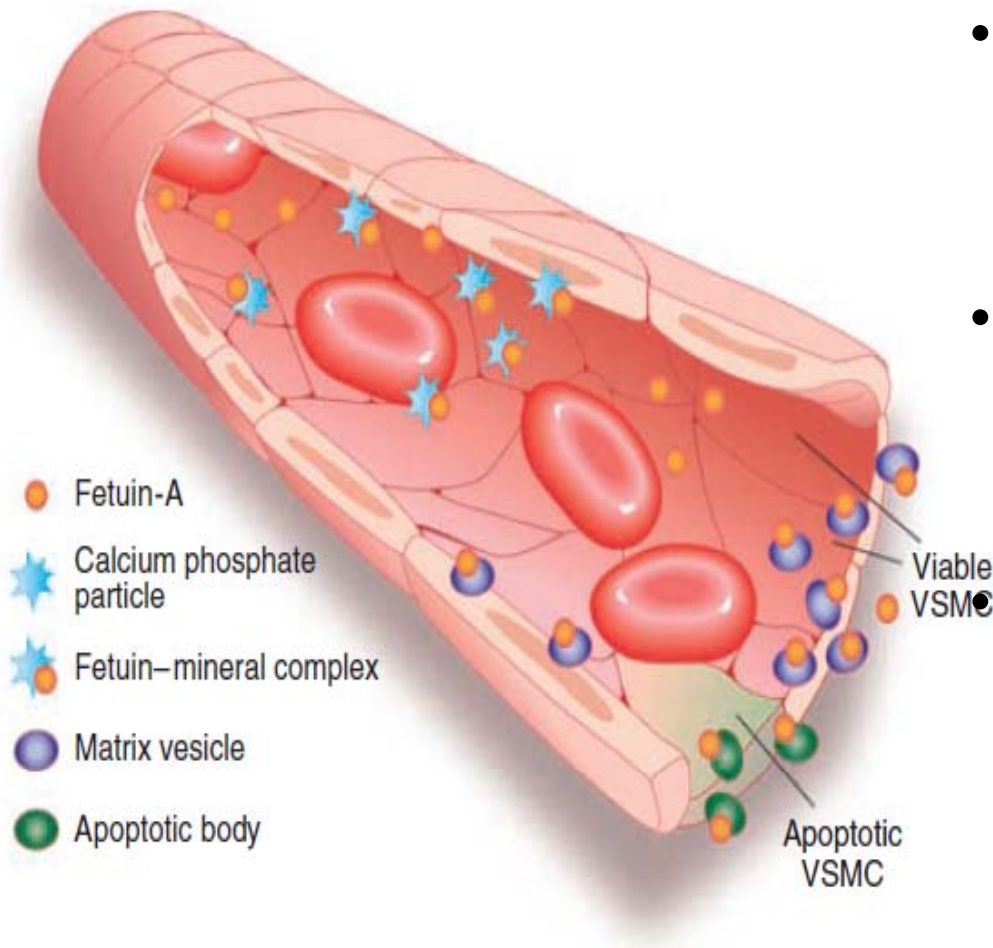


Factors involved in vascular calcification

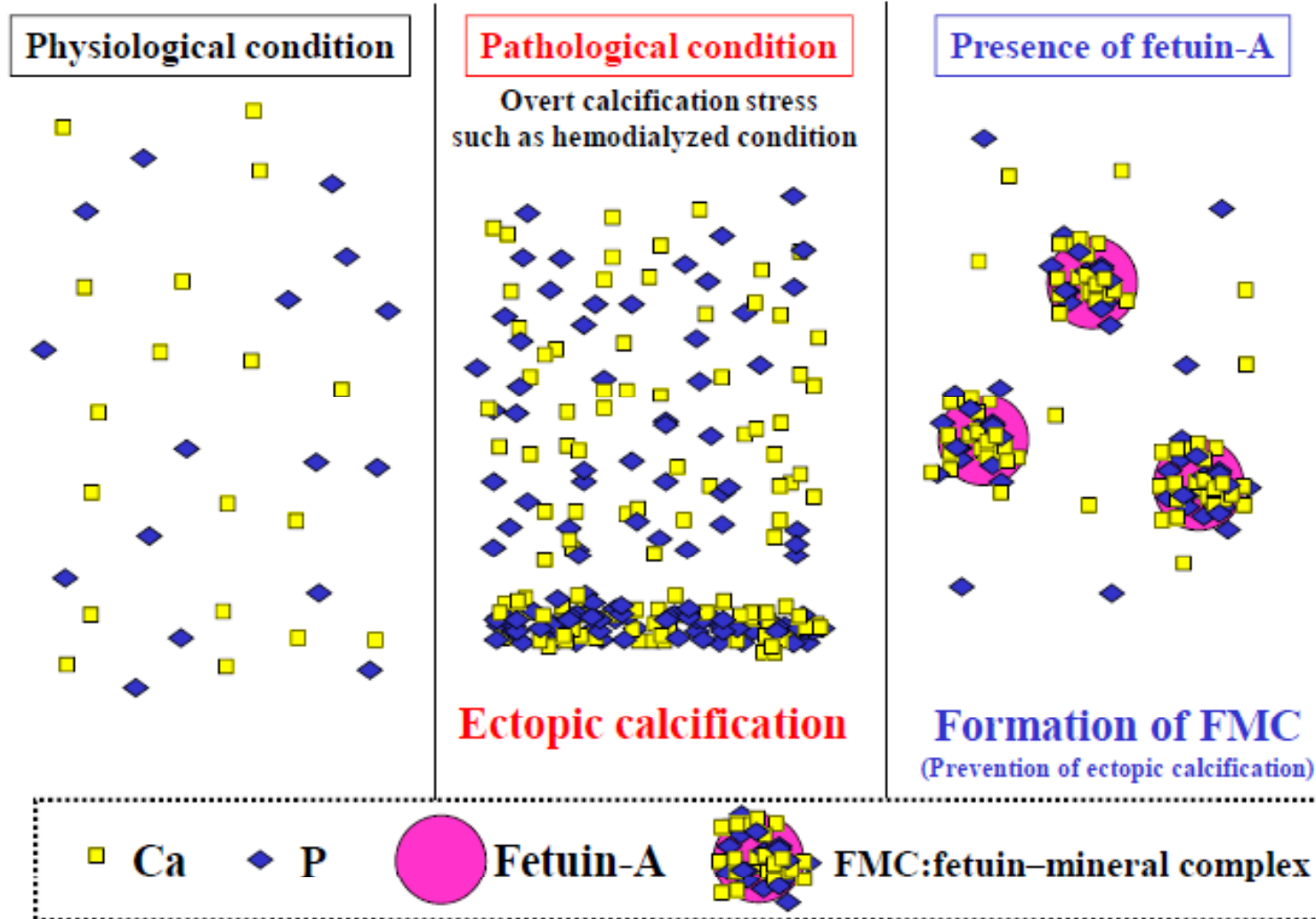


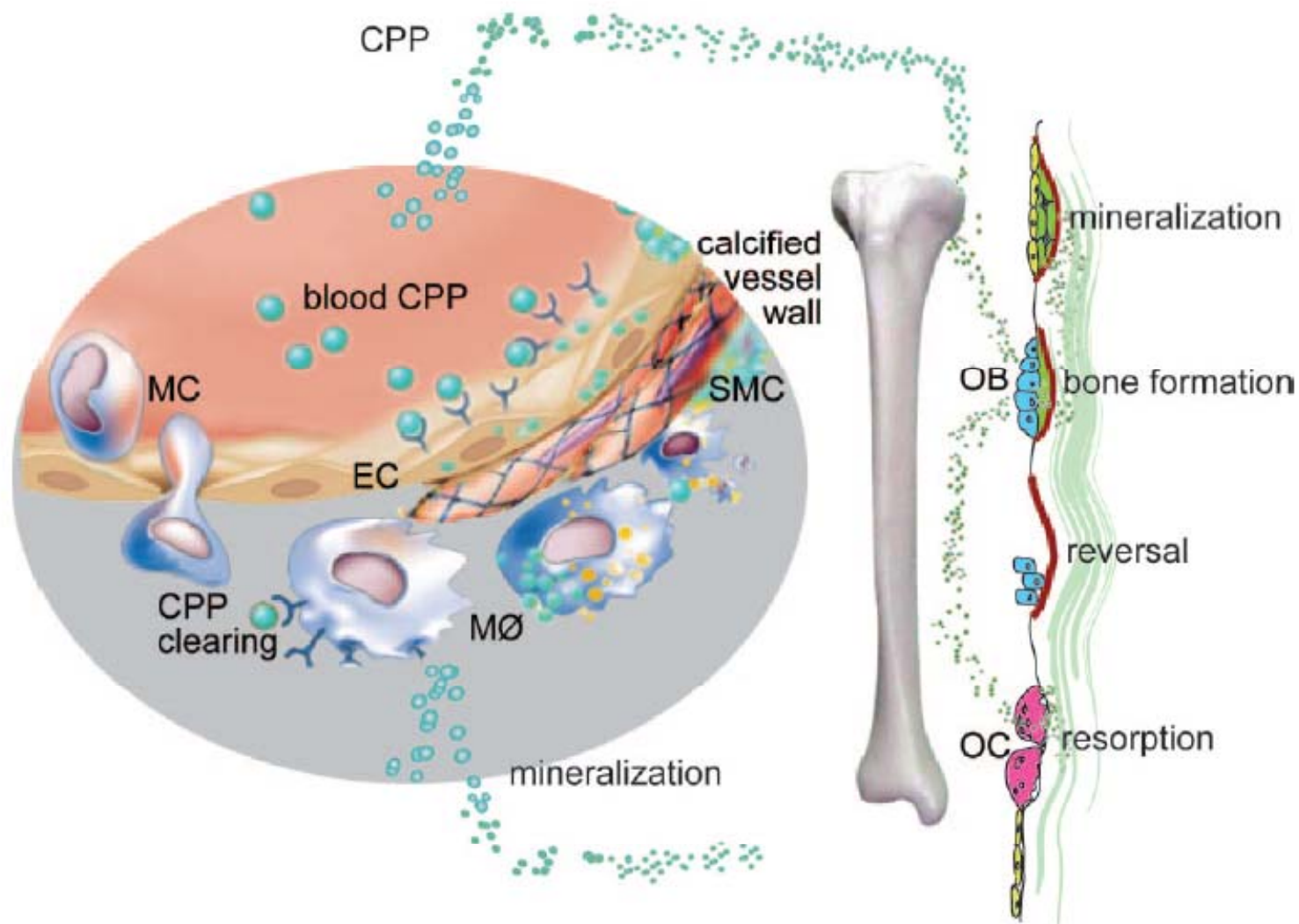
Fetuin A inhibits vascular calcification

- Fetuin-A both locally and systemically inhibits vascular calcification
 - Fetuin-A is incorporated in VSMCs and limits their ability to nucleate basic calcium phosphate
- Fetuin-A also buffers mineral ion supersaturation by forming fetuin–mineral complex (FMC) or calciprotein particles (CPPs) ions

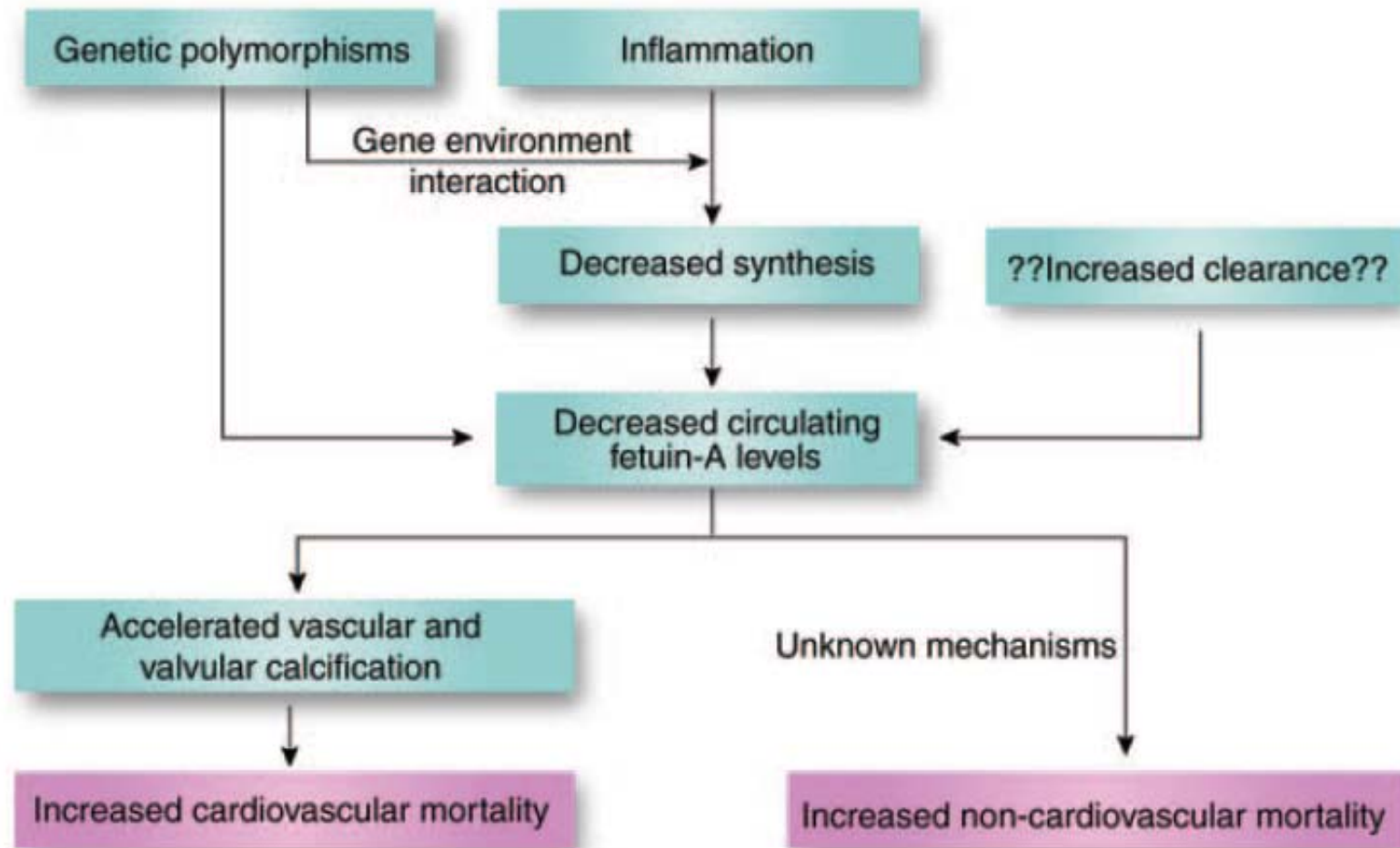


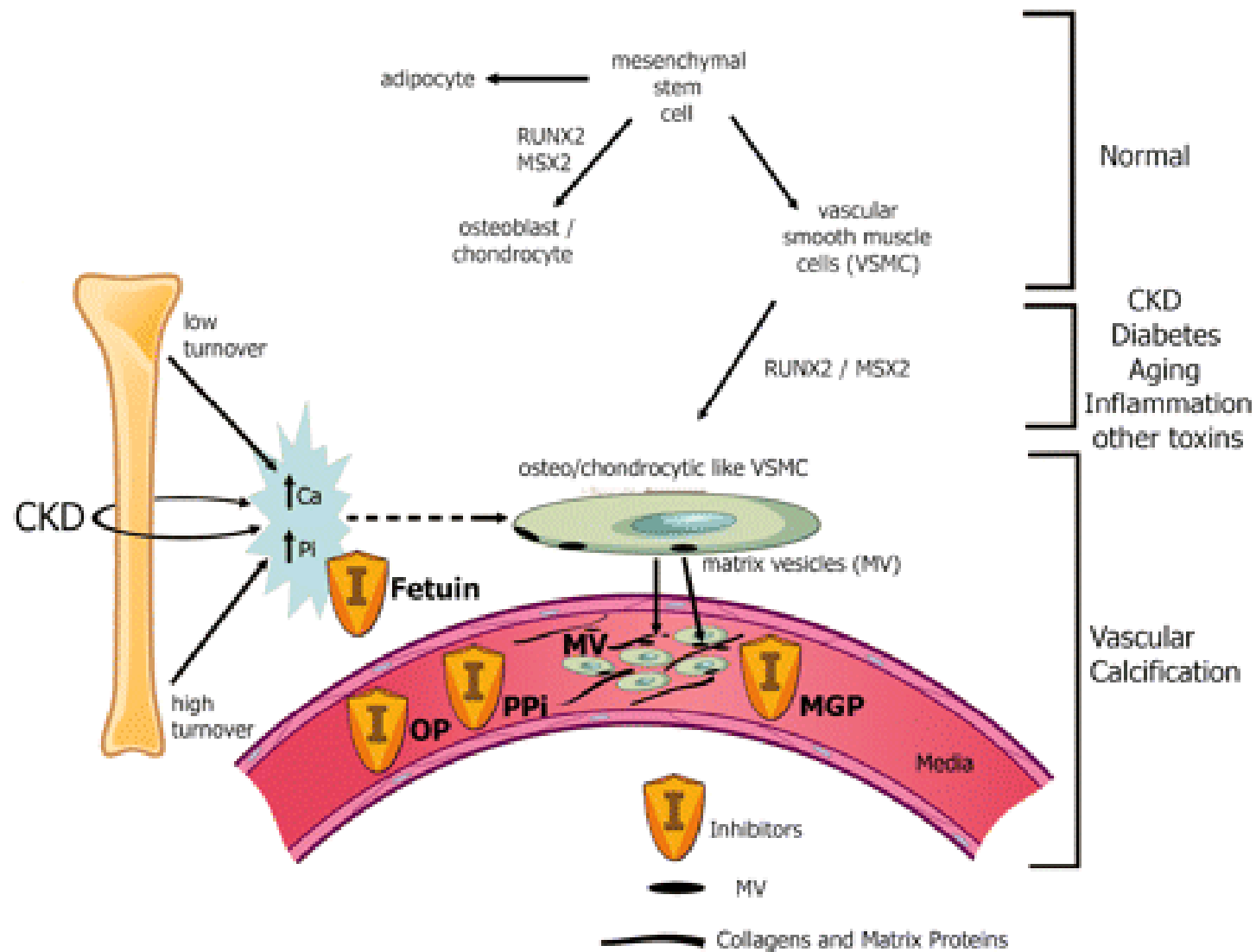
Fetuin-A acts as an inhibitor of ectopic calcification



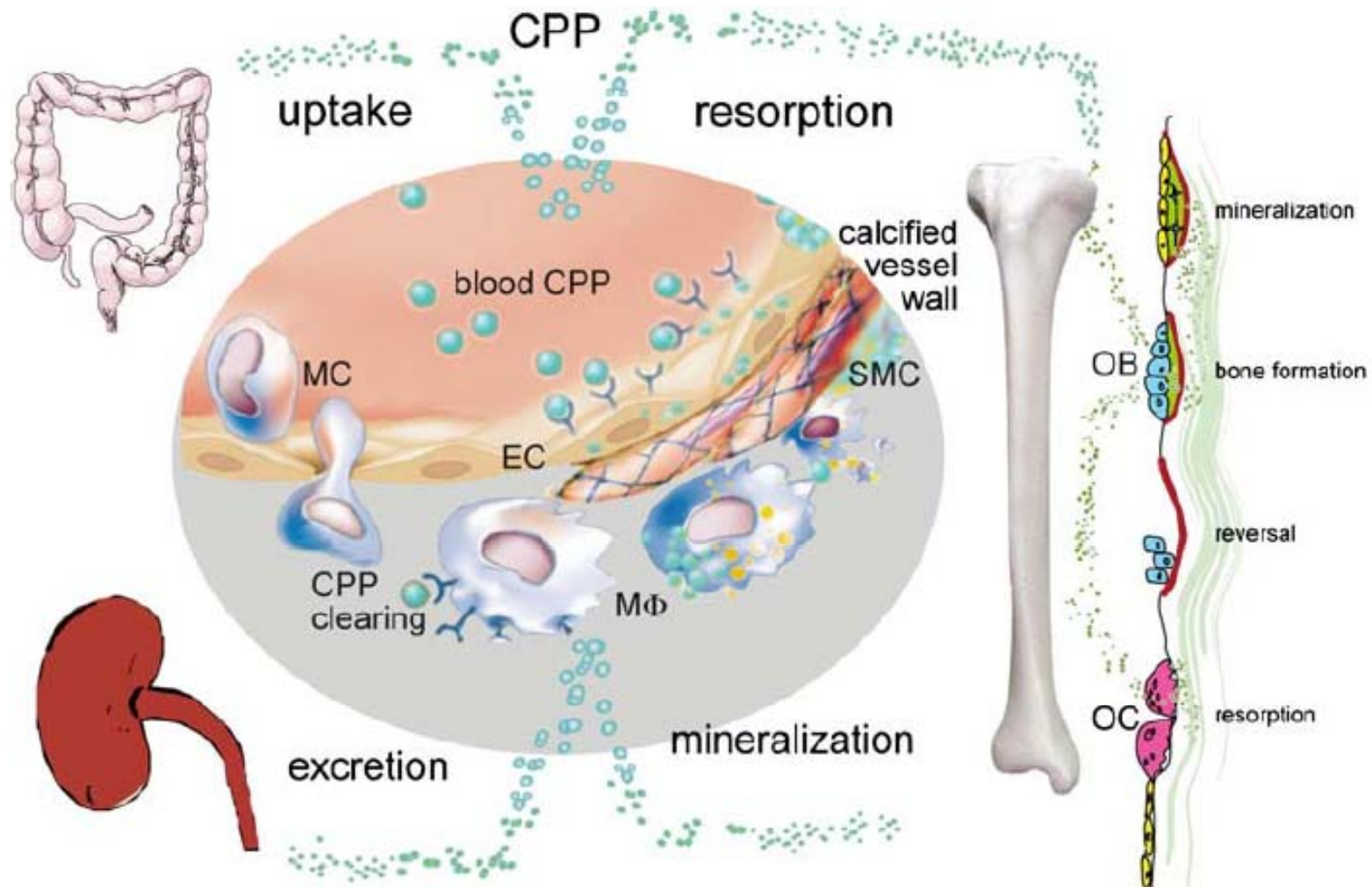


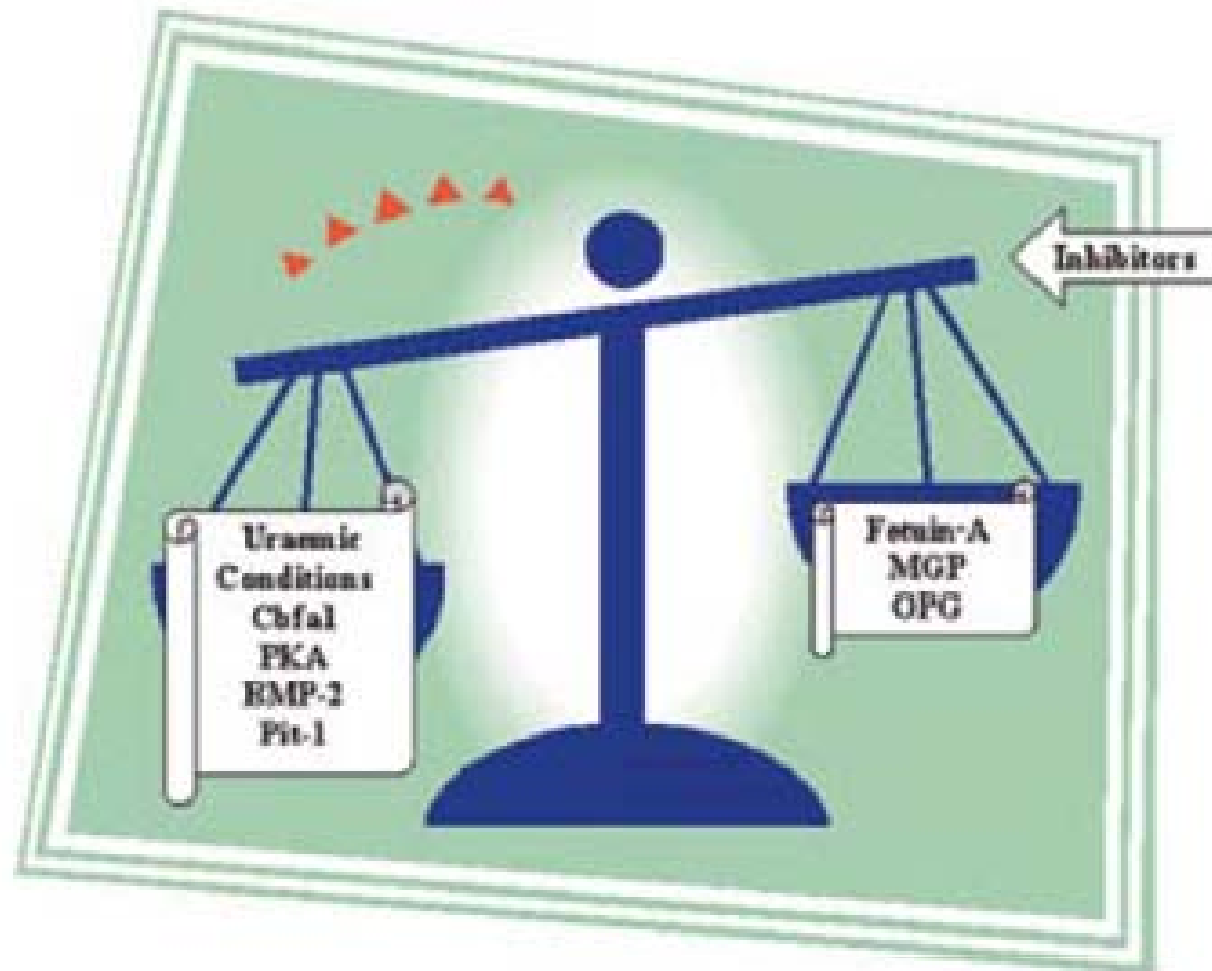
Low Fetuin A and increased mortality in dialysis patients



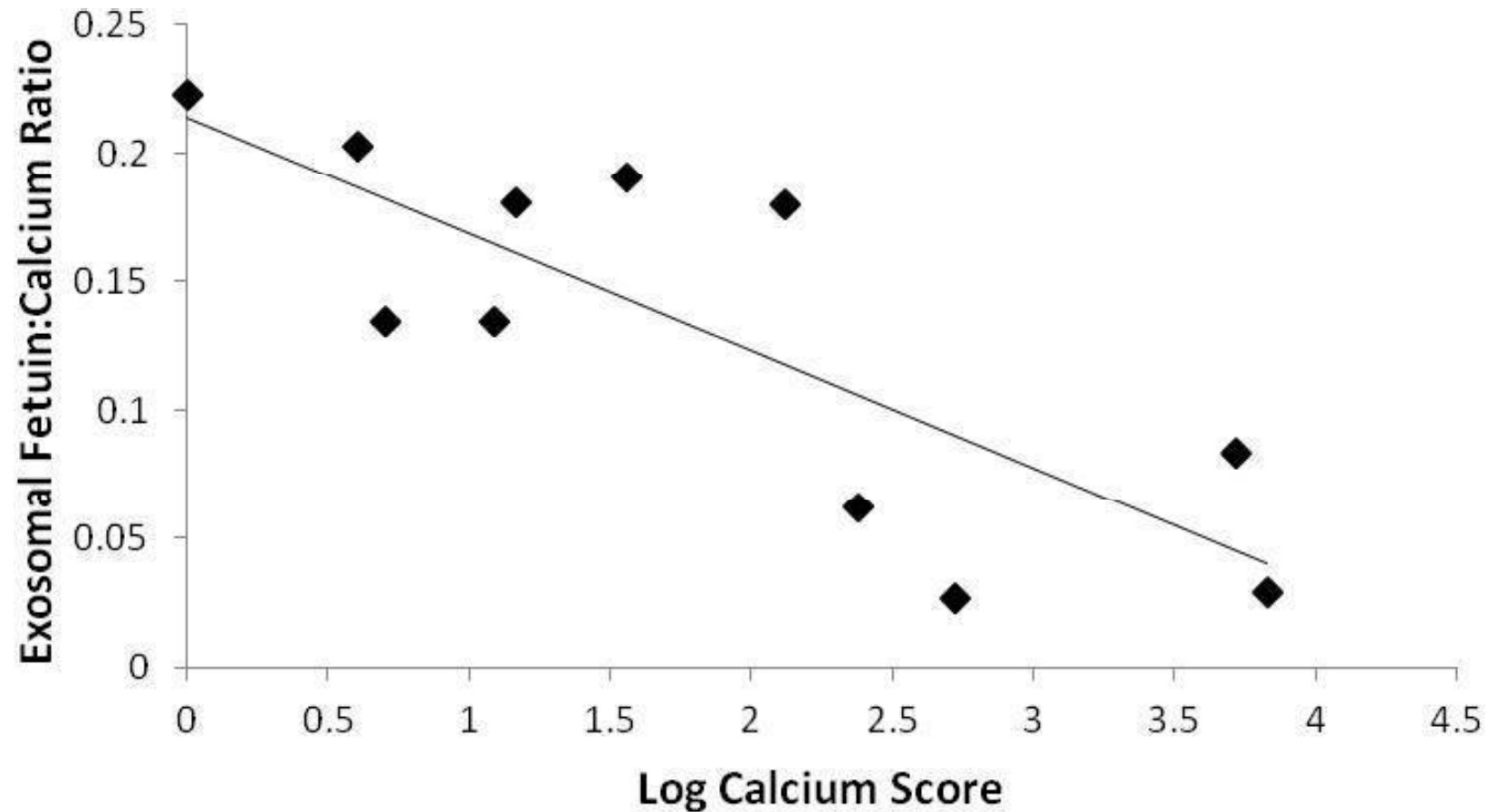


Role of fetuin A in inhibition of vascular calcification





Relationship between calcium scores and VSMC-exosome fetuin-A levels



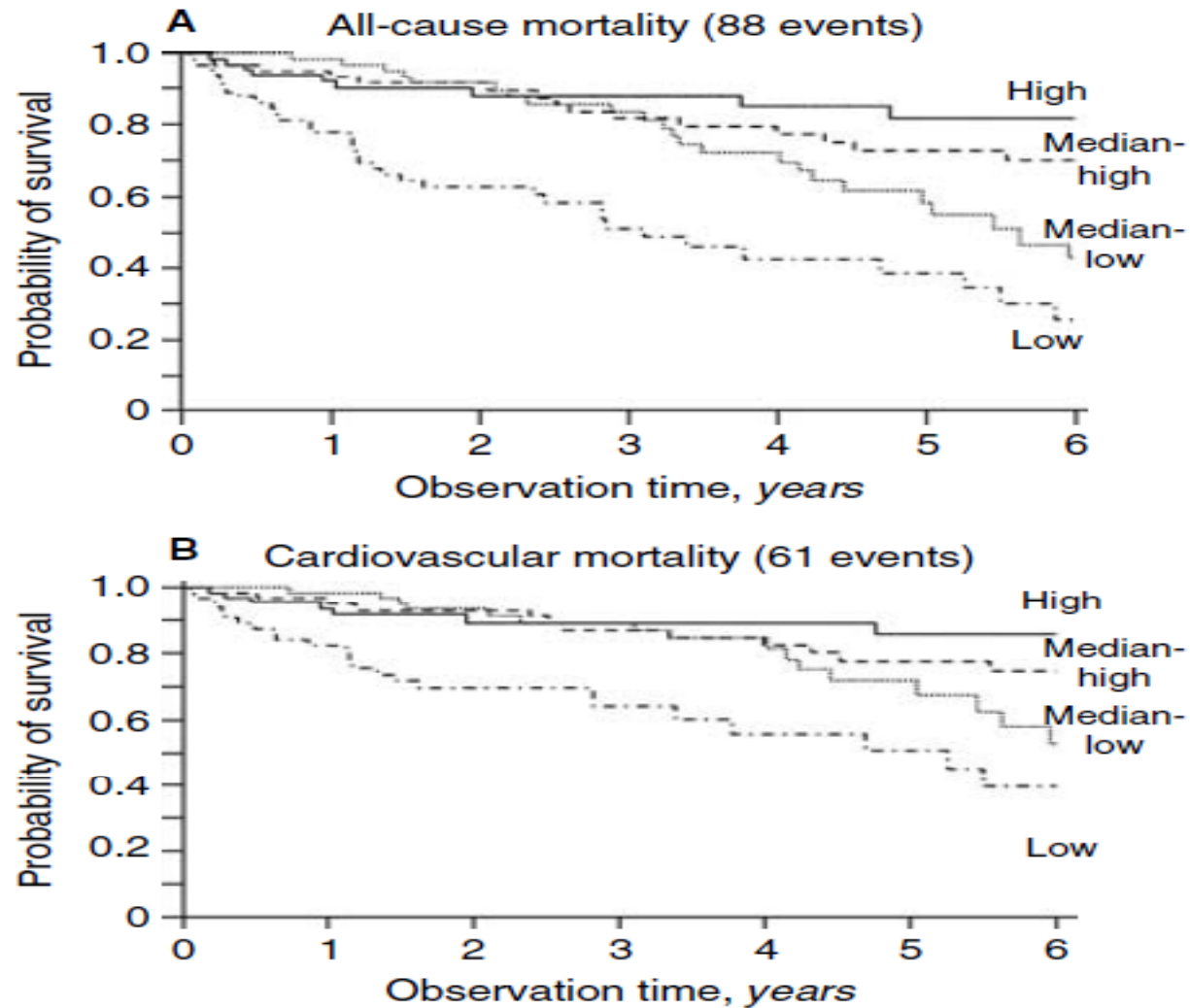
37th Congress of IUPS (Birmingham, UK) (2013)

Risk factors for 1-year increment of CAC in hemodialysis patients

Variables	Bivariate analysis		Logistic Regression		
	Spearman	p-value	OR*	C.I. 95%	p-value
Age	0,401	0,001	1,198	1,006 - 1,426	0,042
BMI	0,390	0,001	1,375	-	0,106
Calcium	0,360	0,001	4,554	1,018 - 20,384	0,047
Ca corrected	0,362	0,001	-	-	NC
PTH	0,384	0,001	1,007	1,001 - 1,013	0,027
Fetuin-A	-0,345	0,012	5,84 E-07**	4,6 E-12** - 0,074	0,017
CRP	0,321	0,020	0,890	-	0,139

BMC Nephrology 2010, 11:10

Low fetuin-A and CV mortality in hemodialysis patients



Kidney International, Vol. 67 (2005), pp. 2383–2392

Fetuin-A and C-reactive protein predict outcome in ACS

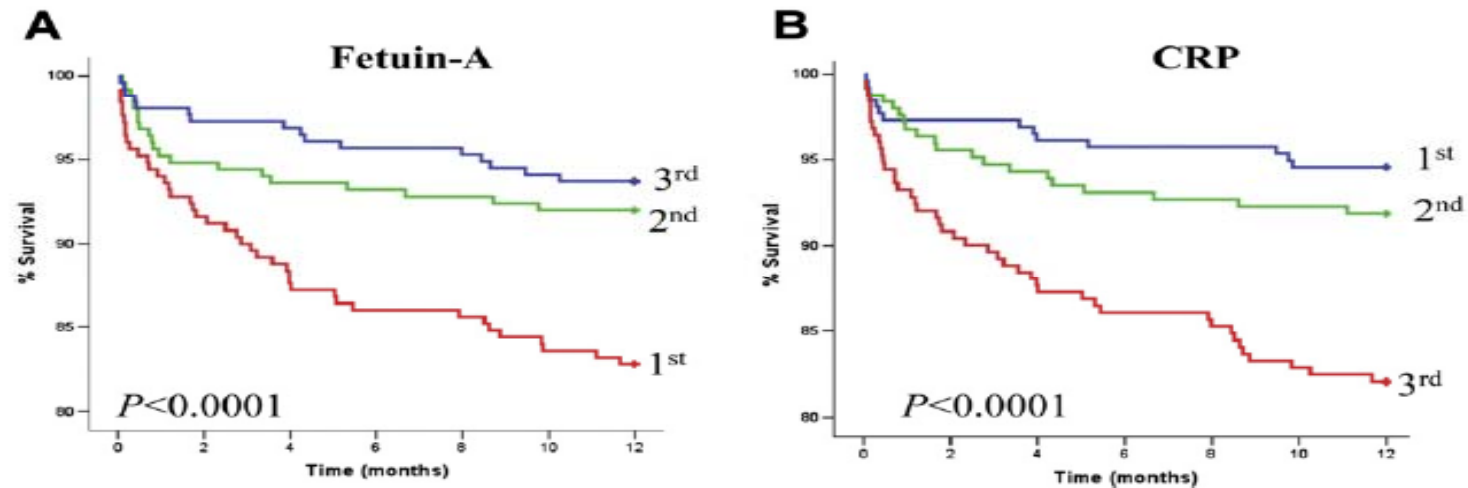
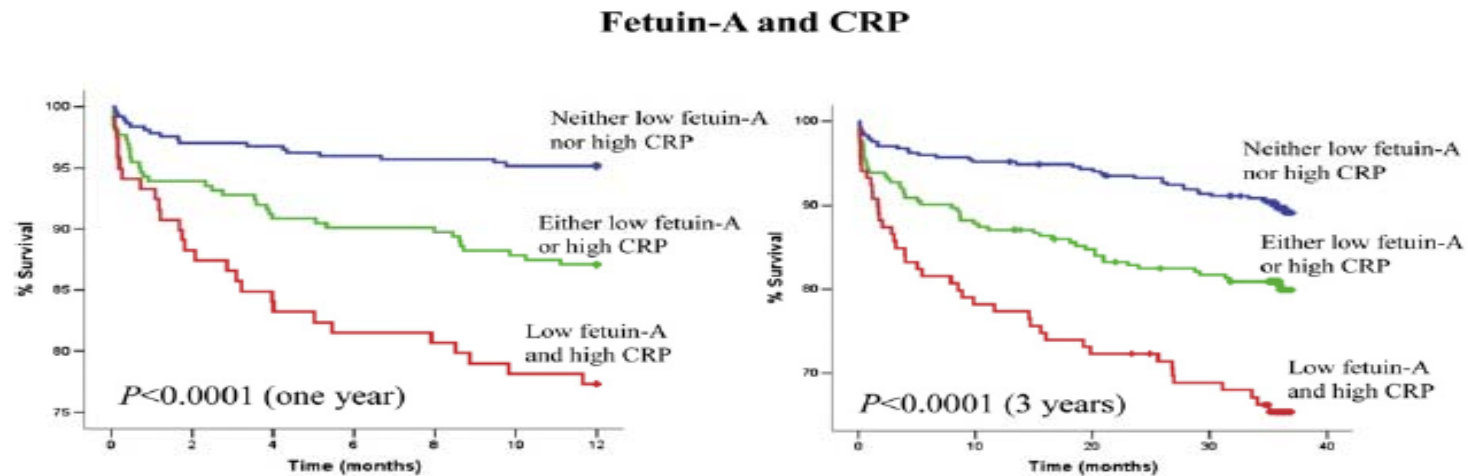


Figure 3. Kaplan-Meier survival curves for 1-year survival according to fetuin-A (A) and CRP (B) concentration:



Association of fetuin-A and carotid IMT in EH

- 105 untreated EH patients with normal renal function
- Fetuin-A level was significantly inversely correlated with carotid IMT ($r = -0.40$, $P < 0.0001$)
- Multiple regression analysis showed that fetuin-A was independently correlated with the IMT ($\beta = -0.268$, $P < 0.0001$)
- Receiver-operator curves demonstrated that fetuin-A levels have a predictive power of $\text{IMT} > 0.9 \text{ mm}$ (AUC 0.738, $P < 0.0001$).



Objective and study design

- Objective: To determine the correlation between serum fetuin-A levels and blood pressure in EGAT cohort age between 20-50 years
- Cross-sectional cohort of the employees of the Electricity Generating Authority of Thailand (EGAT). (EGAT 3/1)
- Serum fetuin-A level was measured by sandwich enzyme immunoassay (R&D Systems, Inc., Minneapolis, MN, USA). Precisions of intra- and inter-assays were 4.9% and 7.3%, respectively.

Clinical characteristics of the study population (n = 1735)

Characteristic	Mean (SD)
Age (years)	39.9 (6.6)
Gender (male)	1245 (71.8%)
Body weight (kg)	63.4 (12.9)
Height (cm)	166.2 (7.7)
BMI (kg/m ²)	23.9 (3.8)
Waist circumference (cm)	86.1 (10.5)
Systolic blood pressure (mmHg)	119.4 (14.0)
Diastolic blood pressure (mmHg)	80.2 (10.2)
Fetuin-A levels (ug/mL)	559.1 (110.4)

Correlation between fetuin-A and metabolic variables

Variable	R	P
Age	0.05	< 0.05
SBP	0.11	< 0.001
DBP	0.12	< 0.001
BMI	0.16	< 0.001
WC	0.15	< 0.001

Relationship between fetuin-A and SBP & DBP in females (n = 490)

	Systolic blood pressure		Diastolic blood pressure	
	Standardized coefficient (β)	P	Standardized coefficient (β)	P
Fetuin-A (ug/mL)	0.13	< 0.001	0.10	< 0.05
Age (year)	0.26	< 0.001	0.08	0.08
BMI (kg/m ²)	0.17	< 0.05	0.17	< 0.05
WC (cm)	0.10	0.22	0.15	0.07

Relationship between fetuin-A and SBP & DBP in males (n = 1245)

	Systolic blood pressure		Diastolic blood pressure	
	Standardized coefficient (β)	P	Standardized coefficient (β)	P
Fetuin-A (ug/mL)	0.02	0.54	0.14	0.12
Age (year)	0.14	< 0.001	0.12	< 0.001
BMI (kg/m ²)	0.04	0.49	0.001	0.99
WC (cm)	0.23	< 0.001	0.33	< 0.001

Conclusions

- **Serum fetuin-A levels were significantly associated with various metabolic parameters, including blood pressure**
- **The association between fetuin-A and blood pressure showed dimorphic response between males and females**
- **Fetuin-A levels were positively associated with systolic and diastolic blood pressure independent of age, BMI and WC only in females, but not in males**
- **Further studies are needed to confirm this finding and to explain the different mechanisms between males and females**



Thank You