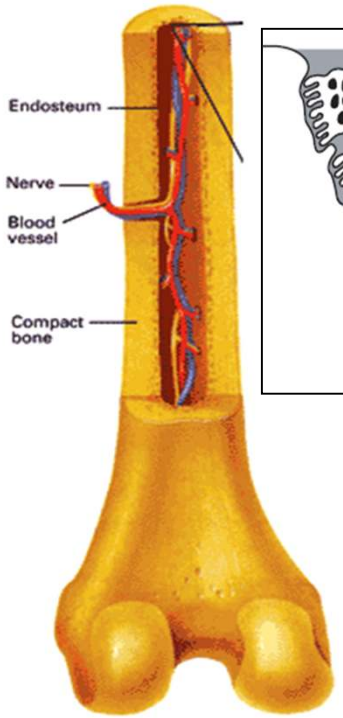
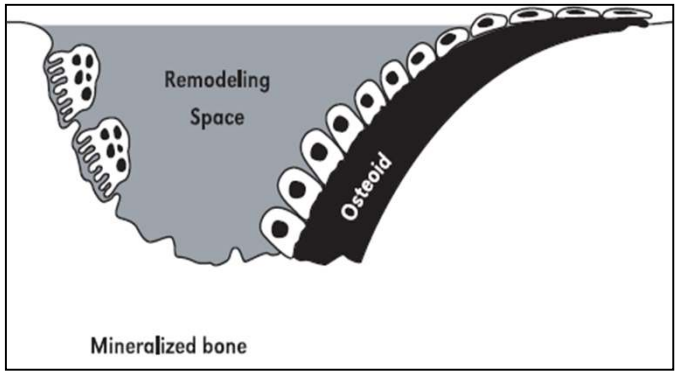
Osteocalcin and DM

정 호 연

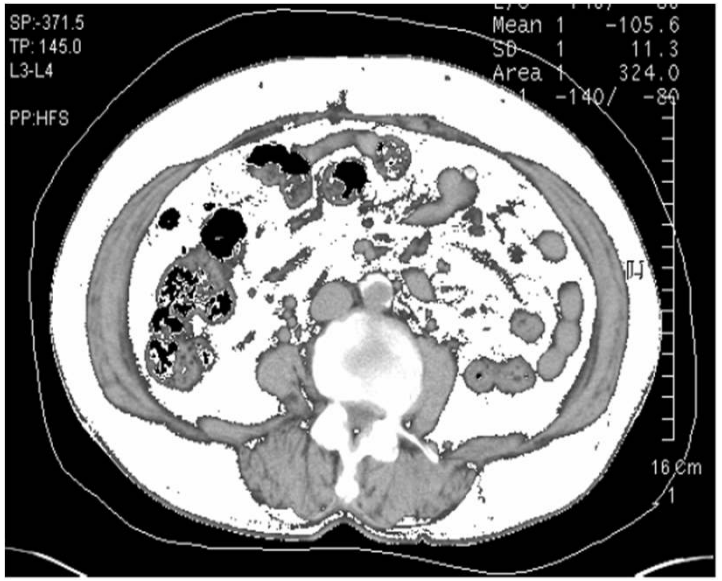
강동 경희대 병원

leptin





osteoporosis
fractures



Obesity, DM

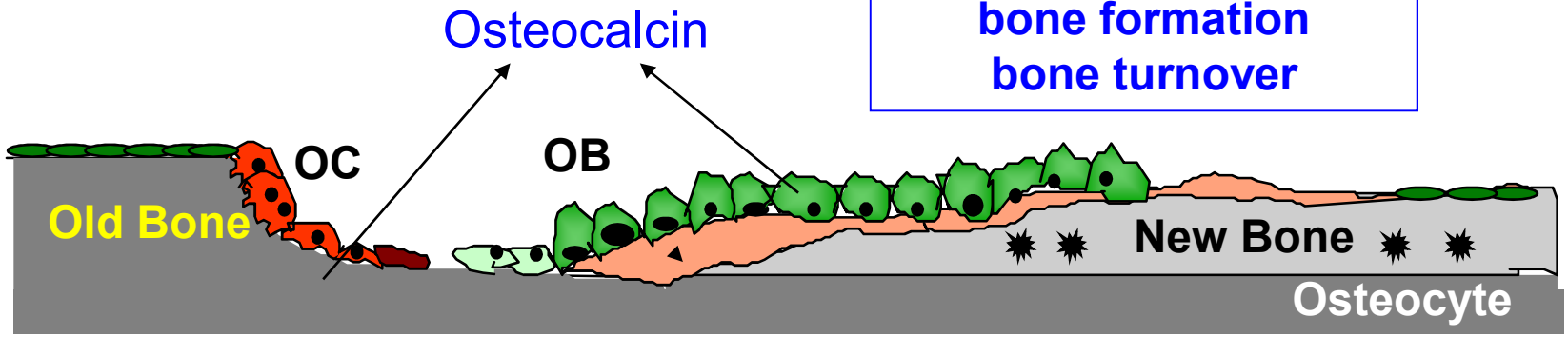
Endocrine feedback

?

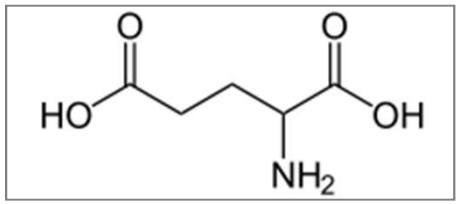
Osteocalcin

OC is osteoblast specific protein
$OC^{-/-}$ shows abnomal visceral fat
Is Osteocalcin a candidate?

Biochemical marker for
bone formation
bone turnover



undercarboxylated OC (ucOC, Glu-OC)

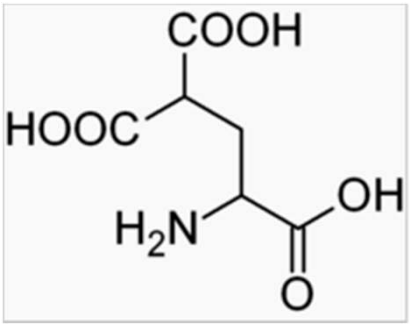


high ucOC is marker of
hip fracture risk in elderly

Vitamin K

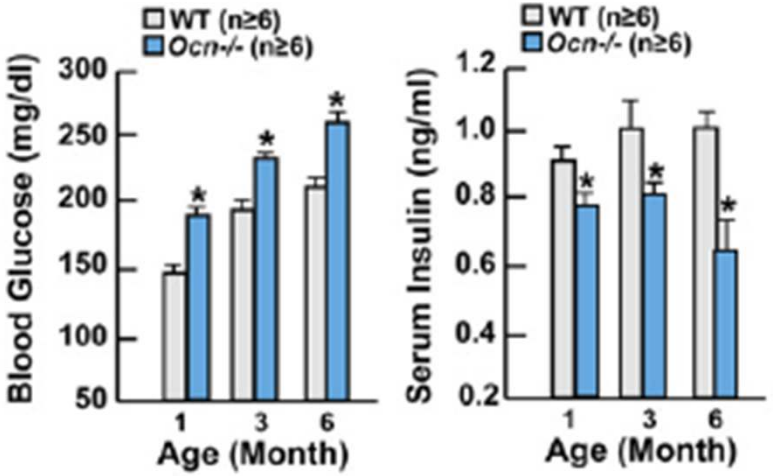
γ-glutamyl carboxylase

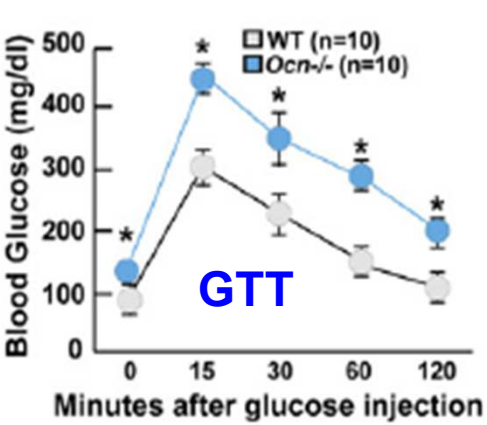
carboxylated OC (cOC, Gla-OC)

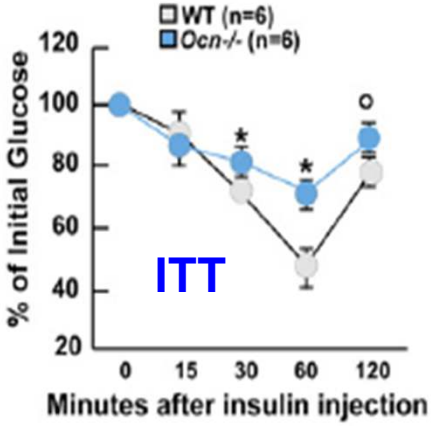


high binding affinity to HA

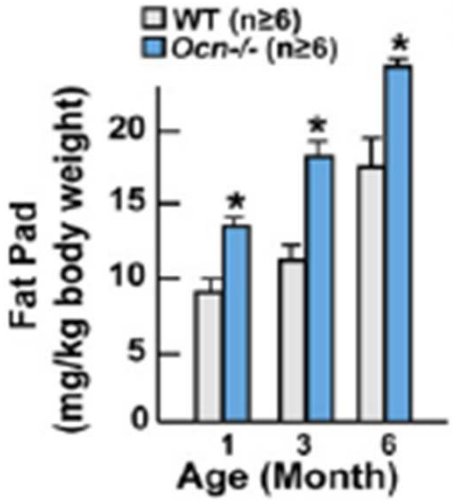
OC regulates insulin secretion





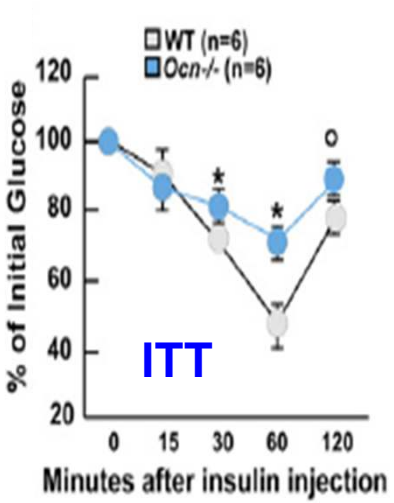


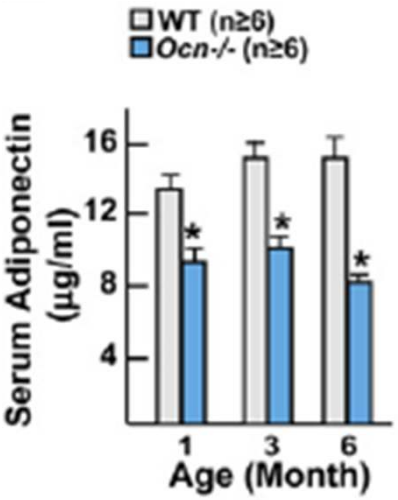
	WT	*Ocn-/-*
Islet No./mm²	0.47 ± 0.09	0.25 ± 0.11*
β-cell area (%)	0.66 ± 0.05	0.36 ± 0.03*
β-cell mass (mg)	0.8 ± 0.1	0.4 ± 0.1*
Insulin content (ng/mg pancreas)	73.2 ± 2.9	50.5 ± 4.1*
Ki67 positive cells (%)	2.1 ± 0.2 2.1 ± 0.4	1.2 ± 0.2° (P5) 1.1 ± 0.1° (3M)

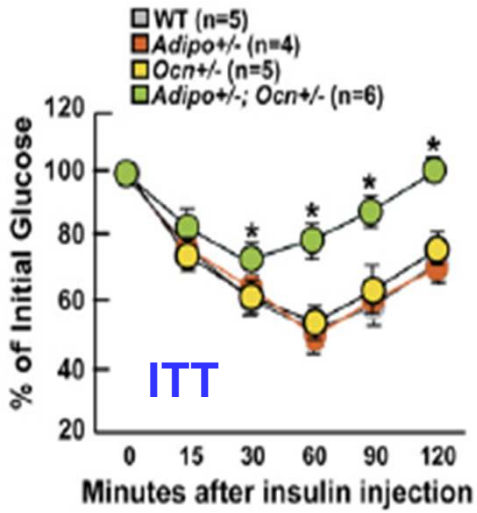


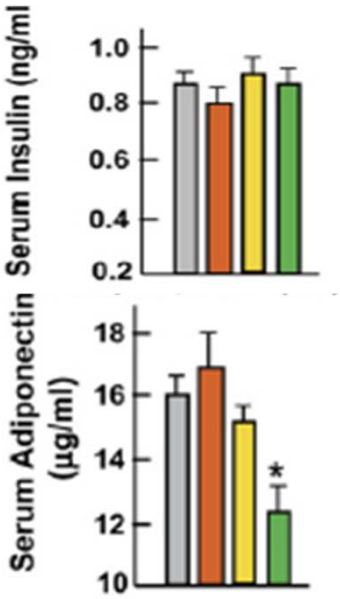
Lee NK et al.Cell 2007;130:456-469

OC regulates insulin sensitivity via adiponectin

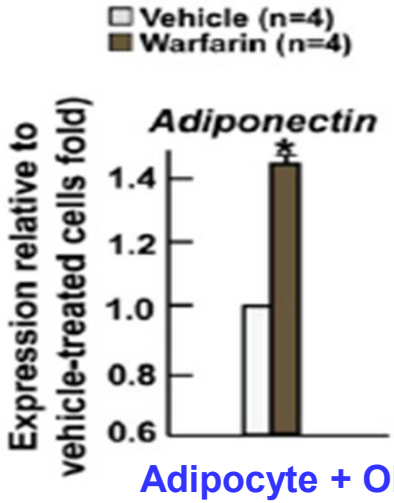


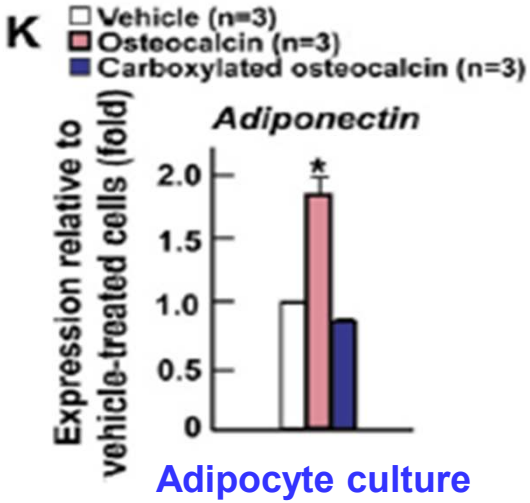


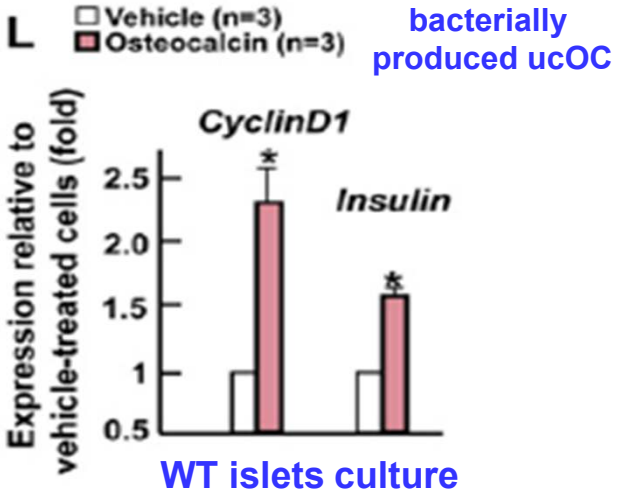




ucOC induces adiponectin and insulin



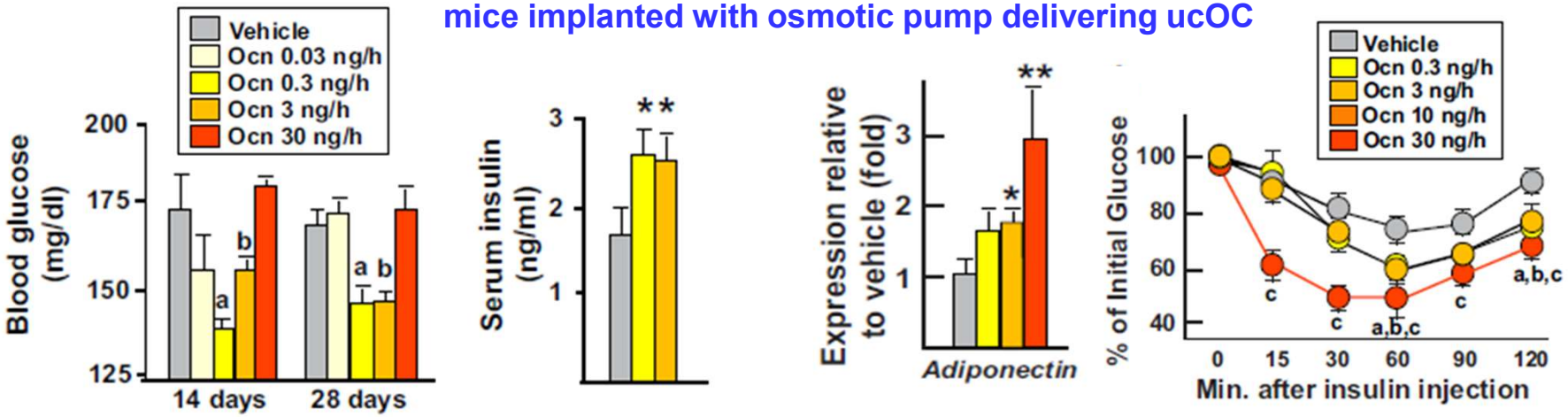


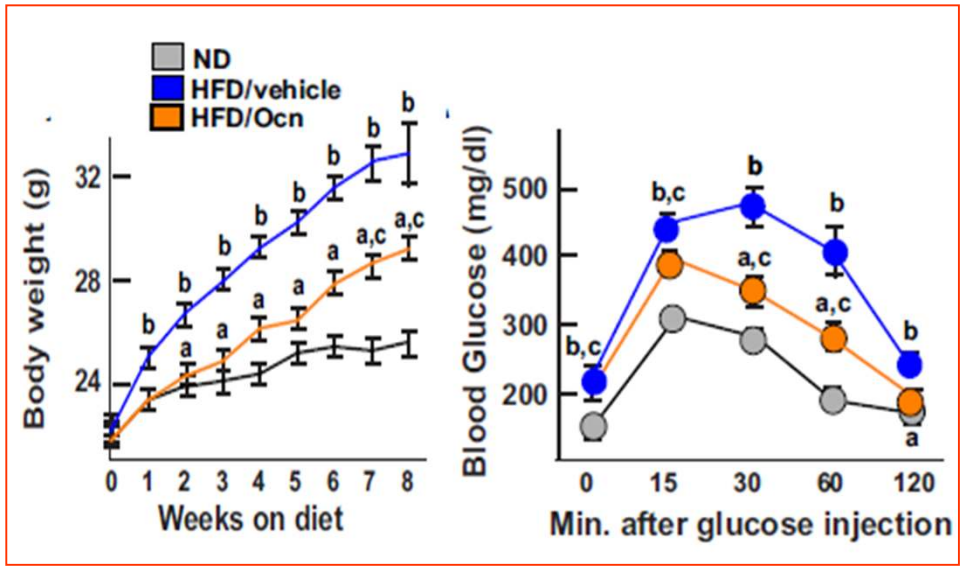


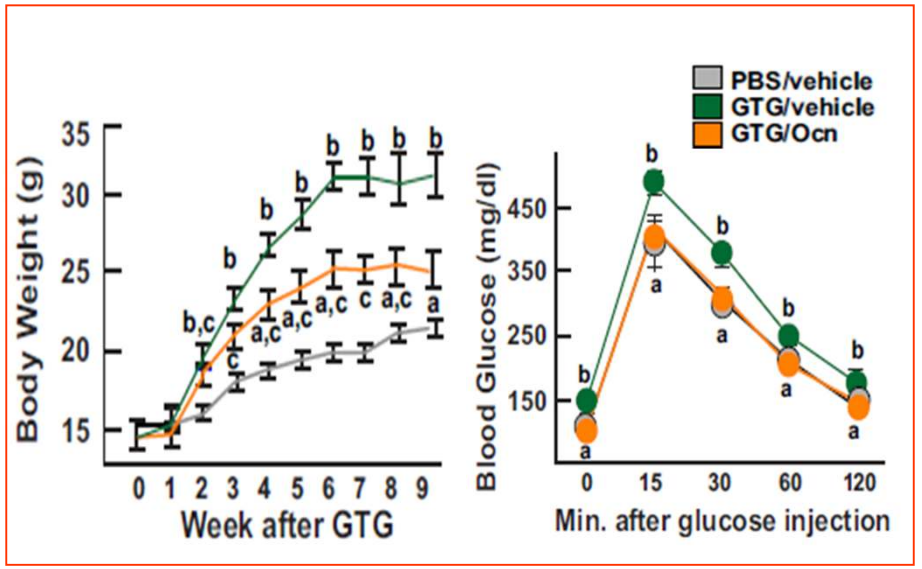
Lee NK et al.Cell 2007;130:456-469

Does ucOC regulate energy metabolism in WT mice?

mice implanted with osmotic pump delivering ucOC

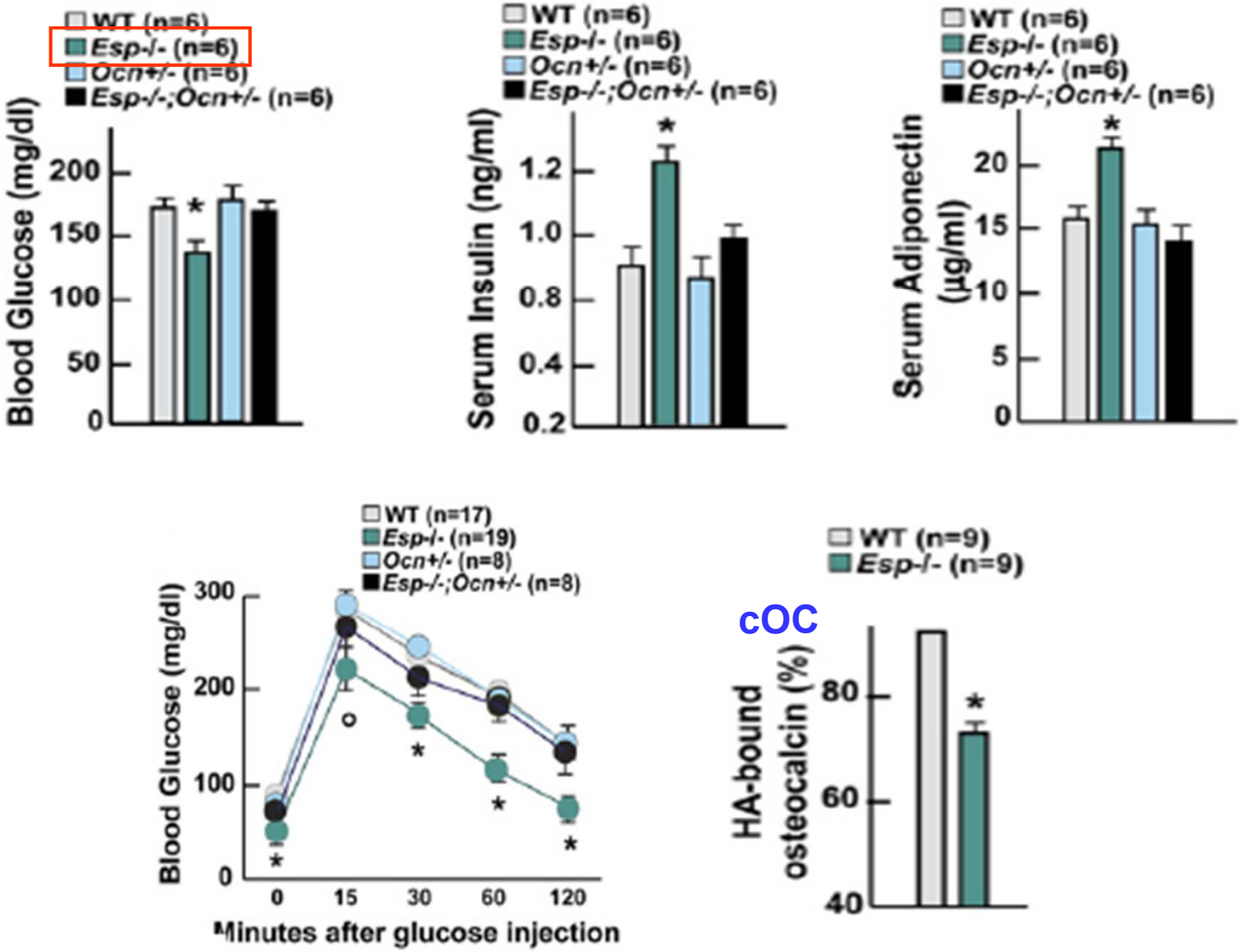






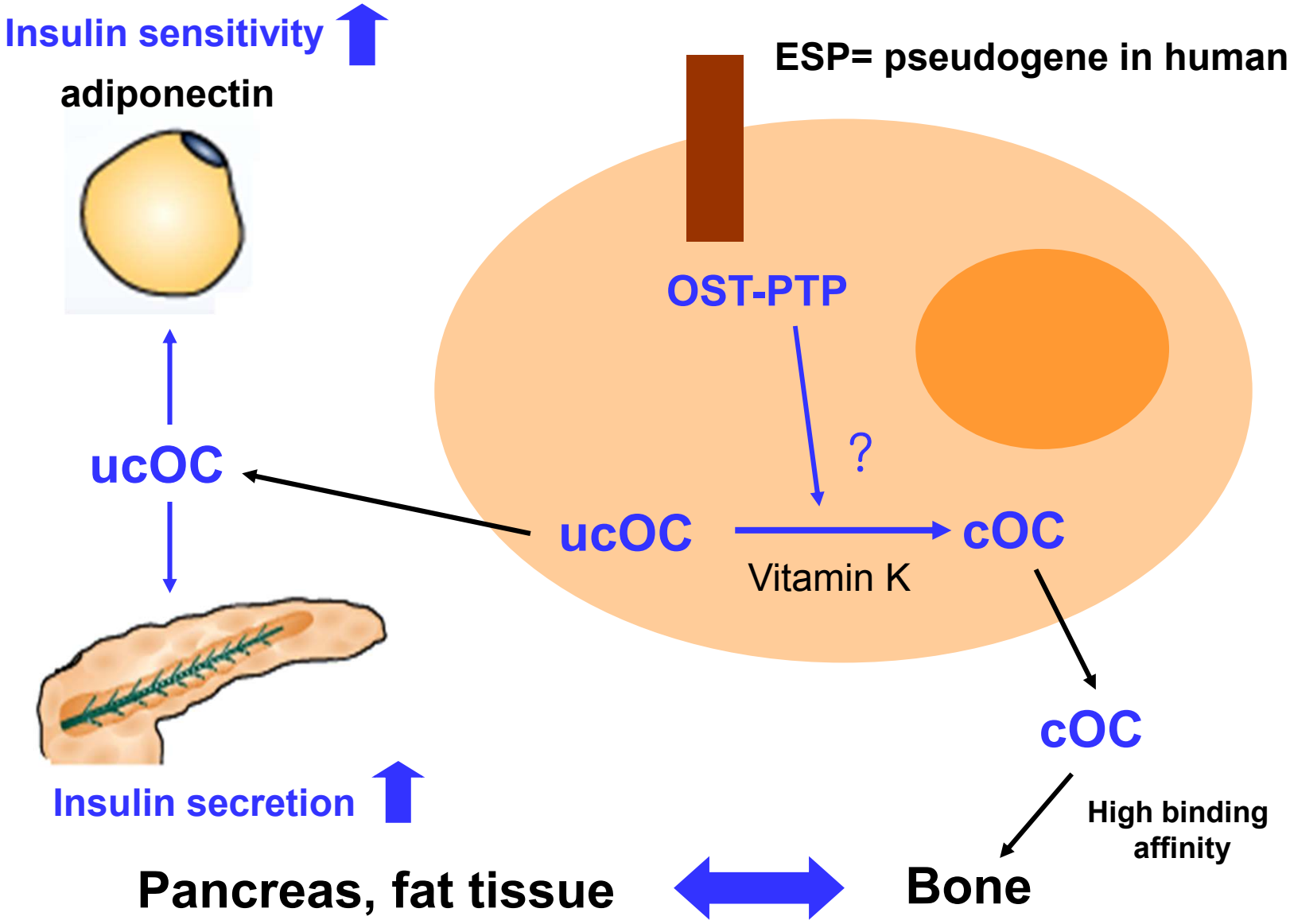
Ferron M et al. PNAS 2008;105:5266-5270

ESP(OST-PTP) controls carboxylation of osteocalcin



Lee NK et al.Cell 2007;130:456-469

Lessons from animal studies



Same role of osteocalcin in human?

- 75g OGTT를 시행한 25-60세 남성 199명
- NGT (8, 4%), prediabetes (46, 23%), DM (145, 73%)
- ucOC (Glu-OC), cOC (Gla-OC) (Takara, Japan)

Category of glucose tolerance by osteocalcin tertiles

	Tertile of uncarboxylated osteocalcin				Tertile of carboxylated osteocalcin			
	Lower (n = 68)	Middle (n = 65)	Upper (n = 66)	P trend	Lower (n = 65)	Middle (n = 67)	Upper (n = 67)	P trend
No. of normal glucose tolerance (%)	1 (12.5)	3 (37.5)	4 (50.0)	0.02	1 (12.5)	1 (12.5)	6 (75.0)	0.11
No. of prediabetes (%)	11 (23.9)	16 (34.8)	19 (41.3)		12 (26.1)	21 (45.7)	13 (28.2)	
No. of diabetes (%)	56 (38.6)	46 (31.7)	43 (29.7)		52 (35.9)	45 (31.0)	48 (33.1)	

Data are presented as numbers of patients (%).

Hwang YC et al. Diabetes Metab Res Rev 2009;25:768-771

Both forms are a/w improved glucose tolerance

	Tertile of ucOC			Tertile of cOC		
	Lower	Mid	Upper	Lower	Mid	Upper
	<0.25	0.42 (0.33-0.64)	1.1 (0.65-11.18)	<0.25	0.42 (0.33-0.64)	1.1 (0.65-11.18)
FPG (mmol/L)	8.7 ± 0.4	7.5 ± 0.2*	7.5 ± 0.3**	8.9 ± 0.4	7.6 ± 0.3**	7.3 ± 0.2**
2h Glucose (mmol/L)	15.9 ± 0.7	13.8 ± 0.7*	13.1 ± 0.6**	16.0 ± 0.8	13.8 ± 0.7*	13.1 ± 0.6**
HOMA-IR	4.28 ± 0.23	4.16 ± 0.37	3.93 ± 0.26	4.93 ± 0.32	4.08 ± 0.31	3.38 ± 0.19*
HOMA-B%	64.7 ± 5.4	68.0 ± 4.3	81.1 ± 7.4*	75.0 ± 7.2	74.3 ± 5.5	64.4 ± 4.8
Insulinogenic index	0.29 ± 0.04	0.39 ± 0.06	0.45 ± 0.07	0.37 ± 0.07	0.39 ± 0.04	0.36 ± 0.04
BMI	NS			27.3 ± 3.3	25.5 ± 2.9#	24.9 ± 3.6#
BP, T-C, HDL-C, TG FPI, c-peptide	NS			NS		

*p<0.05, **p<0.01after adjustment for age and BMI, , #p<0.01

Hwang YC et al. Diabetes Metab Res Rev 2009;25:768-771

Role of total OC and adiponectin?

- **75g OGTT 시행한 남자 223명, 여자 202명 (53 ± 12세)**
  - **NGT (n=23, 5.4%),**
  - **prediabetes (n=150, 35.3%),**
  - **DM (n=252, 59.3%)**
- **total osteocalcin (Cis Bio international, France)**
- **adiponectin, leptin (R & D system, USA)**

Hwang YC et al. Osteoporos Int. provisional accepted

total OC are a/w improved glucose tolerance

	Lower (n=141)	Mid (n=143)	Upper (n=141)	p
Total OC	1.1-13	13.1-18.9	19.0-70.7	<0.001
Glucose (mg/dL)	155.0 ± 66.7	126.0 ± 30.6	118.9 ± 28.8	<0.001
Insulin (uIU/mL)	10.1	10.7	9.9	0.046
HbA1c(%)	7.7 ± 2.4	6.6 ± 1.3	6.4 ± 1.3	<0.001
HOMA-IR	3.44	3.47	2.82	0.002
HOMA-B%	58.6	74.2	75.5	<0.001
Insulinogenic index	0.18	0.29	0.32	<0.001
Adiponectin (ug/mL)	2.2	1.8	2.43	<0.001
Leptin (ug/L)	5.44	4.82	4.57	NS

Mean ± SD or median

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Osteocalcin is a/w improved glucose tolerance independent of plasma adiponectin

Multiple logistic regression analysis for diabetes

	OR	95% CI	P
Age	1.035	1.009-1.061	0.008
FPG	1.142	1.110-1.174	<0.001
Total osteocalcin	0.955	0.919-0.994	0.023

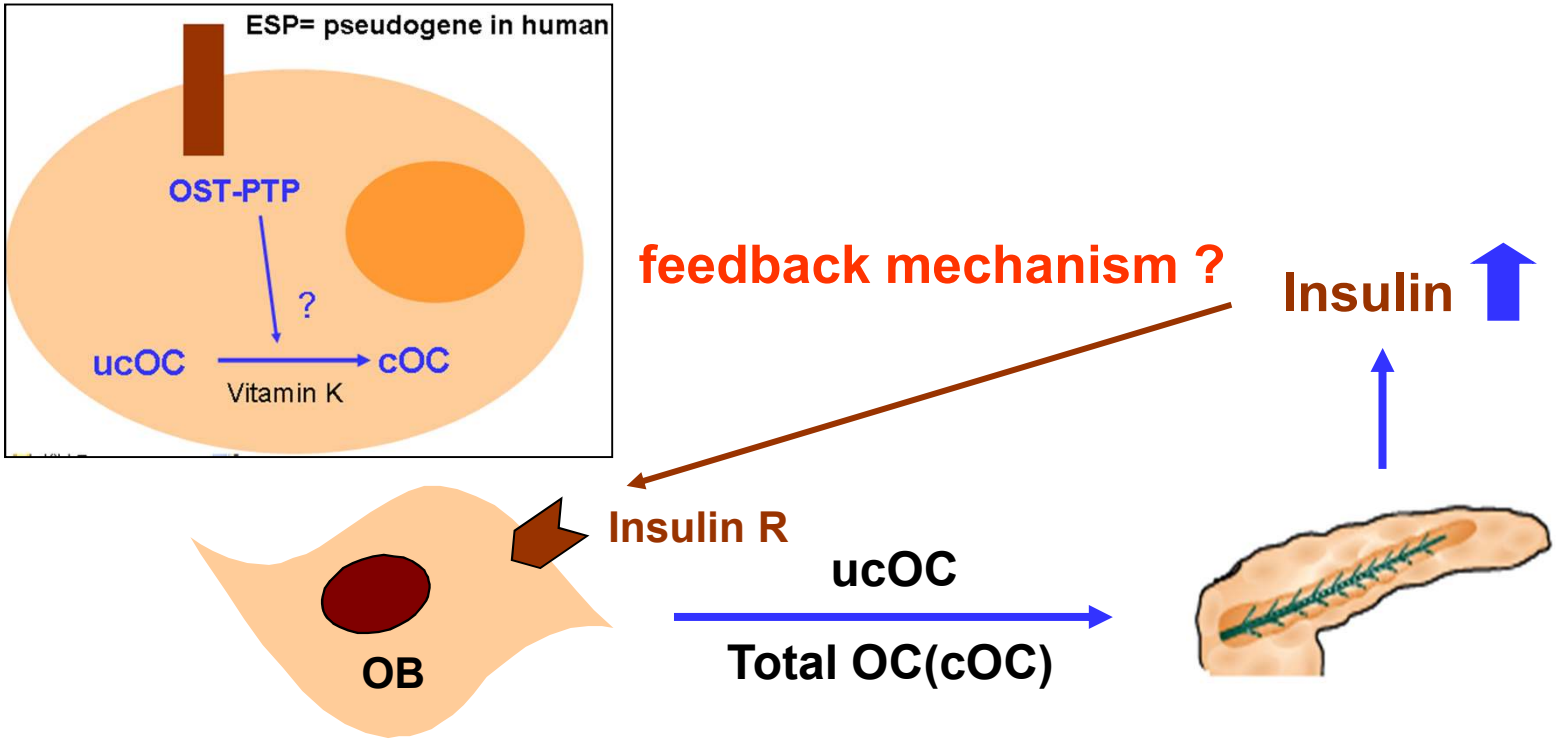
Age, gender, BMI, FPG, adiponectin, leptin and osteocalcin were included as dependent variables

Hwang YC et al. Osteoporos Int. provisional accepted

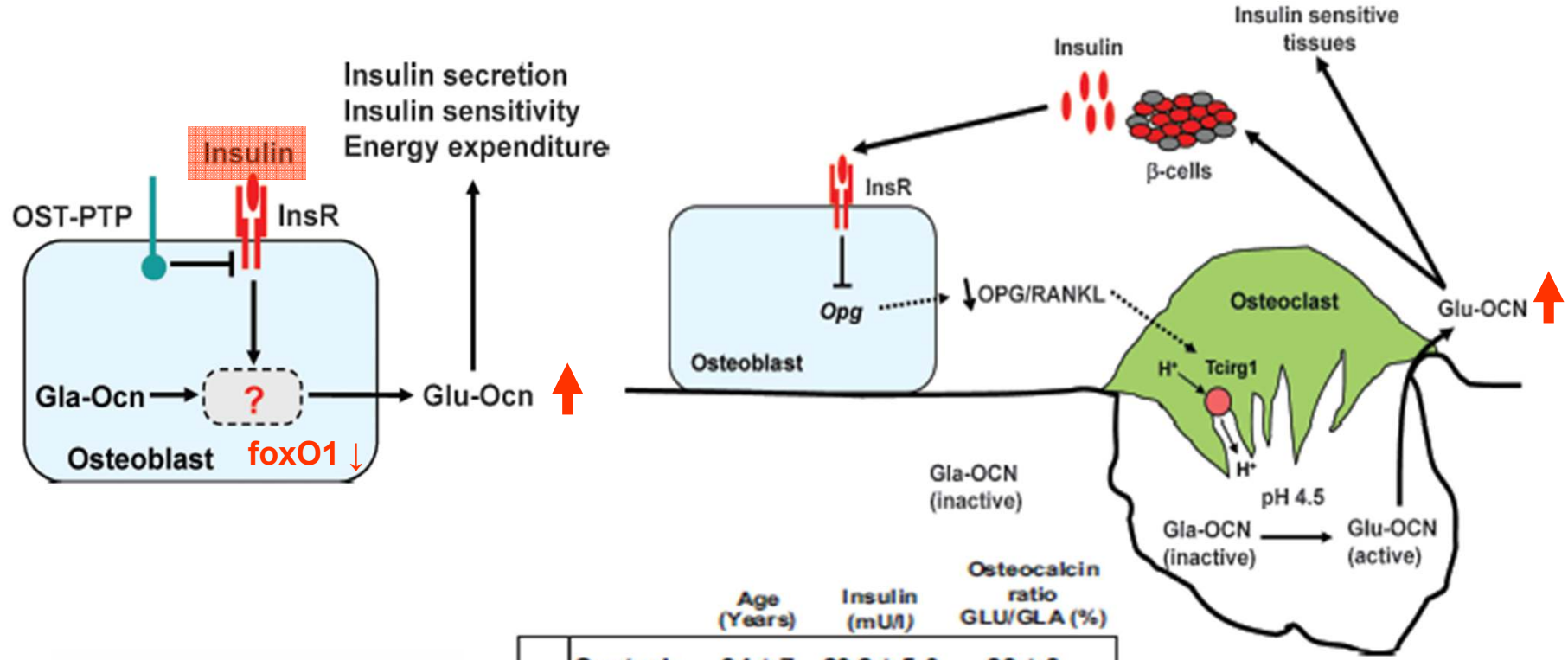
Cross sectional human studies

Author	연령	대상		결과	
Iki	>65	남	DM 17.9%	ucOC not total OC	FPG, HbA1c HOMA-IR, T2DM%
Kanazawa (2011)	25-85	남	DM 100%	log(ucOC)	FPG, HbA1c trunk fat%
	50-87	여	DM 100%	log(ucOC)	No sig. in regression Analysis
Shea	68	남,여	정상	Total OC, cOC No a/w ucOC	HOMA-IR Adiponectin (partial)
Kanazawa (2009)	50-83	남, 여	DM 100%	Total OC	FPG, HbA1c
		남			Fat%, baPWV, IMT
		녀			Log(adiponectin)
Kanazawa (2011)	55 62	남, 여	DM 100%	Log(cOC)	FPG, HbA1c, Trunk fat%, HOMA-IR, HOMA-B%
		여			Log(adiponectin)

Does insulin influence osteocalcin synthesis or activity?



Insulin signaling in osteoblasts and glucose homeostasis model



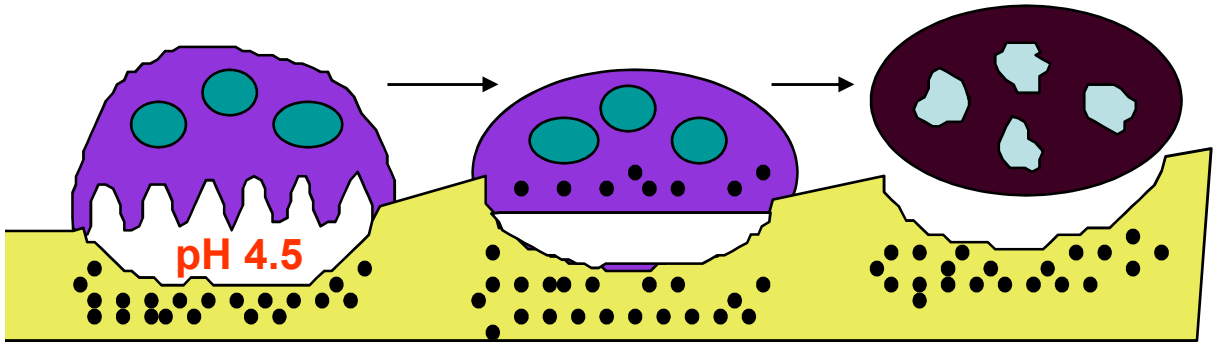
	Ratio GLU/GLA (%)
InsRfl/fl (n=9)	31 ± 2
InsR$_{Osb-/-}$ (n=7)	25 ± 2*

		Age (Years)	Insulin (mU/l)	Osteocalcin ratio GLU/GLA (%)
Males	Controls (n=6-8)	34 ± 7	20.2 ± 5.0	29 ± 8
	ADO-1	45	6.3	4
	ADO-2	47	16.5	1
	ADO-3	34	10.9	14
Females	Controls (n=4-9)	47 ± 16	20.1 ± 2.9	49 ± 18
	ADO-4	64	10	16
	ADO-5	35	9.9	11
	ADO-6	63	11.8	17

Clemens et al. JBMR 2011;26:677-680

Ferron M et al. Cell 2010;142:296-308

Antiresorptive therapy and ucOC



active osteoclast | inactive osteoclast | apoptotic osteoclast

cOC → ucOC ↑ (pH 4.5)

Antiresorptive therapy

Inhibition of bone resorption

↓

Increasing pH

cOC ⫽→ ucOC ↓

↓

deleterious consequences on glucose homeostasis ?

Does antiresorptive therapy increase blood glucose?

- Bisphosphonate 치료 골다공증 환자
  - risedronate 35 mg, weekly
  - 여성 92명, 평균 66.2세
  - 정상 (60, 65.2%) prediabetes(24, 26.1%), DM(8, 8.7%)

- 치료 전, 4개월 후
  - FPG, FPI, ucOC, cOC, CTX
  - HOMA-IR, HOMA-B%

비스포스포네이트 치료 전체 환자의 변화

	전체 대상 (n=92)		p-value
	baseline	4 months	
Glucose (mg/dL)	99.8 ± 19.2	100.6 ± 14.3	0.688
Insulin (uIU/mL)	8.79 ± 8.31	8.8 ± 7.77	0.995
HOMA-B%	95.7 ± 88.8	85.3 ± 70.8	0.277
HOMA-IR	2.28 ± 2.43	2.29 ± 2.23	0.984
Glu-OC (ng/mL)	2.03 ± 1.69	0.92 ± 0.84 (54.7%)	<0.0001
Gla-OC (ng/mL)	12.42 ± 3.13	10.83 ± 3.53 (12.8%)	<0.0001
Total OC (ng/mL)	14.46 ± 3.83	11.76 ± 3.85 (18.7%)	<0.0001
Glu/gla ratio	0.17 ± 0.16	0.09 ± 0.09	0.06
CTX (ng/mL)	0.51 ± 0.22	0.15 ± 0.13 (70.6%)	<0.0001

정상 혈당군의 비스포스포네이트 치료 후 변화

	정상 혈당 군 (n=60)		p-value
	baseline	4 months	
Glucose	90.18 ± 6.31	97.38 ± 11.23	0.0001
Insulin	6.86 ± 4.78	8.01 ± 6.95	0.134
HOMA-B%	100.2 ± 83.47	83.0 ± 67.39	0.074
HOMA-IR	1.52 ± 1.05	2.01 ± 1.95	0.030
Glu-OC	2.20 ± 1.79	1.01 ± 0.95	<0.0001
Gla-OC	12.63 ± 2.97	11.21 ± 3.30	0.0001
Total OC	14.84 ± 3.81	12.22 ± 3.75	<0.0001
Glu/gla ratio	0.18 ± 0.15	0.09 ± 0.07	<0.0001
CTX	0.55 ± 0.24	0.16 ± 0.13	<0.0001

비정상 혈당군의 비스포스포네이트 치료 후 변화

	Prediabetes (n=24) + DM (n= 8)		p-value
	baseline	4 months	
Glucose	117.9 ± 22.16	106.8 ± 17.30	0.012
Insulin	12.42 ± 11.76	10.28 ± 9.05	0.359
HOMA-B	87.39 ± 98.91	89.71 ± 77.79	0.912
HOMA-IR	3.71 ± 3.48	2.81 ± 2.63	0.184
Glu-OC	1.72 ± 1.44	0.76 ± 0.55	<0.0001
Gla-OC	12.02 ± 3.41	10.12 ± 3.89	0.0001
Total OC	13.75 ± 3.83	10.89 ± 3.94	<0.0001
Glu/gla ratio	0.15 ± 0.16	0.09 ± 0.11	0.0002
CTX	0.44 ± 0.18	0.14 ± 0.12	<0.0001

Prediabetes 군의 비스포스포네이트 치료 전 후 변화

	prediabetes (n=24)		p-value
	baseline	4 months	
Glucose	107.6 ± 6.56	104.5 ± 17.36	0.34
Insulin	11.70 ± 12.68	8.42 ± 8.07	0.22
HOMA-B	96.37 ± 111.81	75.35 ± 64.08	0.37
HOMA-IR	3.10 ± 3.27	2.26 ± 2.31	0.22
Glu osteocalcin	1.86 ± 1.58	0.85 ± 0.59	0.0006
Gla osteocalcin	11.98 ± 3.77	9.78 ± 4.12	0.0004
Total osteocalcn	13.85 ± 4.19	10.63 ± 4.19	<0.0001
Glu/gla ratio	0.17 ± 0.18	0.11 ± 0.13	0.002
CTX	0.46 ± 0.19	0.15 ± 0.12	<0.0001

당뇨병 환자군의 비스포스포네이트 치료 전 후 변화

	DM (n=8)		p-value
	baseline	4 months	
Glucose	148.8 ± 24.17	113.6 ± 16.23	0.009
Insulin	14.56 ± 8.82	15.87 ± 10.05	0.79
HOMA-B	60.47 ± 33.79	132.78 ± 102.35	0.09
HOMA-IR	5.53 ± 3.64	4.46 ± 3.01	0.57
Glu osteocalcin	1.3 ± 0.89	0.52 ± 0.26	0.01
Gla osteocalcin	12.14 ± 2.2	11.17 ± 3.12	0.23
Total osteocalcn	13.44 ± 2.7	11.69 ± 3.18	0.059
Glu/gla ratio	0.10 ± 0.06	0.04 ± 0.02	0.02
CTX	0.38 ± 0.12	0.12 ± 0.12	0.005

Correlation between changes of osteocalcin and glucose parameters after risedronate treatment in normal glucose group

	Δ Glu osteocalcin		Δ Gla osteocalcin		Δ Total osteocalcin		Δ Glu/gla		Δ CTX	
	r	p-value	r	p-value	r	p-value	r	p-value	r	p-value
Δ Glucose	**-0.04**	**0.72**	**-0.14**	**0.25**	**-0.12**	**0.35**	**0.06**	**0.62**	**0.13**	**0.32**
Δ insulin	0.14	0.27	0.23	0.07	0.24	0.06	**0.30**	**0.01**	-0.11	0.39
Δ HOMA-B	0.13	0.28	0.14	0.25	0.23	0.07	**0.24**	**0.058**	-0.19	0.13
Δ HOMA-IR	0.17	0.18	0.21	0.09	0.21	0.09	**0.28**	**0.02**	-0.07	0.57

Longitudinal studies of osteoporosis therapies

치료 방법	대상	참고 문헌	OC 결과	혈당 관련 결과
CEE+ MPA	폐경 여성	Menopause 2006;13:314	ucOC ↓	
	폐경 여성	PEPI trial		FPG ↓, FPI ↓ PP2 ↑
	폐경 여성	HERS trial		DM% ↓
	폐경 여성	WHI trial		DM% ↓
Alendronate	폐경 여성	JBMM 2008;26:260	ucOC ↓	
	폐경 당뇨병	Arch Gerontol Geriatr 2002;34:117		Insulin consumption ↓
Risedronate	폐경 여성	J Med Asso Thai 2005;88:s34	ucOC ↑ total OC ↓	
PTH	폐경 여성	Horm Metab Res 2008;40:702	Total OC ↑	No change glucose No change Ins. S.

Other longitudinal studies

치료 방법	대상	Total OC	ucOC	비고
혈당 개선	당뇨병 (일본)	↑		BALP ↓
		↑	↑ (NS)	ucOC/OC ↓
Vitamin K	남		↓	HOMA-IR 개선
	폐경 여성		↓	HOMA-IR 변화없음
Warfarin			↑	혈당 변화 ?

Summary

- *In vitro, animal model*
  - ucOC has a positive effects on insulin secretion and sensitivity
  - ucOC prevents obesity or improve glucose tolerance in WT mice

- *Human studies (association)*
  - cross sectional (our data)
    - ucOC: insulin secretion, cOC: insulin sensitivity
    - Total OC is a/w improved glucose tolerance independent of adiponectin
  - cross sectional (other group)
    - ucOC or total OC are a/w improved glucose tolerance
    - partial correlation with adiponectin
  - Longitudinal
    - bisphophonate therapy increase glucose in normal group, not in prediabetes and DM group

    - few and inconsistent data do not provide sufficient evidence

Conclusion

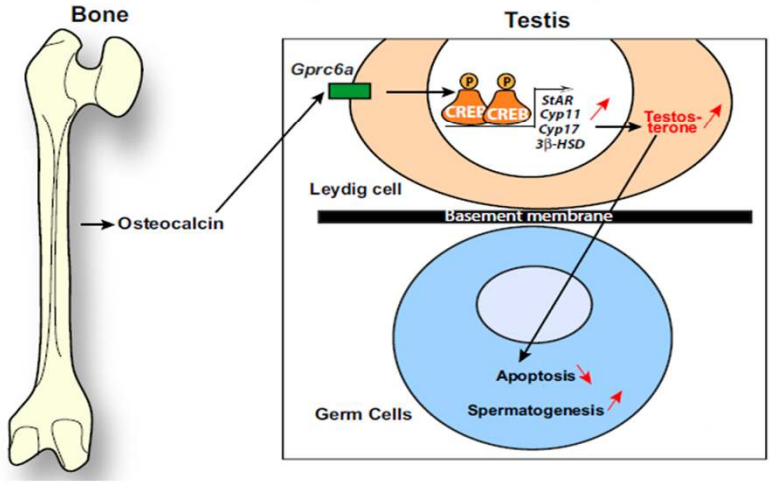
- osteocalcin as a novel hormone regulating glucose metabolism in animal model

- however, further studies are needed to determine whether, and how osteocalcin affects glucose metabolism in human

Endocrine Regulation of Male Fertility by the Skeleton

Cell 2011;144:796-809

Franck Oury,[1,6] Grzegorz Sumara,[1,6] Olga Sumara,[1] Mathieu Ferron,[1] Haixin Chang,[3] Charles E. Smith,[4] Louis Hermo,[4] Susan Suarez,[3] Bryan L. Roth,[5] Patricia Ducy,[2] and Gerard Karsenty[1,*]



GPRC6A Mediates Responses to Osteocalcin in β-Cells *In Vitro* and Pancreas *In Vivo*

Min Pi, Yunpeng Wu and L. Darryl Quarles

J Bone Miner Res 2011