Contribution of Aldosterone in Obesity-Related Hypertension

Colleen Majewski, MD
Section of Endocrinology, Diabetes, and Metabolism
University of Chicago Medicine

Objectives

- Review the link between obesity and hypertension
- Review the link between obesity and elevated aldosterone levels
- Review the management of hypertension in the obese patient
- Review primary hyperaldosteronism

Obesity and Hypertension

Age-specific prevalence of hypertension and obesity in the United States at two time periods, and percent increase over time

	Hypertension prevalence (%)			Obesity prevalence (%)		
Age (years)	1998-1991	2005-2006	Percent Increase	1988-1994	2005-2008	Percent Increase
18–39	5.1	7.4	45	17.2	28.7	67
40–59	27.0	32.1	19	28.0	35.5	27
>60	57.9	65.8	14	23.9	34.0	42

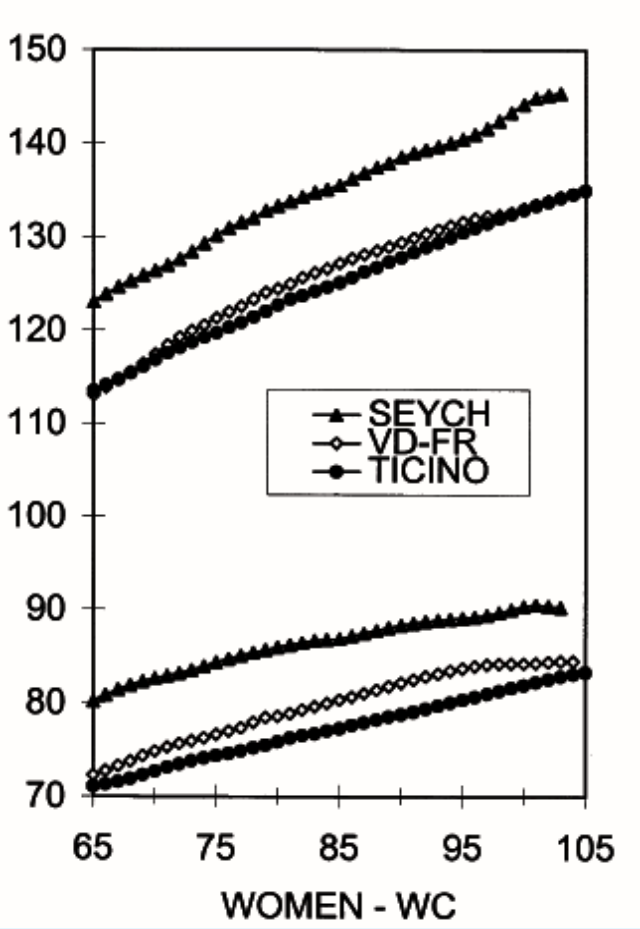
www.cdc.gov/ nchs/nhanes/nhanes2007-2008/nhanes07_08.htm and www.cdc.gov/nchs/nhanes/nh3data.htm.

Obesity and Hypertension

- Cross-sectional study of 3 different regions in Switzerland.
- Relationship of **Blood Pressure** to **Waist Circumference** and **Waist-to-Hip Ratio**. Subjects were on **no antihypertensive medications**.

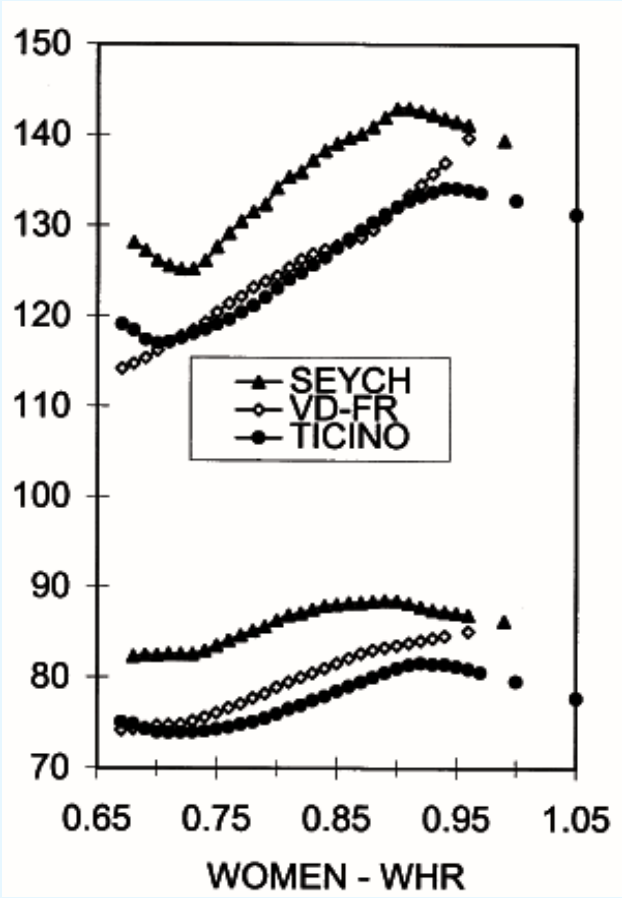
Systolic BP

Diastolic BP



Systolic BP

Diastolic BP



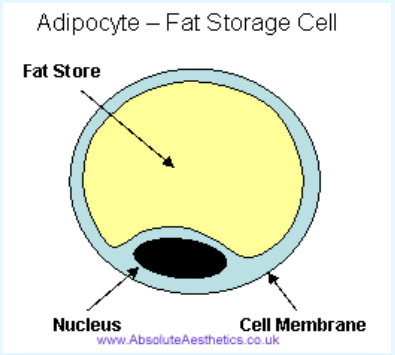
Doll et al. Int J Obes Relat Metab Disord. 2002;26:48-57.

Obesity and Hypertension

- It is estimated that at least 75% of the prevalence of hypertension is directly related to obesity.

AHA, Overweight and Obesity Statistics. 2009

What Is the Link Between Obesity and Hypertension?

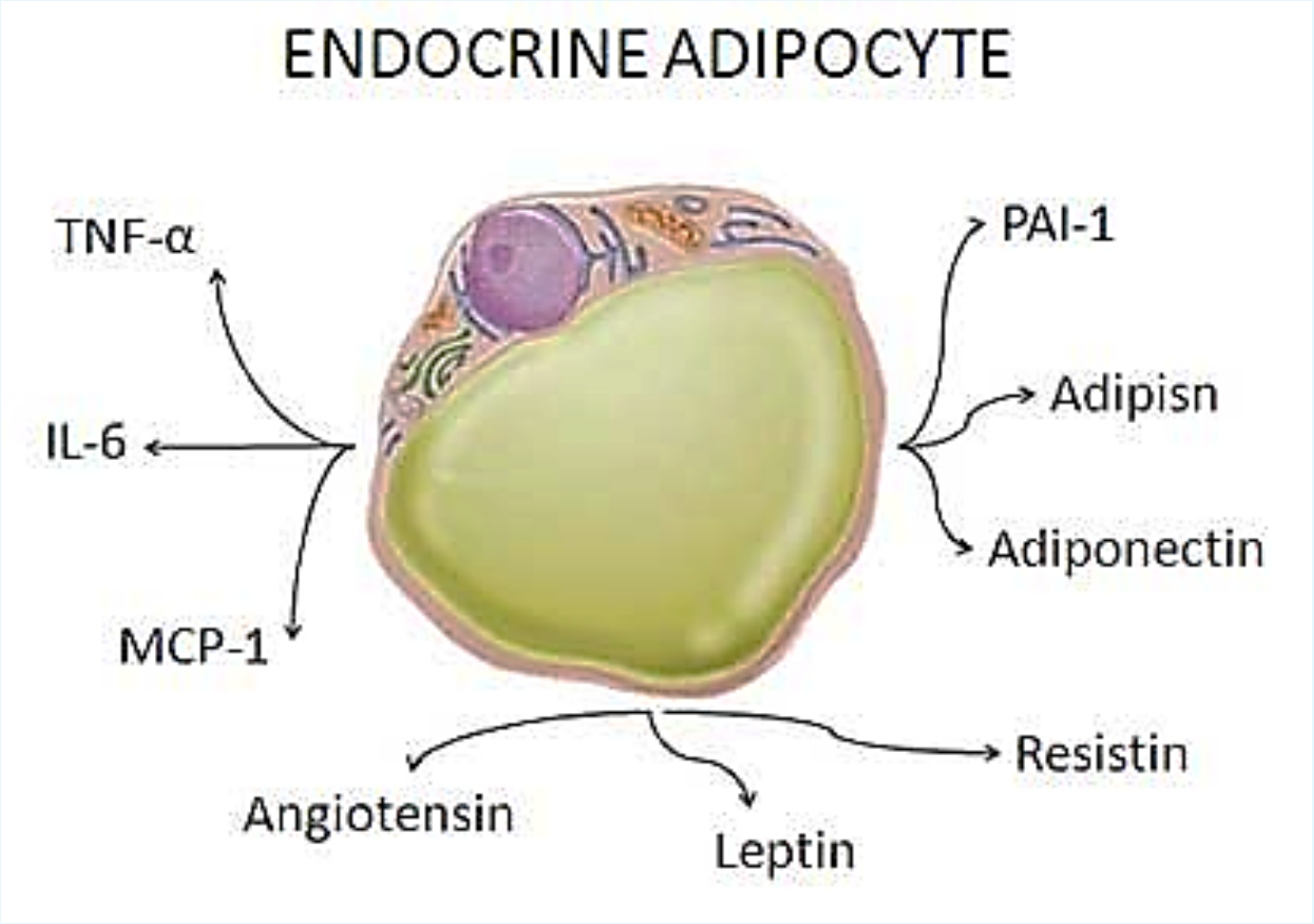


Hypertension

Adipocytes as Endocrine Organs

- The adipocyte is now appreciated as an “endocrine cell” producing substances that stimulate hormonal changes.

Known Factors Produced by Adipocytes



Kershaw and Flier. J Clin Endocrinol Metab2004; 89:2548-56.

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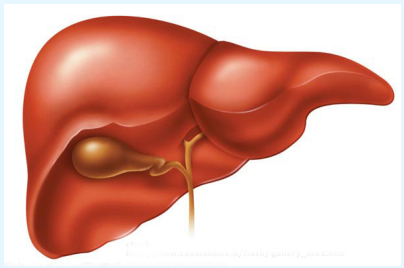
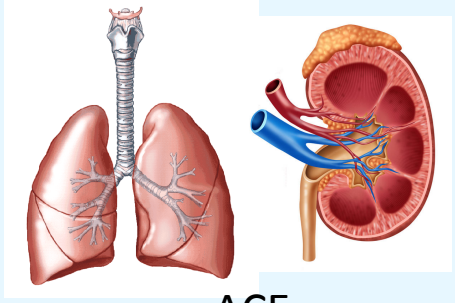
Renin-Angiotensin Aldosterone System





Sympathetic activity

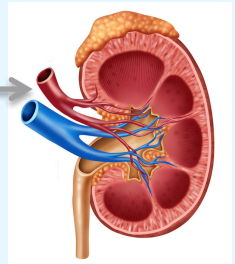
ACE

Arteriolar vasoconstriction

Angiotensinogen → Angiotensin I → Angiotensin II → Adrenal Cortex

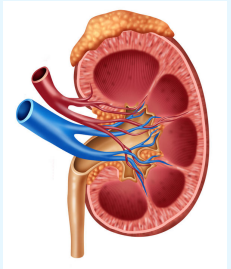
Adipocyte

Renin



Decrease in renal perfusion

Aldosterone



Tubular Na^+Cl^- reabsorption and K^+ excretion. H_2O retention.

Plasma Aldosterone Is Increased in Obese Primary Hypertensive Patients

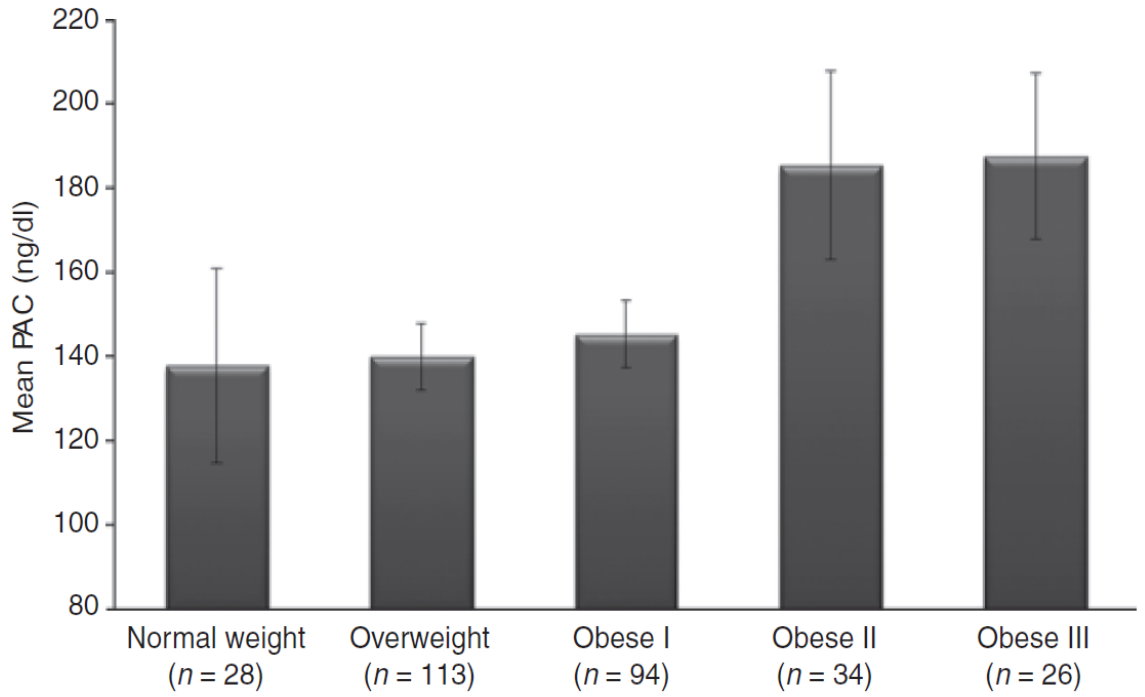


Figure 2 | Mean plasma aldosterone concentration (PAC) levels ± standard errors according to the World Health Organization classification of obesity based on body mass index (*P* among groups = 0.023).

Sarzani et.al. Am J Hypertens 2012;25:818-25

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Obesity and Aldosterone Production

- Study of 100 patients with morbid obesity (81 women and 19 men)
- Testing **before** and **after gastric bypass surgery**

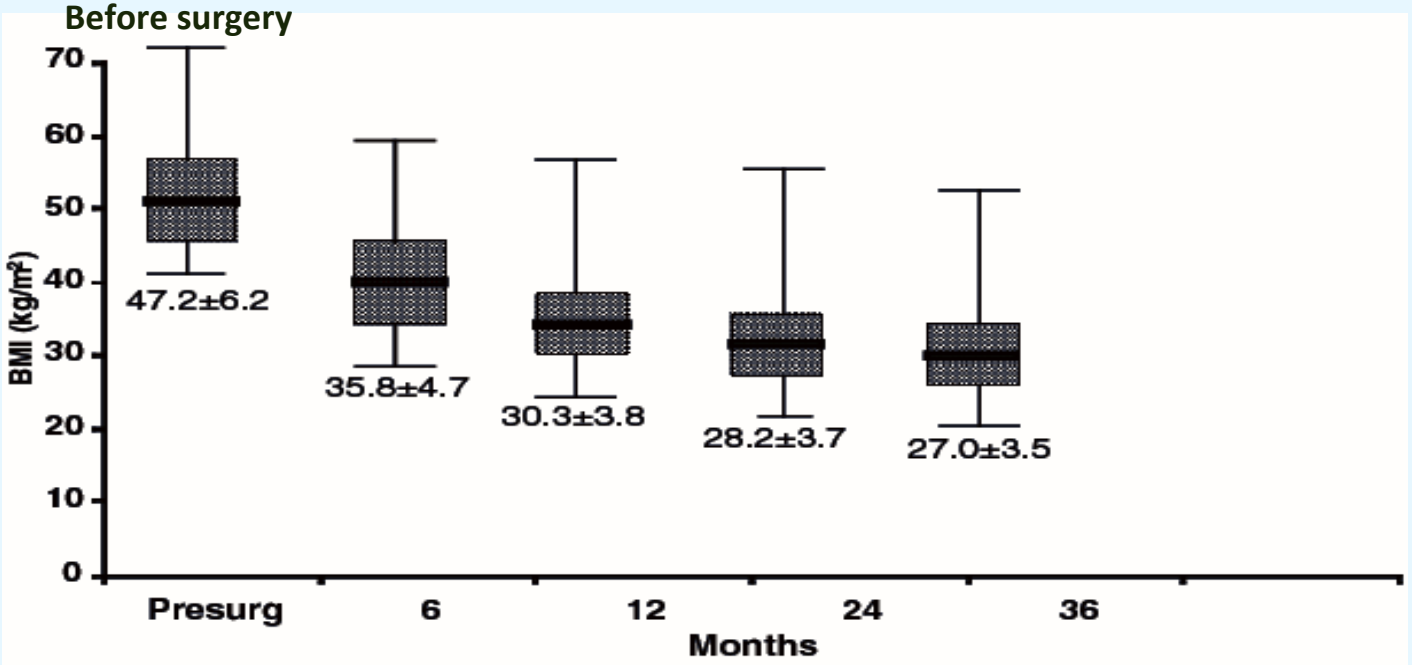

Figure 1. Evolution of the mean ± standard deviation (SD) and maximum and minimum values of the BMI during follow-up.

Ruano et al. Obes Surg. 2005;15:670-6.

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Obesity and Aldosterone Production

Table 4. Mean ± SD of the hormone levels in group A patients

Units	INS pmol/L	RENIN nmol/L/h	ALDOS pmol/L	ACE U/L	Na nmol/L	K nmol/L
Presurgery	260±13.5	5.00±2.5	1070±137	59±29.5	155±3.0	3.20±0.4
6 months	185±11.5	4.85±2.4	900±115	36±18.0	150±3.0	4.00±0.5
12 months	116±7.2	4.65±2.3	820±105	33±16.5	146±4.0	4.30±0.5
24 months	93±5.8	4.30±2.1	701±90	30±16.0	142±3.0	4.50±0.5
36 months	86±5.5	4.20±2.1	699±90	29±14.5	140±3.0	4.50±0.5
Correlation parameter	*	n.s.	*	*	*	n.s.
BMI	r±0.93		r=0.97	r=0.86	r=0.95	r=-0.42
	P<0.01		*P*<0.01	*P*<0.01	*P*<0.01	*P*<0.01
Correlation parameter	*	*	*	*	n.s.	n.s.
WHR	r=0.45	r=0.88	r=0.79	r=0.86		
(x F-M)	*P*<0.05	*P*<0.01	*P*<0.01			

*Statistically significant differences. n.s. Non-significant differences.
WHR (x F-M): Mean value female-male.

Ruano et al. Obes Surg. 2005;15:670-6.

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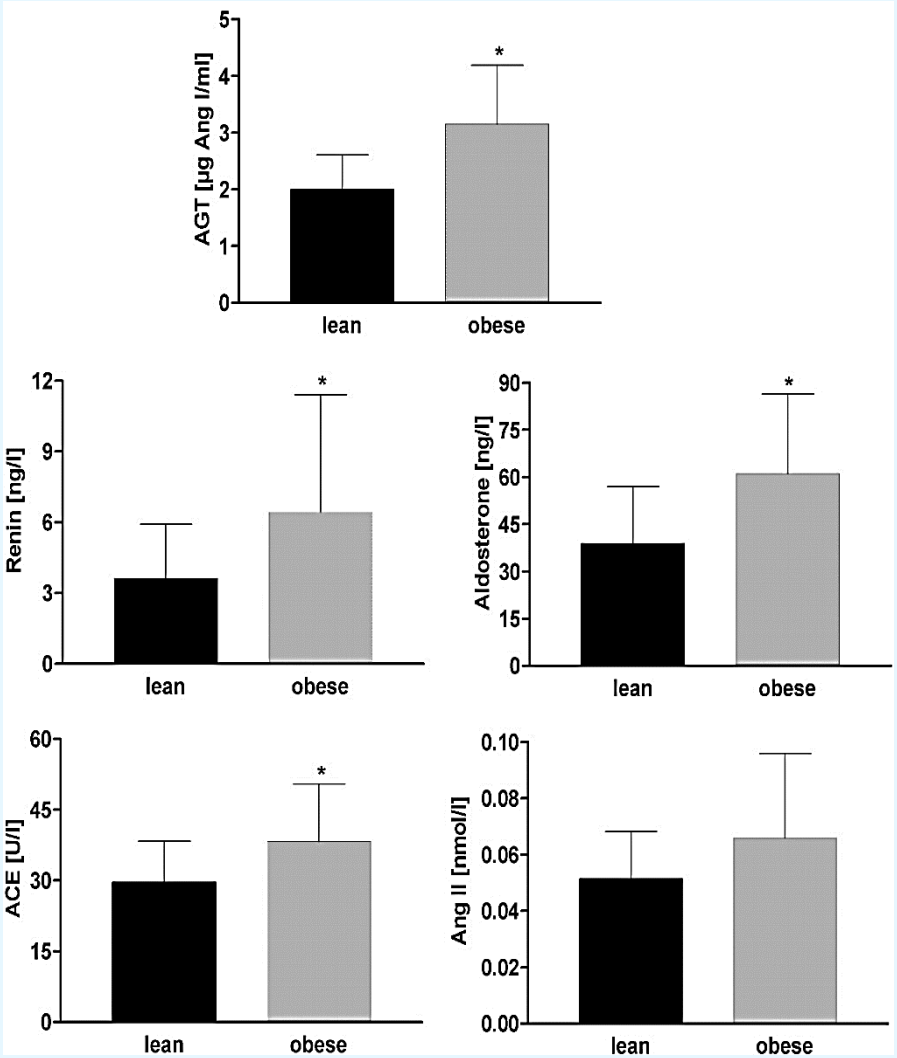
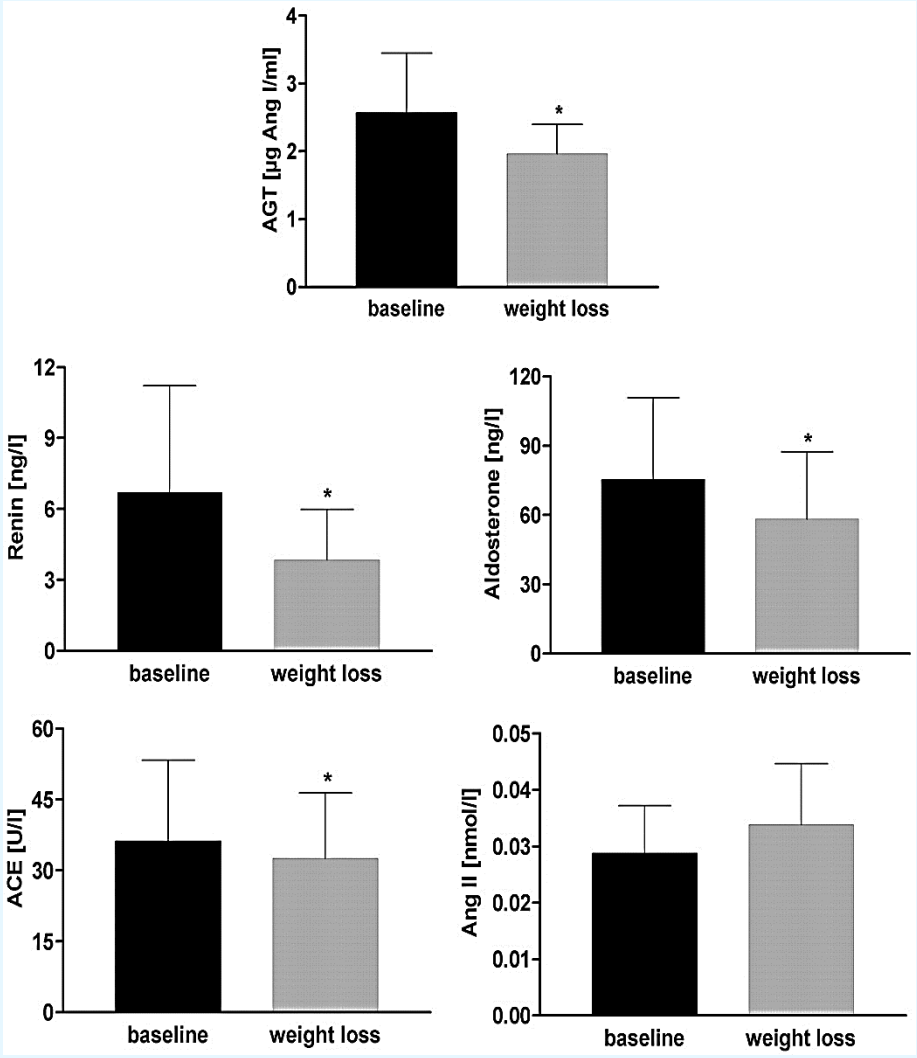
Obesity and the Renin Angiotensin Aldosterone System





Engeli et al. Hypertension 2005;45:356-62

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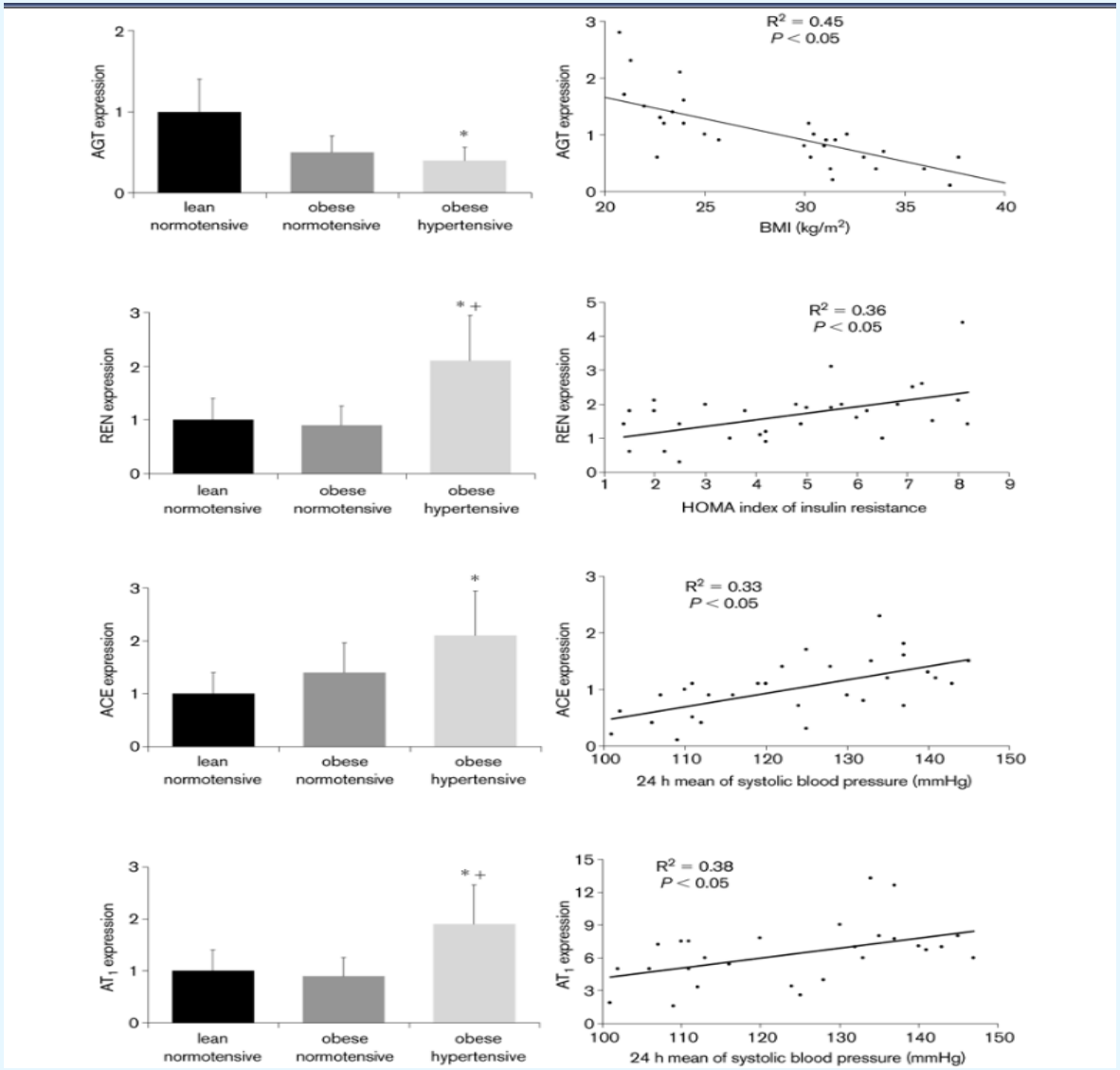
RAAS Gene Expression by Adipocytes



Gorzelniak et al. J Hypertens.2002;20:965-73.

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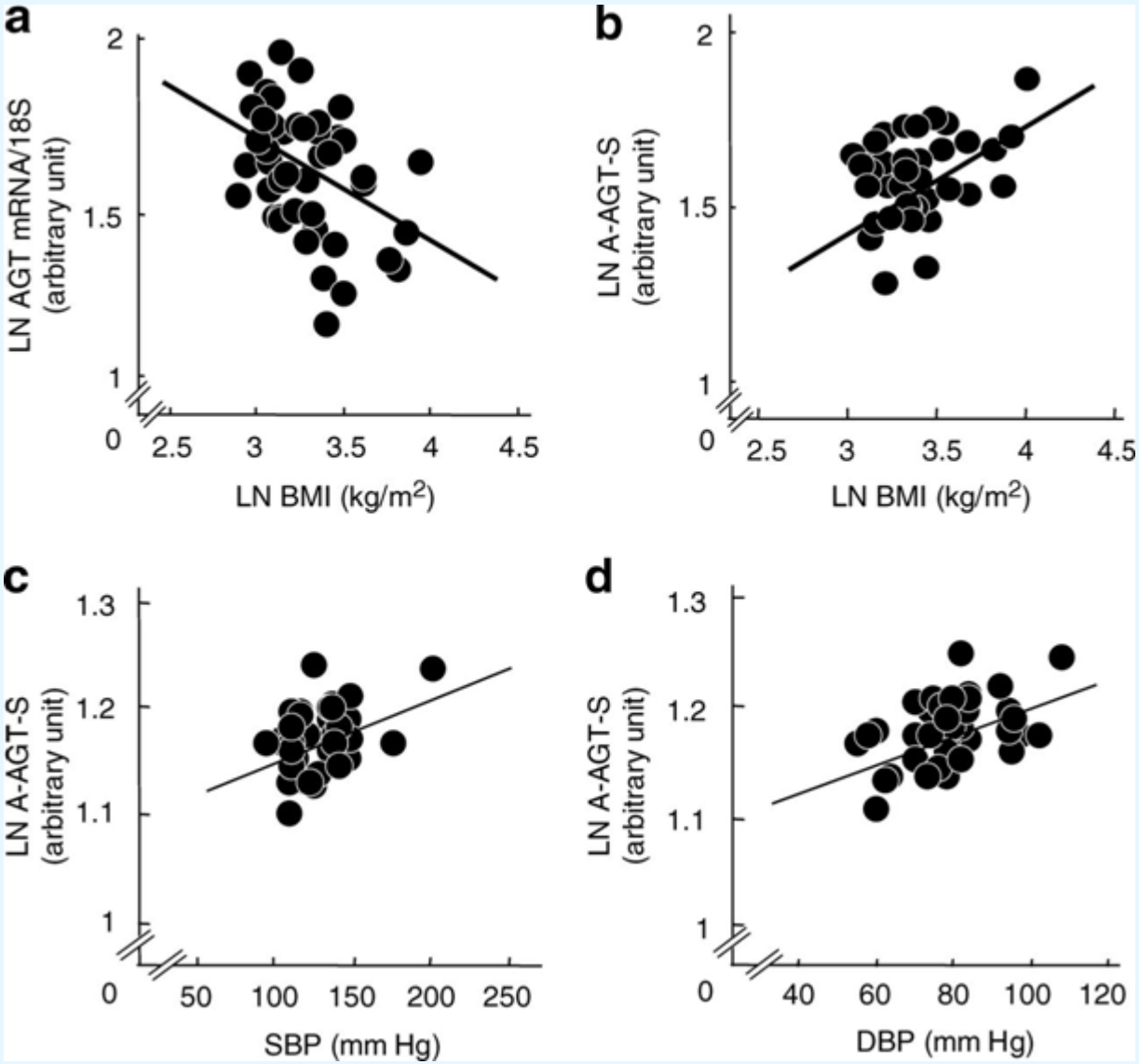
Adipose Tissue-derived Angiotensinogen



Yasue S et al. Am J Hypertens 2010;23:425-431

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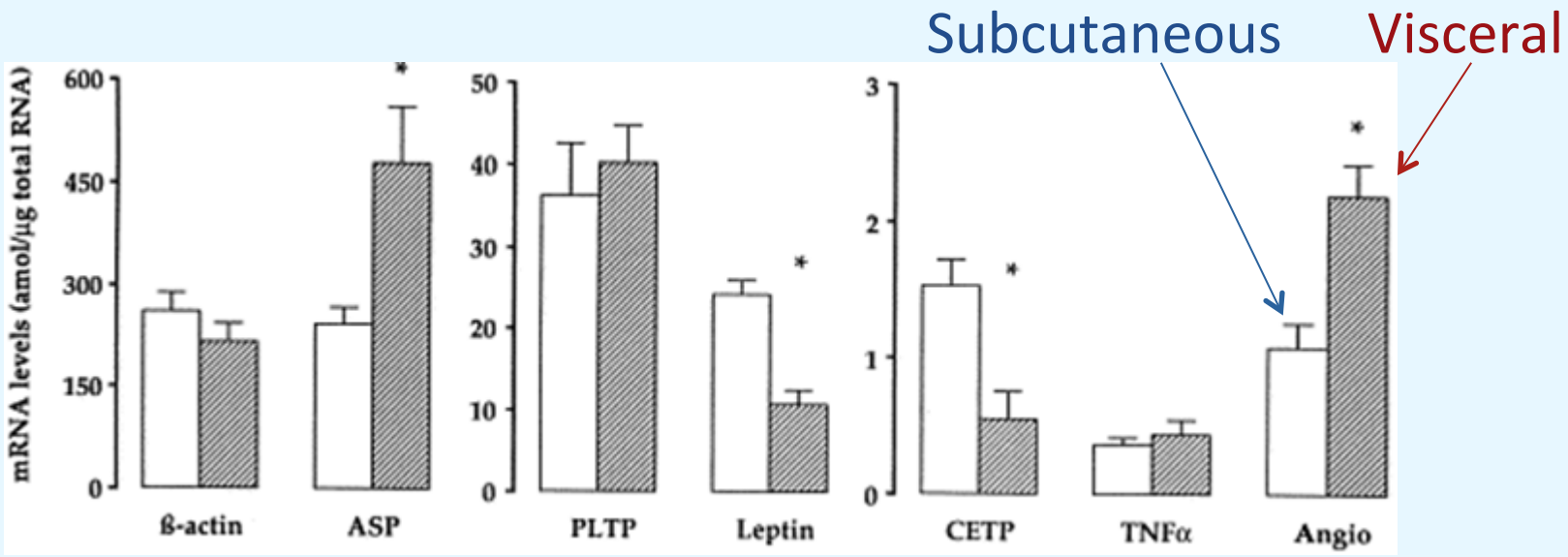
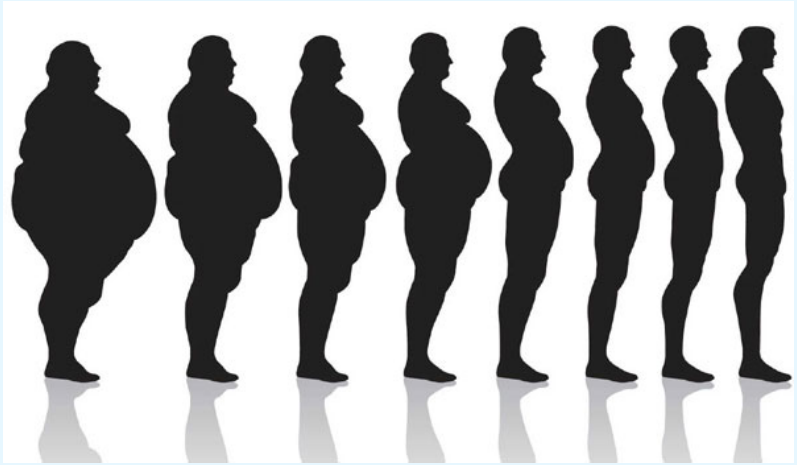
Visceral vs Subcutaneous Fat



Dusserre et al. Biochim Byophys Acta. 2000;1500:88-96.

Management of Obesity-Related Hypertension

- Weight loss



- Per kilogram of weight loss:
  - 1 mm Hg systolic BP reduction
  - 0.92 mm Hg diastolic BP reduction

Neter et al. Hypertension. 2003;42:878-84.

Possible Link to Resistant Hypertension

- Many patients with resistant hypertension have abdominal obesity.
- Aldosterone blockers, spironolactone, are effective in lowering BP in patients with resistant hypertension.
- Spironolactone is underused in patients with resistant hypertension.

Clark et al. Can J Cardiol. 2012;28:318-25; Dorresteijn et al. Obes Rev. 2012;13:17-26; Chapman et al. Hypertension. 2007;49:839-45; Sharabi et al. Am J Hypertens. 2006;19:750-5.

- *Obesity*-related hyperaldosteronism is different than *primary* hyperaldosteronism

Who Should be Screened for Primary Hyperaldosteronism?

- Endocrine Society Guidelines:
  - HTN and spontaneous or low dose diuretic-induced hypokalemia
  - Severe HTN (>160 mmHg systolic or >100 mmHg diastolic)
  - Resistant HTN (3 drug regimen that includes a diuretic)
  - HTN with adrenal adenoma
  - HTN and a family history of HTN or CVA < 40 years old
  - First-degree relative with primary hyperaldosteronism

Funder et al. J Clin Endocrinol Metab. 2008;93:3266-81.

Evaluation for Primary Hyperaldosteronism

- Screening
  - Stop specific anti-hypertensive agents:
    - **Most** agents can be continued
    - Aldosterone blockers (spironolactone, eplerenone): ↑PRA → STOP
    - ACEI/ARBs/direct renin inhibitors: ↑PRA → STOP
  - Plasma Aldosterone concentration > 15 ng/dL
  - Plasma renin activity: less than 1 ng/mL/hr
  - Plasma aldosterone concentration/Plasma renin activity > 20
    - Primary hyperaldosteronism: 30 – 50
    - Essential HTN: 4 - 10
  - Supplement with potassium

Funder et al. J Clin Endocrinol Metab. 2008;93:3266-81.

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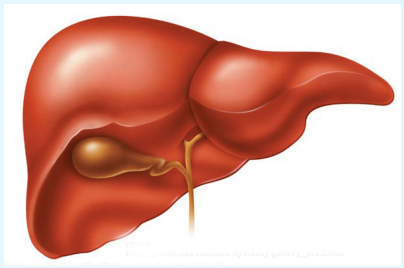
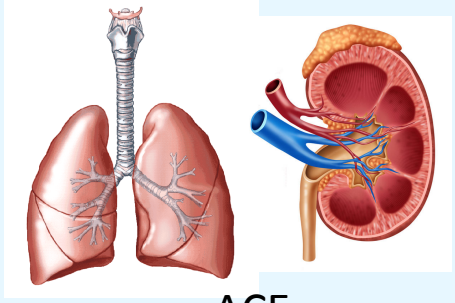
Renin-Angiotensin Aldosterone System





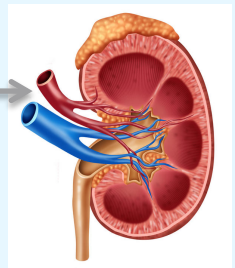
ACE

↑ Sympathetic activity

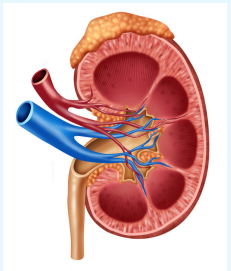
Arteriolar vasoconstriction

Angiotensinogen → Angiotensin I → Angiotensin II → Adrenal Cortex

Renin



Decrease in renal perfusion



Aldosterone

Tubular Na^+Cl^- reabsorption and K^+ excretion. H_2O retention.

Confirmatory Testing

- Salt suppression test:
  - Oral sodium loading: 5000 mg sodium/day x 3 days
    - 24 hour urine aldosterone: > 12 mcg
    - 24 hour urine sodium > 200 mEq
  - IV sodium loading: 2L 0.9% NS over 4 hours
    - Plasma aldosterone concentration > 10 ng/dL
  - Supplement with potassium (K > 4 meq/L)

Funder et al. J Clin Endocrinol Metab. 2008;93:3266-81.

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Primary Hyperaldosteronism

- The average aldosteronoma is small
  - Dedicated Adrenal CT with 2-3 mm cuts
    - Adenoma
    - Hyperplasia
    - Carcinoma

- Adrenal vein sampling if needed

Funder JW, *et al*. JCEM 2008.

Management of Primary Hyperaldosteronism

Medical management

- Aldosterone blocker
  - Spironolactone, Eplerenone
- Amiloride, triamterene:
  - Block the renal effects of aldosterone
- Potassium supplementation

Surgical management

- Unilateral adrenal source of elevated aldosterone

Summary

- Abdominal obesity is associated with hypertension.
- The adipocyte is contributing to elevated aldosterone levels.
- Consider treatment with aldosterone blockers in the patient with abdominal obesity and in the patient with resistant hypertension.
- Elevated aldosterone in obesity is different than true primary hyperaldosteronism.