HYPERTENSION IN CKD - CAUSE AND EFFECT DILEMMA

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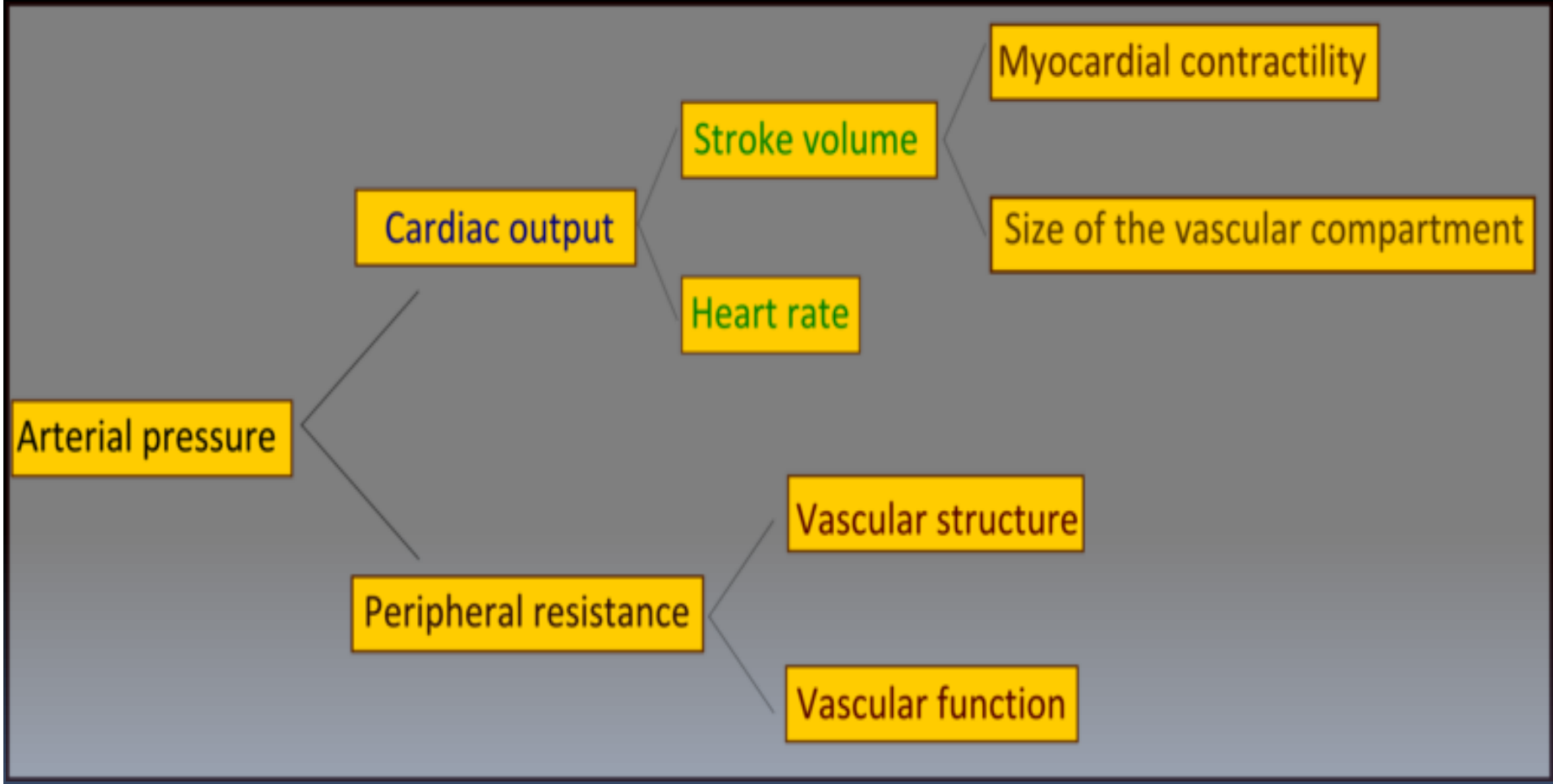
- The relationship between increased blood pressure (BP) and kidneys is multidirectional.
- Chronic kidney diseases (CKDs) are one of the most common causes of secondary hypertension.
- On the other hand, hypertension of any etiology can lead to renal impairment.

‘”Hypertension first or CKD first”

Hypertension



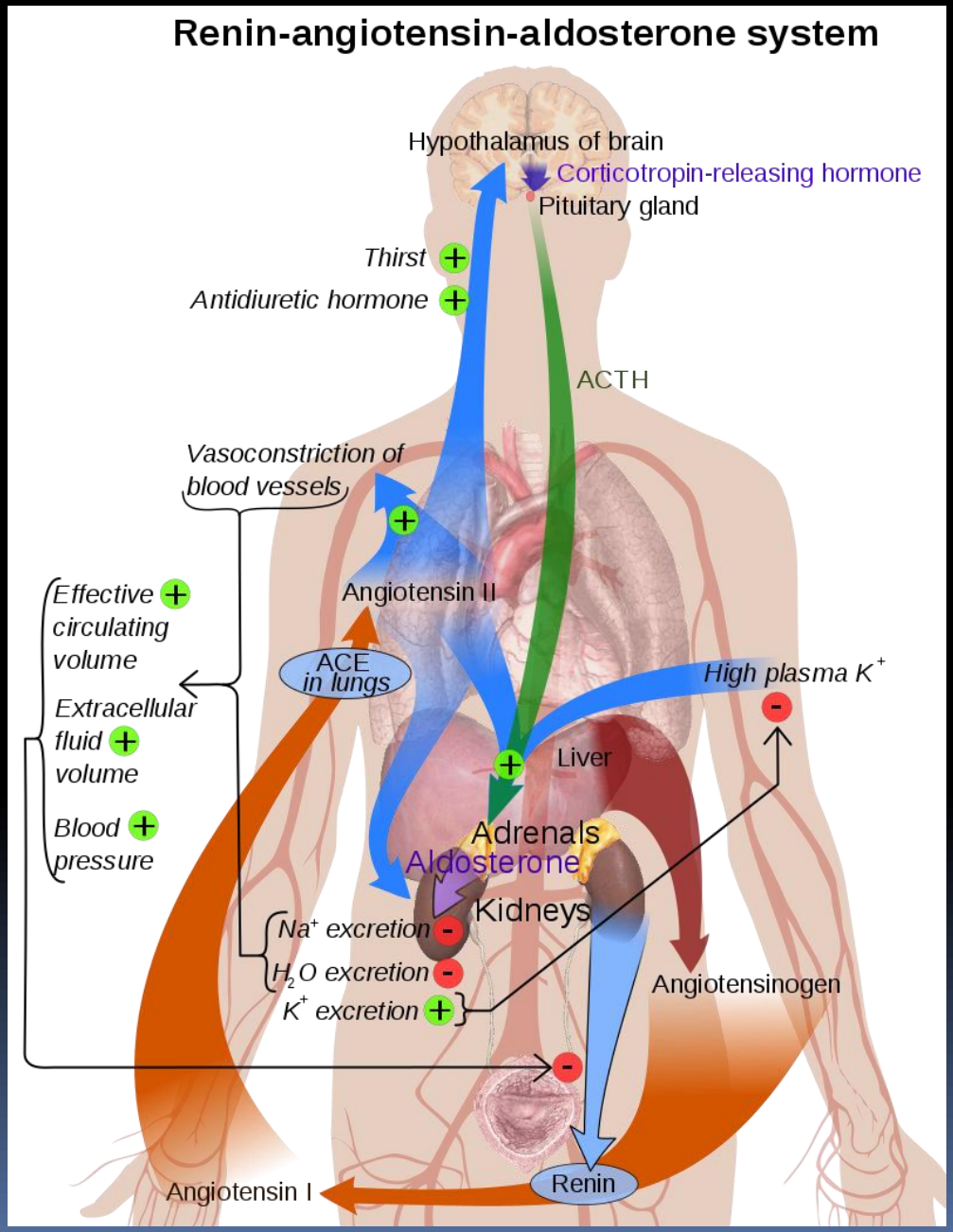
Pathogenesis

- Pathogenesis of essential hypertension has been proposed to be due to interplay of multiple factors like
  1. Overactive renin angiotensin system
  2. Autonomic nervous system
  3. Excess stress
  4. Endothelial dysfunction & vasoactive substances
  5. Genetic predisposition
  6. Hypertension is immunologic in origin
  7. Abnormal salt handling by the kidneys

Renin–angiotensin–aldosterone system

- Renin is secreted from the juxtaglomerular apparatus of the kidney in response to glomerular under perfusion or a reduced salt intake. It is also released in response to stimulation from the sympathetic nervous system.

- Renin is responsible for converting renin substrate (angiotensinogen) to angiotensin I, a physiologically inactive substance which is rapidly converted to angiotensin II in the lungs by angiotensin converting enzyme (ACE)


Renin-angiotensin-aldosterone system
Hypothalamus of brain
Corticotropin-releasing hormone
Pituitary gland
Thirst
Antidiuretic hormone
ACTH
Vasoconstriction of blood vessels
Effective circulating volume
Extracellular fluid volume
Blood pressure
Angiotensin II
ACE in lungs
High plasma K+
Liver
Adrenals
Aldosterone
Kidneys
Na+ excretion
H2O excretion
K+ excretion
Angiotensinogen
Renin
Angiotensin I

Renin–angiotensin–aldosterone system

- Angiotensin II is a potent constrictor of all blood vessels. It acts on the musculature of arteries, raising peripheral resistance and thereby elevating blood pressure.

- Angiotensin II also causes the adrenal glands to release aldosterone, which stimulates the epithelial cells of the kidneys to increase re-absorption of salt and water, leading to raised blood volume and raised blood pressure

Autonomic nervous system

- Arterial baroreceptors are reset to a higher pressure in hypertensive patients
- This baroreflex resetting seems to be mediated by a central action of angiotensin II
- Additional small-molecule mediators to exaggerated sympathetic drive in hypertension include reactive oxygen species and endothelin

Stress

- Exposure to stress increases sympathetic outflow, and repeated stress-induced vasoconstriction and salt retention may result progressive increases in blood pressure

Endothelial dysfunction

- Vascular endothelial cells play a key role in blood pressure maintenance by producing a number of potent local vasoactive agents, including the vasodilator molecule nitric oxide and the vasoconstrictor peptide endothelin.

Endothelial dysfunction

- Endothelin activates local renin-angiotensin systems, is a powerful vascular vasoconstrictor, which may produce a salt sensitive rise in blood pressure also.
- Nitric oxide, produced by arterial and venous endothelium diffuses through the vessel wall into the smooth muscle causing vasodilatation.

Endothelial dysfunction

- In patients with essential hypertension, the balance between the vasodilators and the vasoconstrictors is upset, which leads to changes in the endothelium and sets up a "vicious cycle" that contributes to the maintenance of high blood pressure

Genetic predisposition

- Multiple genes are most likely contribute to the development of the disorder in a particular individual
- Hypertension is about twice as common in subjects who have one or two hypertensive parent
- Gene mutations affect blood pressure by exaggerated angiotensin response and altering renal salt handling.

Genetic predisposition

- Animal and human studies show that a transplanted kidney from a hypertensive donor raises the blood pressure and increases the need for antihypertensive drugs in recipients coming from “normotensive” families.

- Conversely a kidney from a normotensive donor does not raise the blood pressure in the recipient.

Hypertension May Have an Immunological Basis Also

- Studies have revealed that hypertension is associated with renal infiltration of immune cells
- Presence of agonistic antibodies directed to angiotensin II and adrenergic receptors
- Evidence suggests that T lymphocytes and T-cell derived cytokines (eg, interleukin 17, tumor necrosis factor alpha) play an important role in hypertension

Hypertension May Have an Immunological Basis Also

- Pharmacologic immunosuppression (such as with the drug mycophenolate mofetil) or pathologic immunosuppression (such as occurs with HIV) results in reduced blood pressure in animals and humans.

- **Subtle renal defects** underlie the pathogenesis of essential hypertension in humans is supported further by several lines of evidence

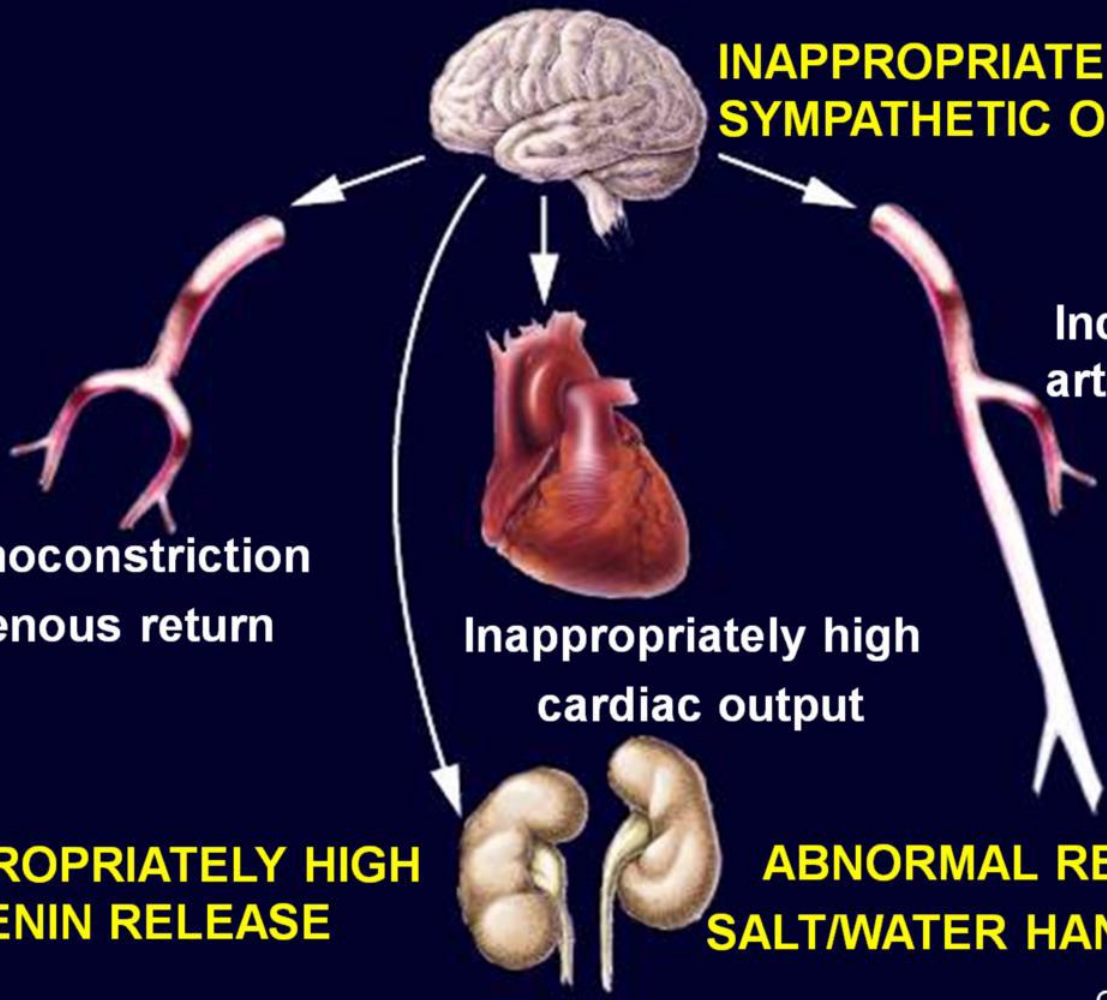
- In experimental models using large animals it has been found that acute rise in blood pressure results in brisk increase in renal sodium excretion and normalization of blood pressure

- It has also been also shown that normotensive individuals with family history of hypertension respond to salt loading with less natriuresis and higher blood pressure than those who has no family history

- In a series of patients with renal failure due to histologically proven hypertensive nephrosclerosis, transplant with kidneys from normotensive donors resulted in the resolution of their hypertension

- Hypertensive victims of fatal accidents were endowed with fewer nephrons than normotensive controls in an autopsy series

Pathophysiology of hypertension



Courtesy of JL Izzo Jr, MD.

so…

Sustained hypertension cannot occur without the involvement of kidney

Hypertension in CKD

Hypertension in CKD

- The prevalence of hypertension increases with worsening renal function.
- An inverse relationship between renal functional impairment and prevalence of hypertension has been reported in the Chronic Renal Insufficiency Cohort (CRIC) study
- Hypertension is very frequent in patients with CKD with an estimated prevalence of about 60%, reaching about 95% in stages III-IV CKD

Hypertension in CKD

- CKD is characterized by sodium and water retention, leading to increases of plasma volume and cardiac output
- The excess salt and water retention increases the blood flow to the tissues.
- The tissue arterioles constrict to decrease the excessive blood flow.
- The resulting vasoconstriction raises the peripheral vascular resistance, which is the most consistent findings in HTN (whether essential or renal in origin)

Blood volume in CKD

- Role of volume expansion in hypertension due to CKD is underscored by the effect of ultrafiltration or diuretics on blood pressure control in CKD patients

- Dialysis units that employ eight-hour thrice-weekly or short daily hemodialysis report that only a minority of patients require antihypertensive medications for blood pressure control

Hypertension in CKD

- In CKDs, activation of the renin-angiotensin system plays an important role. Most often, it is caused by ischemia, which can be related to atherosclerotic narrowing, scar formation in inflammatory diseases, pressure of masses (tumors, solitary cysts) or calyx dilation in hydronephrosis

- Treatment of such patients with bilateral nephrectomy or inhibitors of RAS has been shown to result in control of blood pressure, suggesting failing kidneys as the source of excess renin

Hypertension in CKD

- Secondary hyperparathyroidism, accompanied by increase of the intracellular calcium concentration, can lead to vasoconstriction and hypertension

Hypertension in CKD

- In the Framingham cohort, over a 3-year follow-up, Wang reported that urinary albumin excretion predicted blood pressure progression in 1499 non-diabetic, non-hypertensive individuals incrementally over established risk factors

- Based on their data, authors suggested that urine albumin-to-creatinine ratio may be a useful biomarker for identifying individuals at higher risk for future hypertension development.

Hypertension in CKD

- In the Nurses' Health Study, performed on ~2000 relatively low-risk pre- and post-menopausal women without diabetes or hypertension, Forman *et al.* reported that higher ACR, even within the normal range, were independently associated with an increased risk of hypertension.

Hypertension in CKD

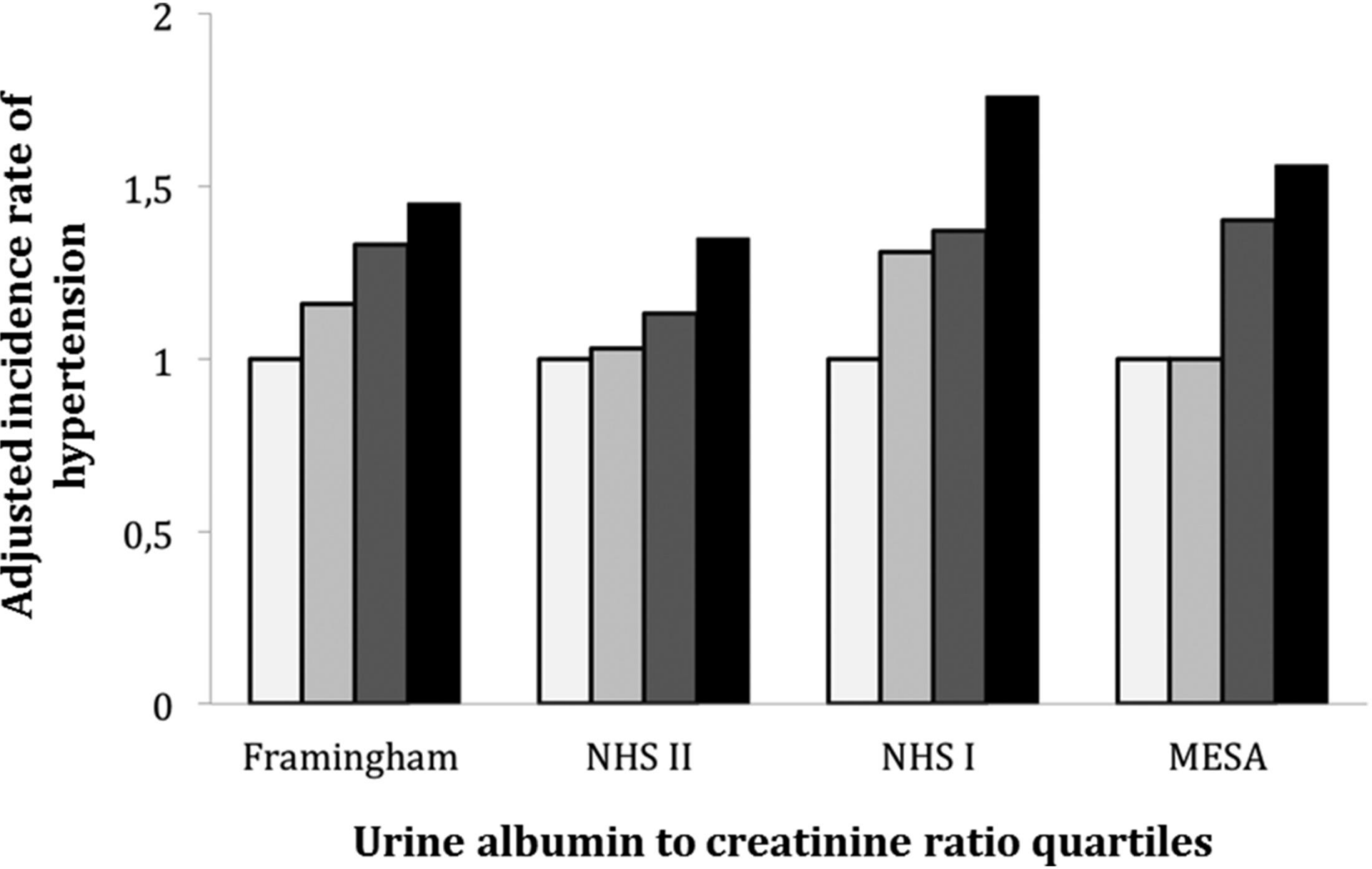
- The hypothesis that mild renal damage may precede the development of hypertension was also tested in the PREVEND study.

- Brantsma *et al.* in a series of 4635 normotensive subjects over a mean follow-up of 4.3 years, reported that baseline UAE was significantly associated with the risk of developing hypertension,

- Elevated UAE and low GFR, although still within the normal range, the risk of developing hypertension was highest.

Hypertension in CKD

- In the Multi-Ethnic Study of Atherosclerosis carried out on >2700 community-based, non-hypertensive, middle-aged adults, the reduction in eGFR turned out to be a more relevant marker of hypertension risk than urinary albumin excretion after adjustment for confounders.



From: Blood pressure, albuminuria and renal dysfunction: the 'chicken or egg' dilemma

Nephrol Dial Transplant. 2014;29(8):1453-1455. doi:10.1093/ndt/gfu183

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Hypertension in CKD

- In microneurographic studies, patients with CKD have increased sympathetic nerve activity that responds to angiotensin-converting enzyme (ACE) inhibition or bilateral nephrectomy

Hypertension in CKD

- Even when renal function is well preserved, activation of the RAS is an important factor in the pathogenesis of hypertension in polycystic kidney disease, and is believed to be due to compression of the renal vasculature by enlarging cysts

In CKD hypertension is inevitable

Hypertension causing CKD

Hypertension causing CKD

- Long-term, uncontrolled hypertension leads to high intraglomerular pressure which causes leakage of protein i.e. microalbuminuria.

- Microalbuminuria is often the first sign of CKD. and is associated with a poor prognosis.

Hypertension causing CKD

- Elevated BP leads to damage of blood vessels within the kidney, as well as throughout the body. This changes impairs the kidney's ability to filter fluid and waste from the blood, leading to an increase of fluid volume in the blood

- Hypertension in the long term damages the endothelium also. This leads to a build-up of plaques and they can be deposited in the renal arteries causing luminal narrowing and ischemic kidney disease.

- In this situation, the kidneys are supplied by the narrowed renal arteries giving inadequate blood flow, which in turn causes smaller kidneys

- The resulting inadequate blood flow produces tubular atrophy, interstitial fibrosis, and glomerular alterations and scarring

Hypertension causing CKD

- In hypertension, glomerular filtration has been reported to decline more rapidly at a rate of 1.5 mL/ min per 1.73 m^2 every year compared to those without hypertension whose decline is at 0.75–1.00 mL/ min per 1.73 m^2 every year after the age of 40 years.

Chronic kidney disease is consequence of hypertension

The kidney plays an undisputed role in the pathogenesis of hypertension and it takes most of brunt of hypertension also

It's a Cycle

- Sustained hypertension cannot occur without the involvement of kidney
- Chronic kidney disease is consequence of hypertension
- In CKD hypertension is almost inevitable

"Your Patience was Extra Ordinary"

Thank You

Factors that may cause hypertension in CKD

Factors	Dominant Mechanism
Impaired Na excretion	Expansion of ECF volume
Activation of RAS	Vasoconstriction
Sympathetic activation	Direct vasoconstriction Stimulation of renin release
Imbalance in PG or kinins	Vasoconstriction
Endothelin	Vasoconstriction & renal injury
Reduced nitric oxide	Loss of vasodilator effect

Renal dysfunction

Hypertension

CKD