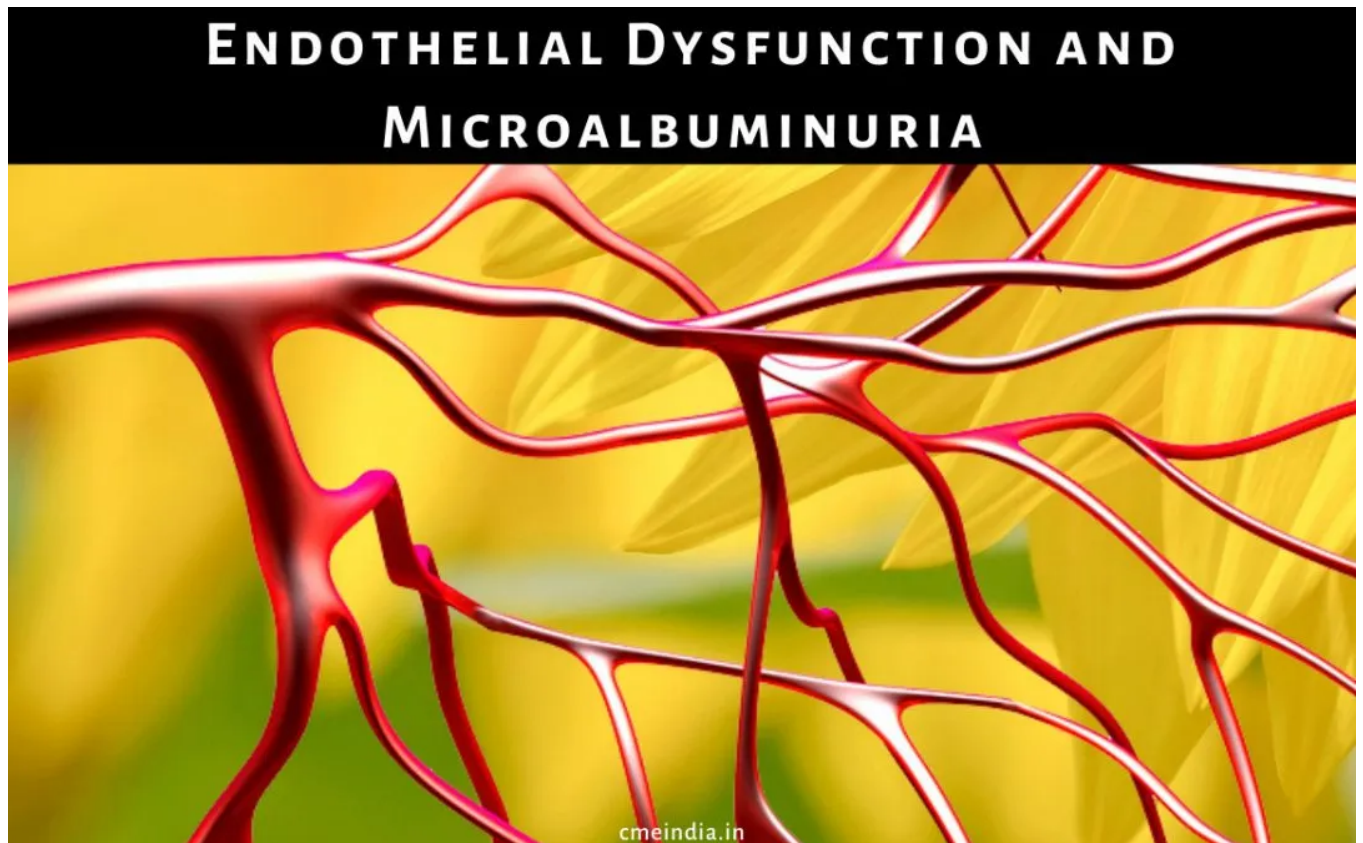


# Endothelial Dysfunction and Microalbuminuria

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[CME INDIA](#) Presentation by **Dr. Mritunjay Kumar Singh**, MD, Consultant Physician and Nephrologist, Chandraneel Clinic & AIMS, Gaya.

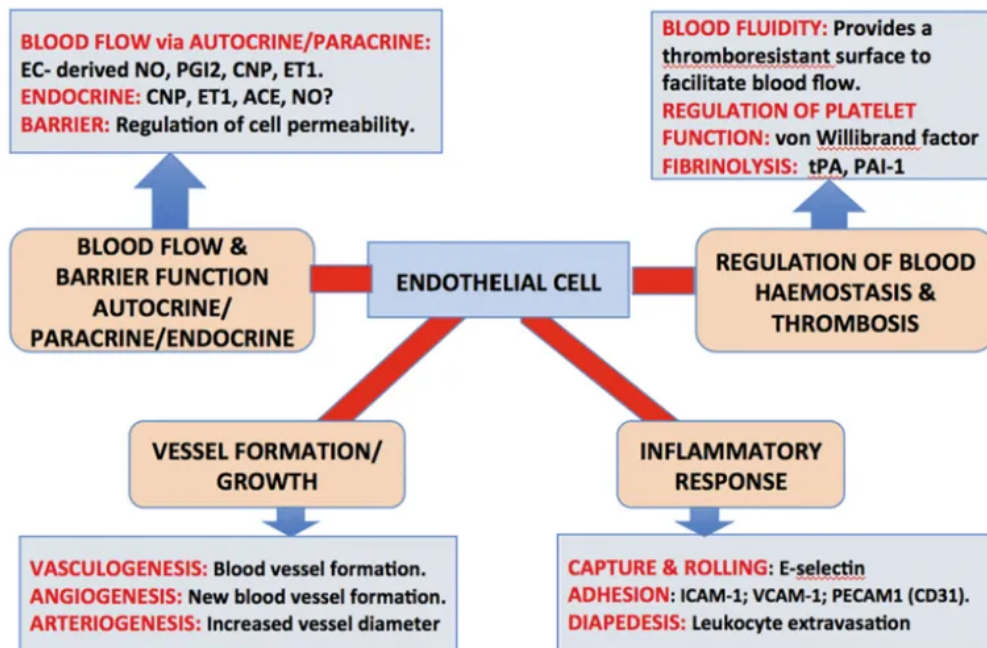
***One Is Only as Old as One's Endothelium***

Based on presentation at APICON-2022, Jaipur.

# "One Is Only As Old As One's Endothelium"

- Dr. Rudolf Altschul

## The Endothelium – Not just a barrier



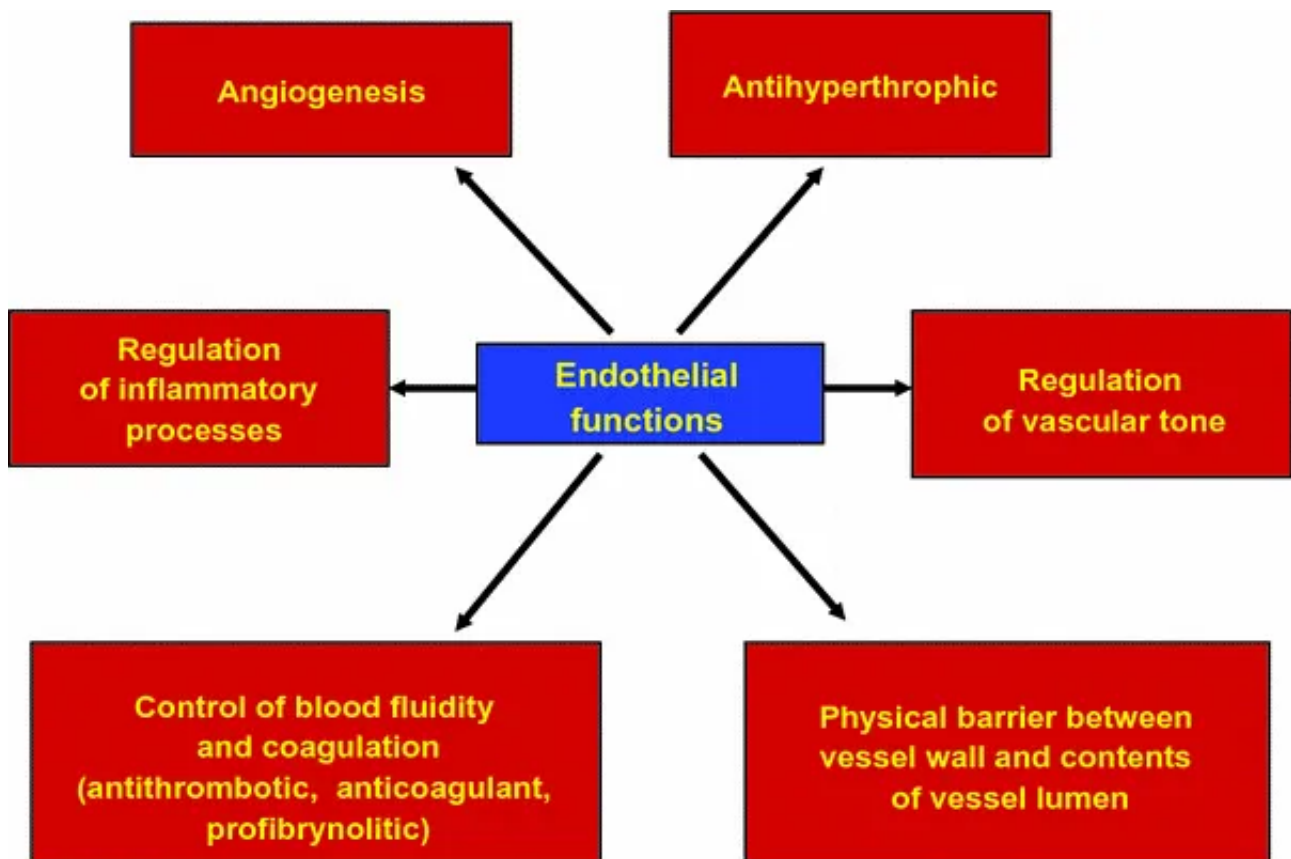
Chris R. Triggle, et al

Canadian Journal of Physiology and Pharmacology. **98**(7): 415-430

## Endothelial Dysfunction: Does It Matter?

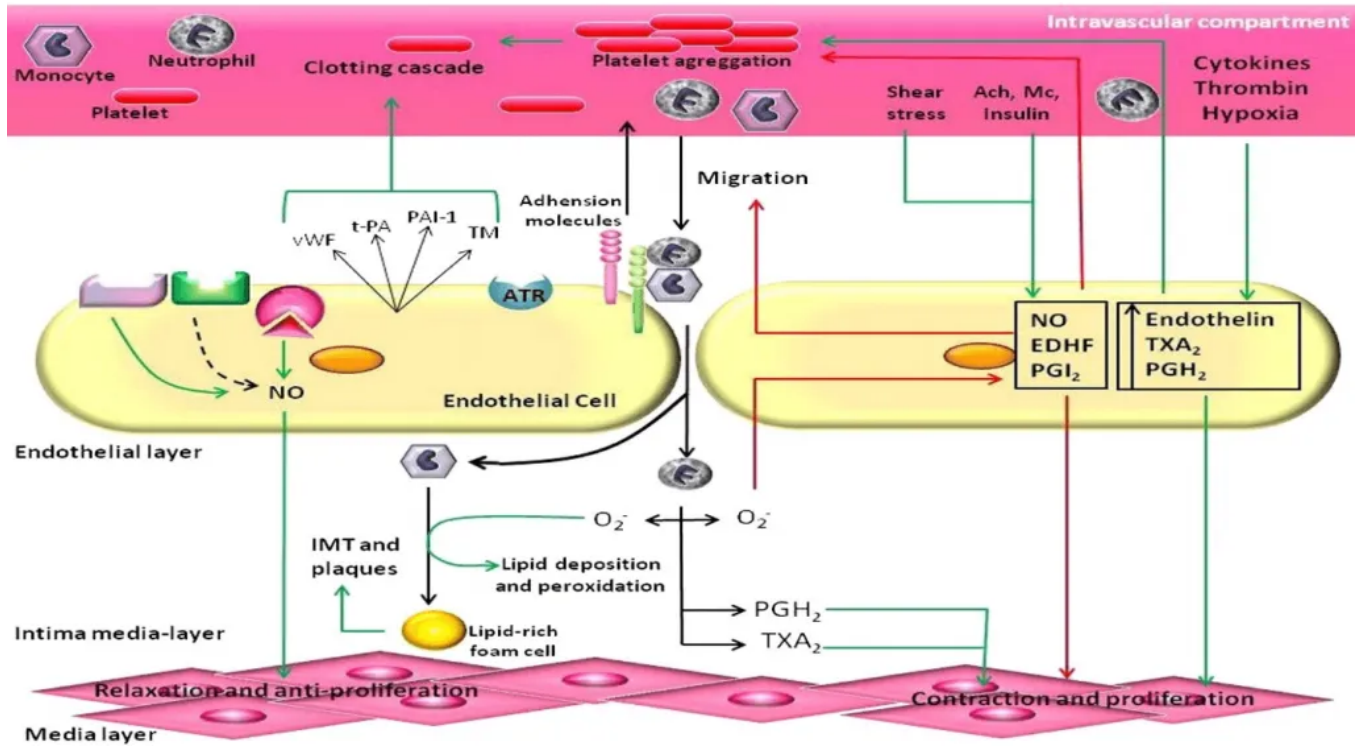
- The endothelium is responsible for maintaining a balance between vasodilation and vasoconstriction.
- It is also involved between inhibition and stimulation of smooth muscle cell proliferation and migration.
- It is also involved between thrombogenesis and fibrinolysis.
- If this balance is broken and there is an endothelial dysfunction, it leads to damage to the arterial wall.
- It is considered to be an early sign of atherosclerosis, before evidence of atherosclerotic plaque shows up on angiogram or ultrasound scan.
- The damage or injury of endothelial cells induced by physical,

chemical, and biological risk factors is a leading contributor to the development of mortal cardiovascular and cerebrovascular diseases.



### Nitric oxide is a crucial player in vascular homeostasis

- Endothelial dysfunction can lead to a reduction in nitric oxide (NO) bioactivity and an increase in oxygen free radical formation.
- Nitrites are the product of the oxidation of the NO derived from the endothelium.
- Under physiological conditions, 70%–90% of the nitrites in plasma stem from endothelial nitric oxide synthase (eNOS) activity.
- Brachial artery flow-mediated dilation (BAFMD) is one of the most reliable indirect methods for measuring endothelial dysfunction.
- BAFMD test is based on the ability of endothelial cells to detect changes in shear stress.

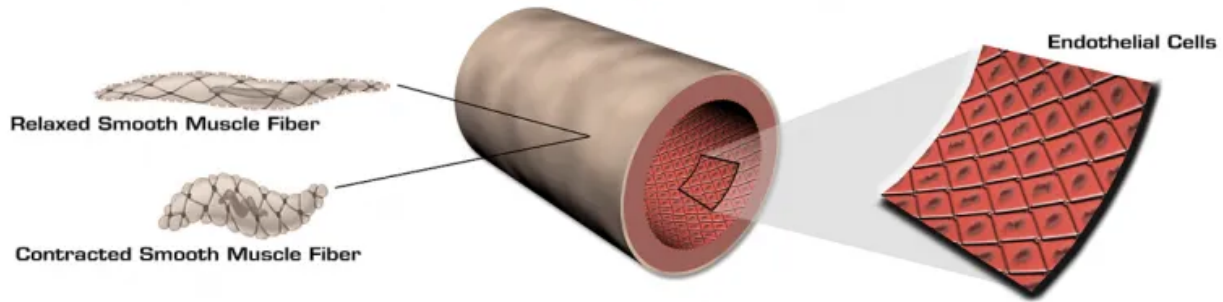


## Endothelial Dysfunction (Vascular Dysfunction) and Various Diseases

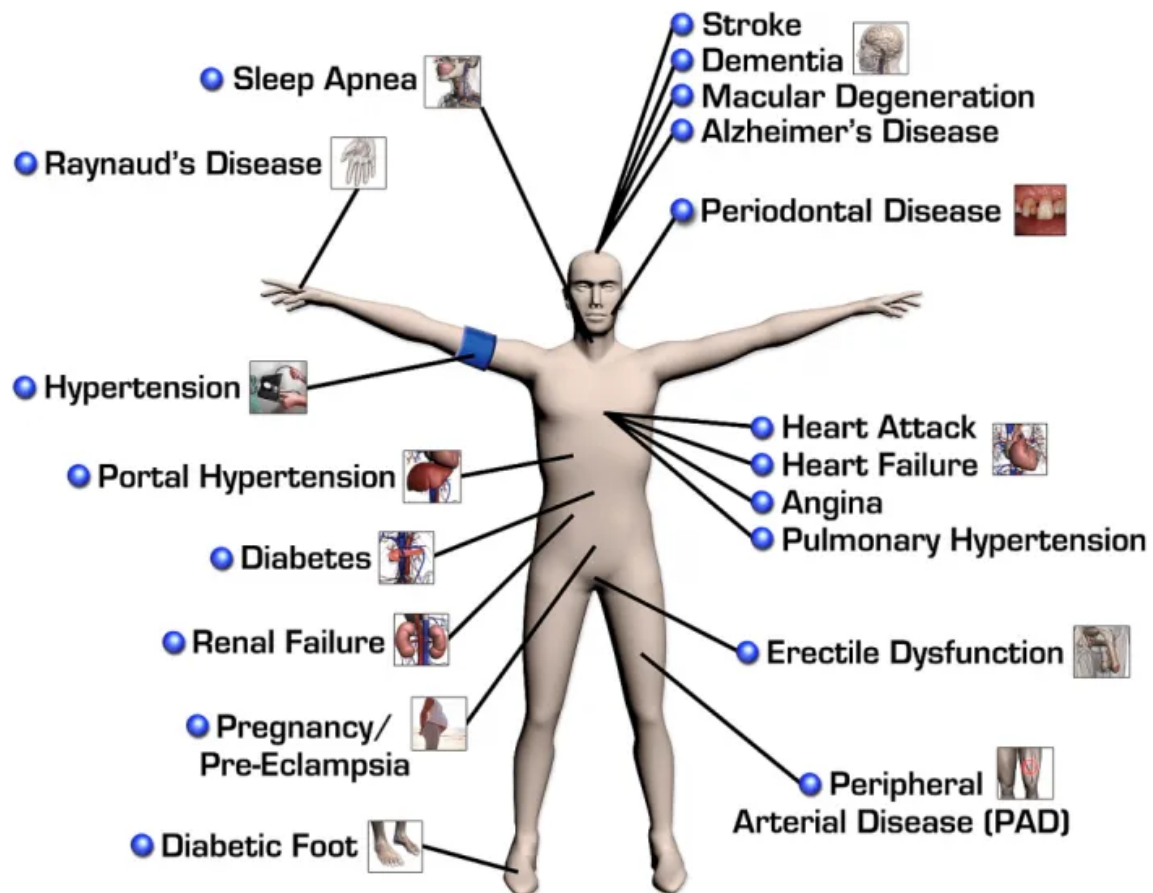
- The extent of involvement of endothelial dysfunction in various diseases, much like fever that is indicative of different problems.



# Vascular Dysfunction



**is Present in or a Precursor of:**



**and the Result of:**

**Smoking, High Cholesterol, High Blood Pressure, Overweight or Obesity, Diabetes, Poor Diet, Stress, Genetics, and Other Factors**

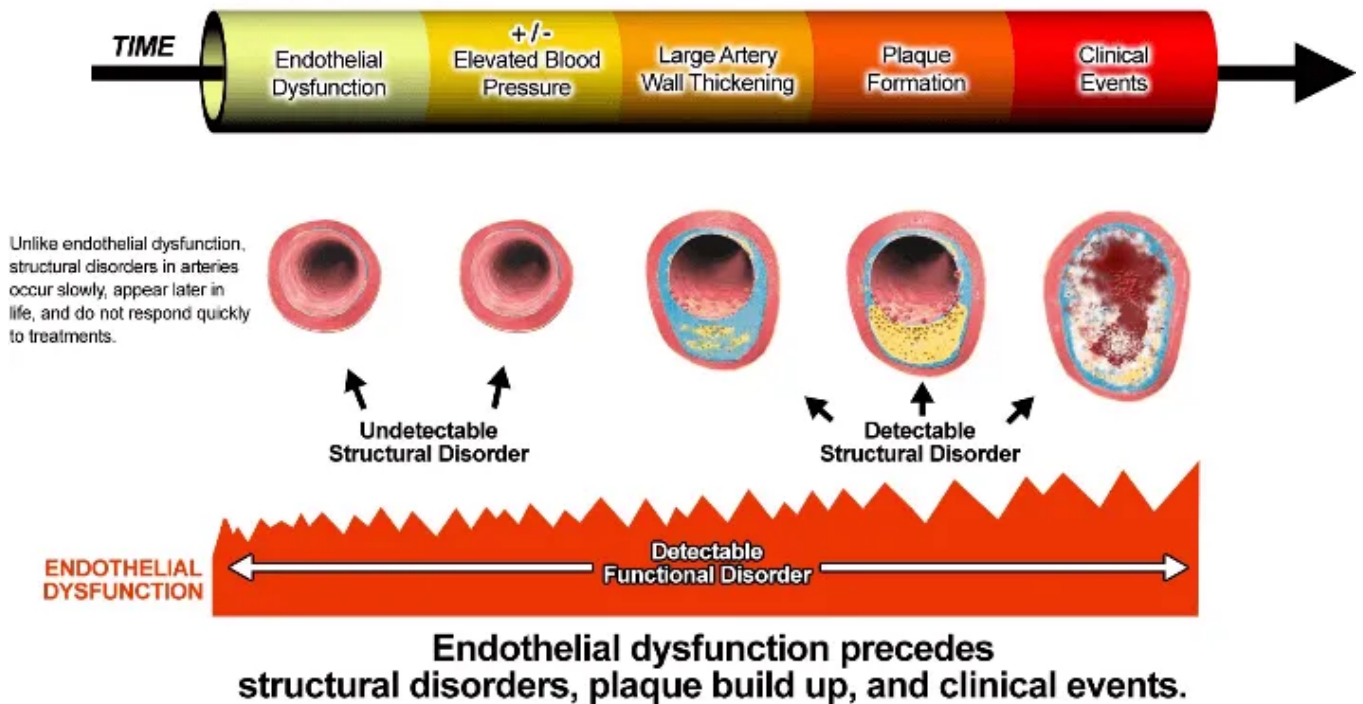
**Image Credit:**

[http://www.hivandhepatitis.com/recent/2010/0709\\_2010\\_b.html](http://www.hivandhepatitis.com/recent/2010/0709_2010_b.html)

**CVD Burden**

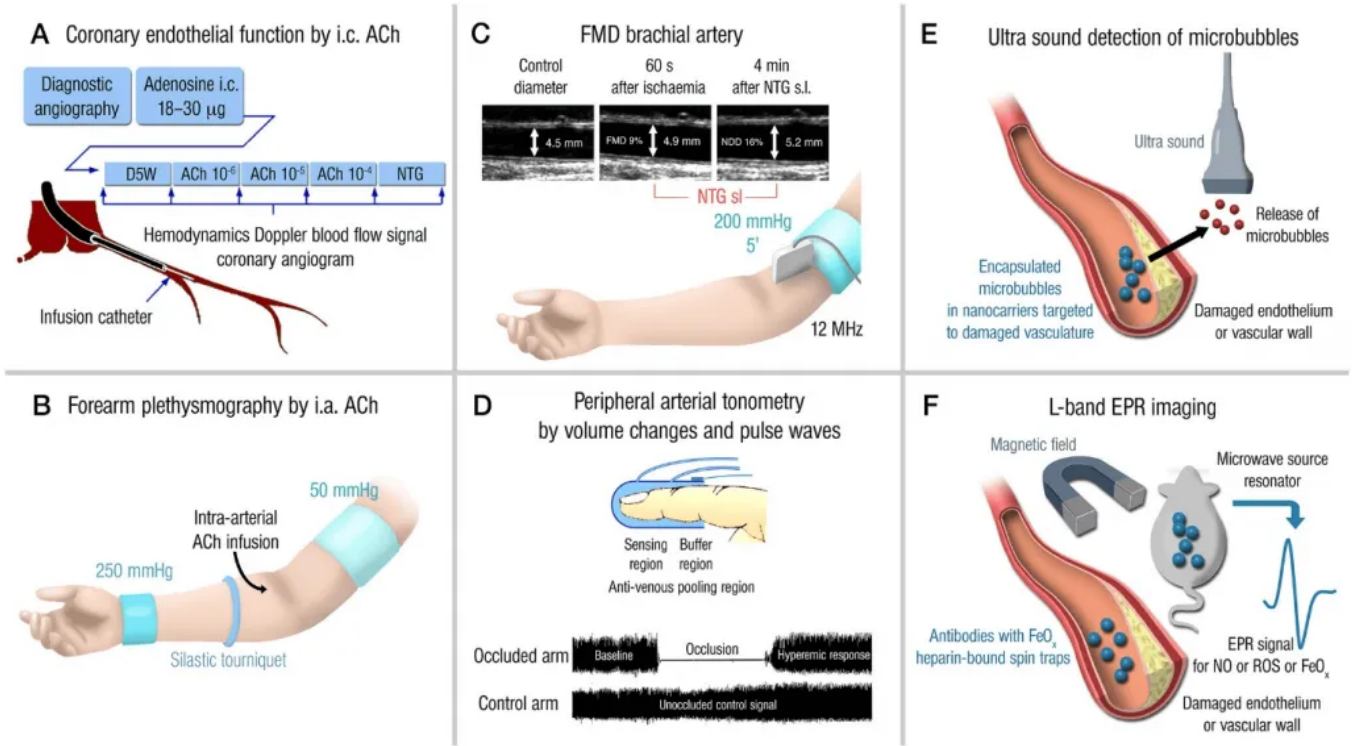
- Globally cardiovascular diseases (CVDs) accounts for 31% of mortality, the majority of this in the form of CHD and Stroke.
- Endothelial dysfunction is equal to vascular failure, which cannot keep the balance of normal vascular conditions.

### Natural Course of Atherosclerotic CVD (heart attack, stroke, PAD,....)

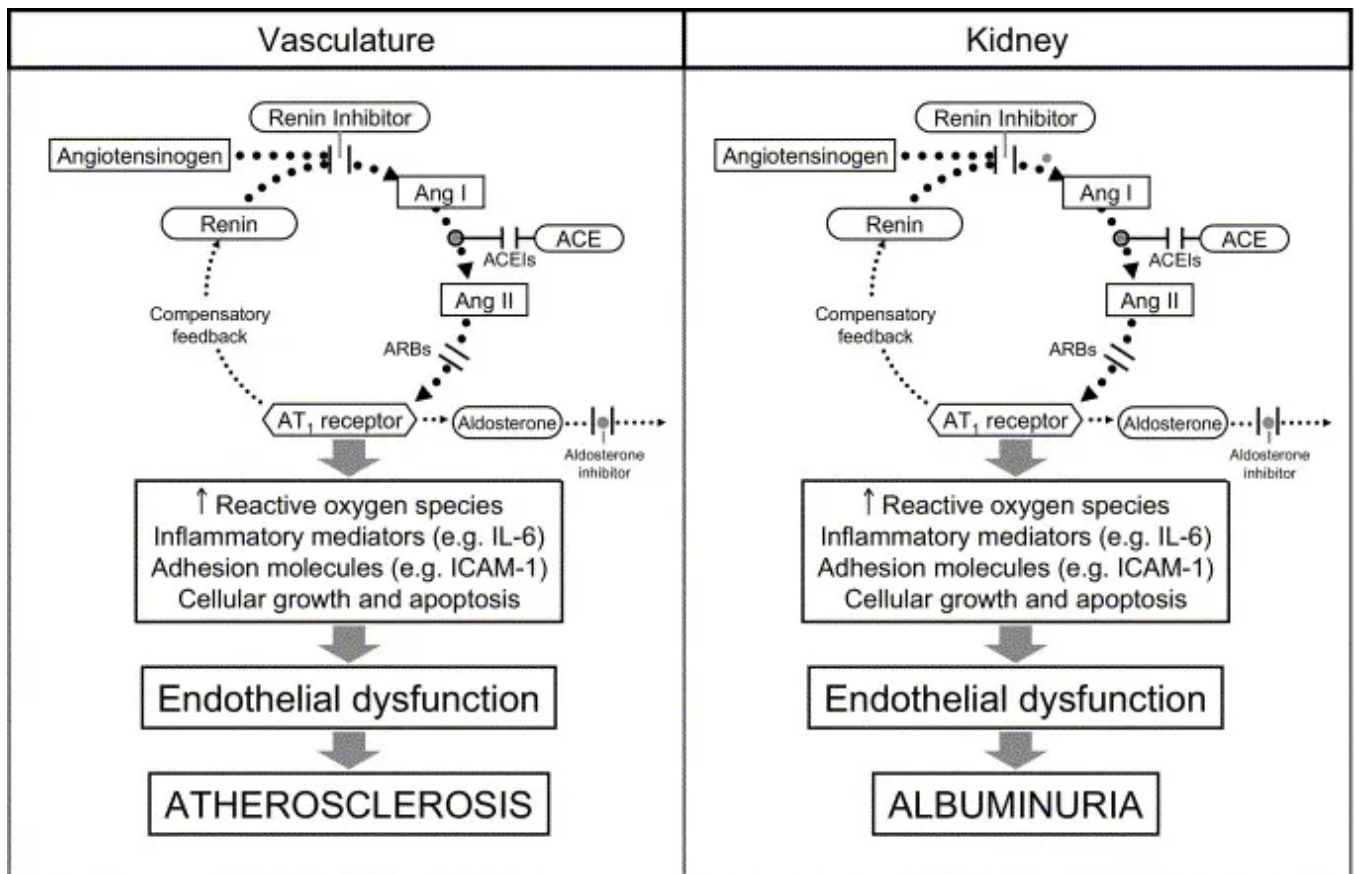


### Invasive and non-invasive methods for the determination of endothelial function

- Endothelial function monitoring needs to be adopted as part of routine vital sign monitoring, not as an indicator of an acute condition but rather for chronic health and preventive maintenance.



## Link between endothelial dysfunction and microalbuminuria



## Transient elevation in albumin excretion

- Fever
- Infection
- Exercise
- Heart failure
- Nonspecific joint inflammation
- Poor glycemic control (HBA1C>8)
- Elevated blood pressure (>160/100)
- Hyperlipidemia (LDL > 120mg/dl)

## Endothelial function and microalbuminuria correlations

- It is now clear:
  1. Microvascular endothelial function has been strongly associated with greater albuminuria and CKD, independent of diabetes and blood pressure.
  2. These insights to explain in part the excess systemic cardiovascular risk associated with albuminuria and CKD.

## Prevend Study

- **P**revention of **R**enal and **V**ascular **E**nd-Stage Disease.
- This is the first study to show that urinary albumin excretion is a strong predictor of all-cause mortality in the general population at large.
- Age – 28–75yr. Inhabitants of city of Groningen, the Netherlands
- Inclusion criteria:
  - All with urinary albumin concentration >10 mg/L
  - Random sample with UAC <10 mg/L
- n – 40,548
- Median follow up – 961 days (maximum up to 1139 days)
- Conclusion:
  - **Positive dose-response relationship between increasing UAC and mortality.**
  - **A 2-fold increase in UAC was associated with a relative risk**



**of 1.29 for CV mortality (95% CI 1.18 to 1.40), after adjustment for other well recognized CV risk factors.**

### **Prevalence of albuminuria in the general population:**

Normal 0-10mg/l	75%
High-normal albuminuria 10-20 mg/l	16.6%
Micro-albuminuria 20-200 mg/l	7.2%
Macro-albuminuria >200 mg/l	0.7%

### **Proteinuria and CVD risk**

- The presence of proteinuria has been associated with an approximate 50% increase in coronary risk (risk ratio 1.47, 95% confidence interval [CI] 1.23–1.74) after adjustment for known risk factors. (As per one study)
- These data confirm a strong and continuous association between proteinuria and subsequent risk of coronary heart disease, and suggest that proteinuria should be incorporated into the assessment of an individual's cardiovascular risk.

### **Cardio vascular risk assessment and microalbuminuria**

- Risk assessment is a critical step in the current approach to primary prevention of atherosclerotic cardiovascular disease. Knowledge of the 10-year risk for atherosclerotic cardiovascular disease.
- FRS-CVD (Framingham Risk score- Coronary heart disease) appears to be the most useful for CVD risk assessment in Indians.
- QRISK3 is most appropriate for Indian population as per new consensus.

- UAE testing improves the accuracy of cardiovascular risk assessment in patients with hypertension.
- It also may be as reliable as an ultrasound evaluation of cardiac and carotid structure in predicting cardiovascular risk in hypertensive patients.
- Combined ultrasound and microalbuminuria screening can improve the accuracy of target organ damage detection by 10-fold compared with routine investigation.

**What is the most important strategy to reduce microalbuminuria?**

**Whether lowering urinary albumin will reduce CV event?**

**Irbesartan Microalbuminuria-2 trial**

- In the Irbesartan Microalbuminuria-2 trial, normalization of

microalbuminuria in patients with type 2 diabetes and hypertension occurred in approximately **20%** of patients who attained traditional **BP goals of 140/90 mmHg** with medications such as **diuretics, blockers, and vasodilators**.

- An improvement of the normalization rate to approximately **33%** occurred when the full dosage (**300 mg**) of the **renin-angiotensin system blocking drug irbesartan (an angiotensin II receptor blocker)** was used as part of the **BP lowering regimen to 140/90 mmHg**.
- **The most important strategies to reduce microalbuminuria is the reduction of BP.**

### **PREVENT IT (Prevention of Renal and Vascular End Stage Disease Intervention Trial) study**

- Only one where therapeutic intervention aimed to evaluate if lowering urinary albumin excretion would reduce CV events in microalbuminuria subjects.
- **Treatment with fosinopril had a significant effect on urinary albumin excretion and a trend in reducing CV events with a 40% lower incidence.**

### **LIFE (Losartan Intervention for End-point Reduction in Hypertension) study**

- Showed the urine albumin level in 568 patients with diabetes and hypertension, who were treated with losartan was significantly lower than that in 609 control patients treated with atenolol.
- In addition, the CV mortality and all-cause mortality in losartan treated patients were significantly lower than that in control group.
- **Losartan arm significantly lowers albuminuria, CV mortality and all-cause mortality.**

**Microvascular endothelial dysfunction is associated with albuminuria**

## and CKD

- New study has found that LDF-based (Laser doppler flowmetry) measures of endothelial function and microvascular reactivity are the strongest determinants of albuminuria in older hypertensive population of patients with and without CKD, irrespective of diabetes status.

## Role of Endothelin receptor-A

- **It mediates degradation of the glomerular endothelial surface layer via pathologic crosstalk between activated podocytes and glomerular endothelial cells**
- Podocyte-derived Edn1 interacts with increased GEC EdnrA expression resulting in mitochondrial reactive oxygen species (ROS) and activation of ESL degradation and remodelling pathways.
- Together, these cross-talking events could underlie increase in glomerular permeability to albumin in kidney disease.

## Measures to improve ED and CVD end points

- Endothelial function can be improved significantly by exercise, smoke cessation, weight loss in overweight or obese persons, and improved diet.
- Mediterranean diet, which consists of mono saturated fats from olive oil, pasta, fruits, vegetables, fish, whole grains, legumes/nuts, and moderate alcohol consumption, is considered to be good for our health.
- Treatment of hypertension and hypercholesterolemia are also critical.
- Statins have major pleiotropic anti-inflammatory and anti-oxidative effects besides the cholesterol reduction effect.

## Microalbuminuria: Beyond



## Limitation of MAU:

- Non-specific
- Lower sensitivity
- Larger variability

## Urine proteomics

- Urinary peptide biomarkers characteristic of atherosclerosis particularly CAD (CAD237)
- ACS-specific urinary peptide biomarkers (ACSP75) capable of predicting the onset of an ACS up to 4.89 years before the event with a sensitivity of 73.8% in individuals who were asymptomatic at baseline.

## Final Points

- MAU and CVD linked by a common pathophysiological process (generalized endothelial dysfunction).
- Risk of adverse clinical outcomes start below the traditional MAU threshold.
- It is a treatable marker, and blood pressure control is most effective means to reduce MAU.
- Urine proteomics propose more sensitive and specific urine biomarkers than microalbuminuria for cardiovascular risk evaluation.

## Hippocrates (460 –355 BCE)

*“One can obtain considerable information concerning the general health by examining the urine”*

## CME INDIA Tail Piece

### A – “French Paradox”

- Studies seemingly demonstrate that, despite a diet high in fat, French people have a comparatively low risk of coronary artery disease.
- Wine consumption and notably red wine that is high in the antioxidant polyphenol resveratrol has been linked to vascular protection and has been argued to be the basis of the French Paradox (Catalgol et al. 2012).
- Many in vitro studies that demonstrate the vascular protective effects of resveratrol that indicate that resveratrol enhances NO generation.
- It is said that low concentrations of resveratrol in wine would be insufficient, given even moderate wine consumption, to generate blood levels that would be required to mediate the putative beneficial vascular effects of wine consumption.
- *One 150 mL glass of red wine provides the equivalent antioxidant activity of two cups of tea, four apples, or seven glasses of orange juice.*
- **William Shakespeare was aware of the benefits of wine** – With reference to Coriolanus (Act V, Scene 1) the Roman consul, Agrippa Menenius Lanatus, says: "The veins unfill'd, our blood is cold, and then we pout upon the morning, are unapt to give or to forgive; but when we have stuff'd these pipes and these conveyances of our blood with wine and feeding, we have suppler souls than in our priest-like feasts" (Shakespeare 1605).

## **B – Believe strongly on Physical Exercise to improve Endothelial Health**

**Image Credit:** Gao, J., Pan, X., Li, G. *et al.* Physical Exercise Protects Against Endothelial Dysfunction in Cardiovascular and Metabolic Diseases. *J. of Cardiovasc. Trans. Res.* (2021).

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