2005년도 대한 지질 동맥경화학회 춘계 학술대회

Metabolic syndrome and IMT: A community study in adult Koreans

Jeong Seul-Ki, M.D.

Department of Neurology
Chonbuk National University Hospital

목 차

- Stroke in diabetics
  - Overview
  - Pathophysiology
- IMT as a surrogate marker of atherosclerosis in the metabolic syndrome
  - Namwon study
- Conclusion

Stroke in diabetics

1. Type 2 DM: A strong independent risk factor for stroke

A risk factor for stroke, according to Framingham & other studies.

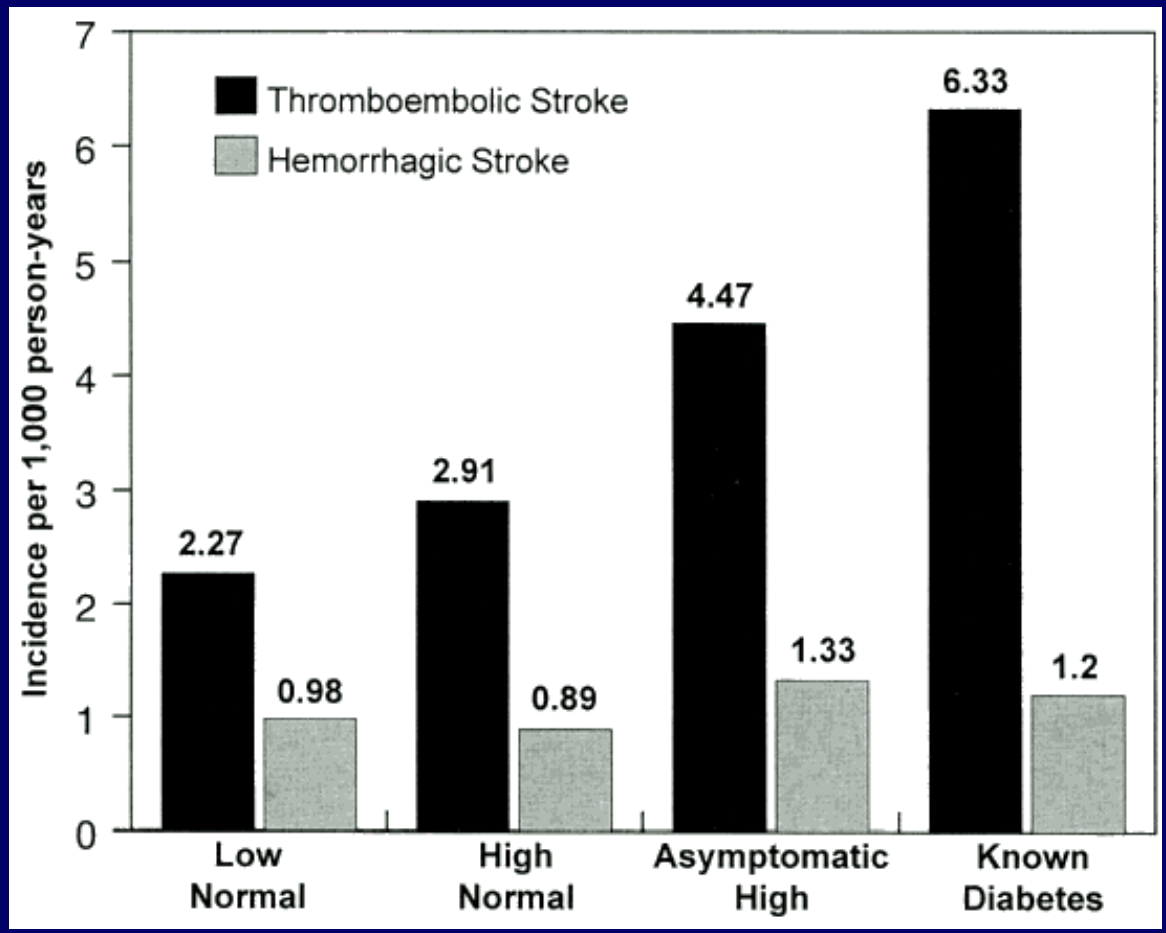
A consistent 2–5 fold increase in stroke incidence in diabetes

In the stroke population younger than 55 years (≤ 55 years), diabetes increases the risk of stroke more than 10-fold (OR 11.6, 95% CI 1.2-115.2)

You RX. Stroke 1997:28;1913-1918

Stroke in diabetics

Stroke incidence and fasting blood glucose, diabetes



Burchfiel CM. Stroke 1994;25:951

Stroke in diabetics (pathophysiology)

2. Pathophysiologic mechanisms of diabetic angiopathy

1) Changes in arterial wall (atherosclerosis)

abnormal endothelium

Diabetes mellitus — abnormal endothelium

Function	Mechanism	Abnormality	Result
Permeability barrier	Tight cell junctions	↑ permeability – delayed regeneration	LDL, mitogens subendothelial
Thromboresistant surface	NO, PGI_2, t-PA, heparan [spelling?] sulfate thrombomodulin	↓ NO, ↓PGI_2, ↑ PAI-1, ↑TF	Enhanced impaired
Block leukocyte adherence	NO	Induction of adhesion molecules (VCAM-1, E-selectin)	Recruitment macrophages to vascular
Regulation of vascular tone	NO, PGI_2, bradykinin ET-1, AT-II	↓ NO, PGI_2, bradykinin; ↑ ET-1, AT-II; ↑ AGEs	Impaired vasodilation
Secrete growth inhibitors/cytokines	NO, heparan sulfate, IL-6, TNF	Inactivation of NO, C-reactive protein	↑ VSMC proliferative activity, ↑ inflammation

Stroke in diabetics (pathophysiology)

2) Hyper-coagulability

Alteration in coagulation, fibrinolysis, and platelet function in DM.

- Clotting abnormality

  (antithrombin and protein C deficiency, activated intrinsic pathway)

- Reduced fibrinolysis (elevated plasminogen activator inhibitor-1)
- Platelet dysfunction

  (platelet vessel wall interaction, platelet-platelet interaction, platelet secretion, platelet-coagulant protein interaction)

3) Changes in blood flow

- Increased fibrinogen & globulins → ↑ increase blood viscosity → low flow.
- Poor collateral circulation
- Chronic impairment of auto-regulation.

Stroke in diabetics

2. More severe stroke and more frequent worsening

Elevated glucose in acute stage:

- Determinant of initial infarct volume & early infarct progression (esp. non-lacunar stroke).

The mechanisms of the deleterious effects of hyperglycemia

- The production of lactic acid from glucose under hypoxic conditions

  →cerebral intra- and extra-cellular acidosis → damage to neurons, glial cells

- Hyperglycemia inhibit the reuptake of the neurotransmitters: glutamate and aspartate

  →may eventually cause neuronal death.

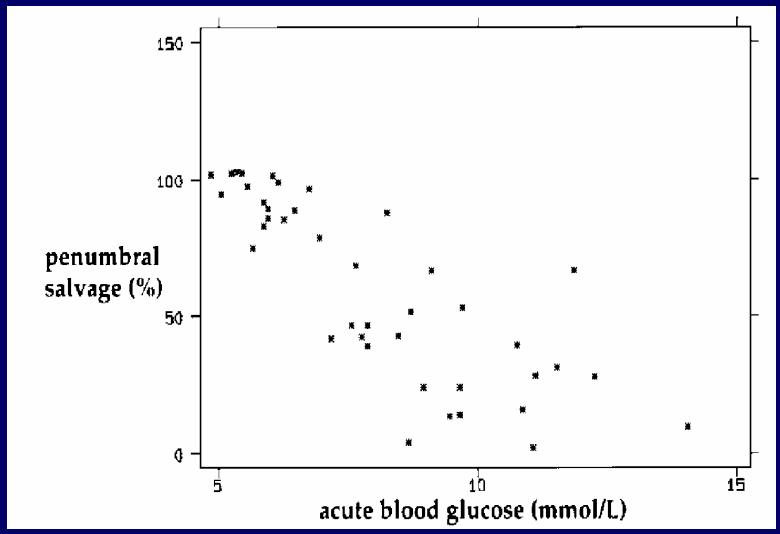
- The development of intracranial atheroma in large, medium and small arteries

  → poor collateral circulation, impaired auto-regulation.

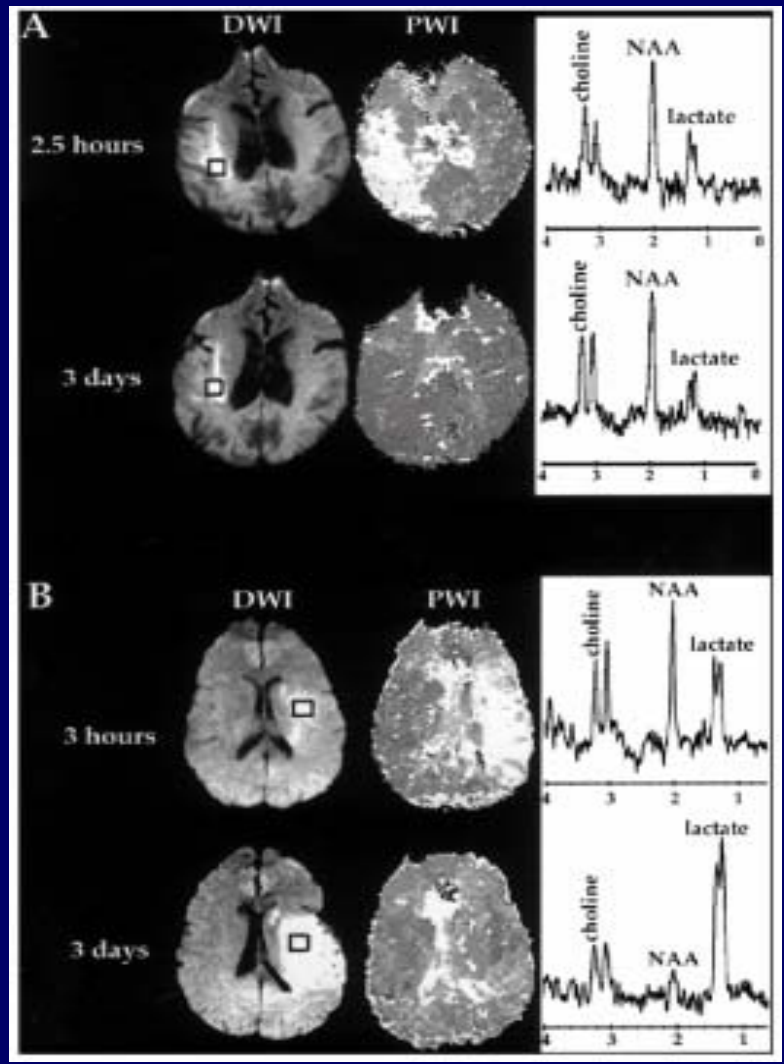
Lindsberg PJ. Stroke 2004;35:363-364

Stroke in diabetics

The deleterious influence of acute hyperglycemia
1. On *penumbral* tissue
2. Due to increased tissue lactate production.



In patients with an acute PWI > DWI mismatch, increasing blood glucose levels
→ reduced penumbral salvage,
larger final infarct size,
worse clinical outcome.



Parsons MW, Ann Neurol 2002:52:20-28

Stroke in diabetics

4. A higher frequency of recurrent stroke

Olsson T, et al. (1990)

People with diabetes may also be more likely to suffer recurrent stroke (24% vs. 17%)

Hier DB, et al. (1996)

Higher frequency of recurrent stroke in diabetic stroke population compared to non-diabetic population (15.2% vs. 11.4% / 2yr)

Statton IM, et al. (2000) [UKPDS study]

A 12% reduction in the hazard ratio for fatal & non-fatal stroke per 1% decrease in HbA1c (12% reduction / 1% decrease of HbA1c)

Stroke in diabetics

5. Predictor of poor outcome

- Mortality
  - Systematic overview of 33 studies: Hyperglycemia on admission – associated c 3-fold risk of fatal 30-day outcome and 1.4-fold risk of poor functional outcome

Stroke 2004;35:363-364

- Hemorrhagic transformation of ischemic stroke

Patients with an initial s-glucose > 200mg/dl or a known diabetes had a symptomatic hemorrhage (following rtPA administration): 25% vs. 9%

Demchuk AM, Stroke 1999:30;34-39

As the admission glucose increased, the odds for symptomatic ICH also increased (OR 1.75 per 100 mg/dL increase in s-glucose, p=0.02).

The NINDS rt-PA study group, Stroke 1997 & Neurology 2002

2부 들어갑니다.

Hypothesis

Metabolic syndrome and IMT

- Is IMT a good surrogate marker of atherosclerosis in the metabolic syndrome, a preclinical state of type 2 diabetes mellitus?

Subjects & methods

- Since 2004, 4715 + 1620 participants in community
- Major variables
  - Age, sex, education, past history, anthropometry, K-mMMSE, BMD, PFT, Chest PA, etc
  - Resting BP, IMT, ABI, Arterial stiffness, EKG, etc
- Namwon Stroke Registry (NSR)
- samples
  - Plasma, serum, urine, DNA, Buffy coat

Subjects & methods

Carotid IMT

- More than 20 clinical trial and observational studies : carotid IMT as a primary end point.

Pauciullo P. Arterioscler Thromb. 1994;14:1075-79

- Increased carotid IMT is a better predictor of stroke than of ischemic heart disease and myocardial infarction (MI).

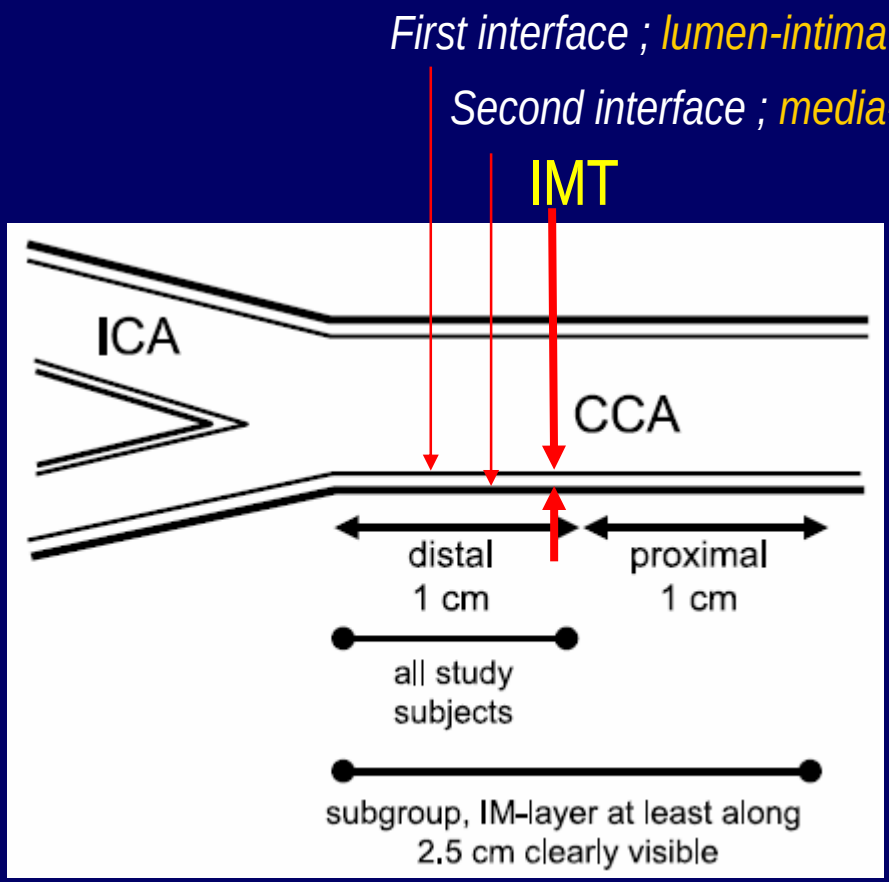
Ebrahim S. ***Stroke*** 1999;30:841–850.
Bots ML. ***Circulation*** 1997;96:1432–1437.

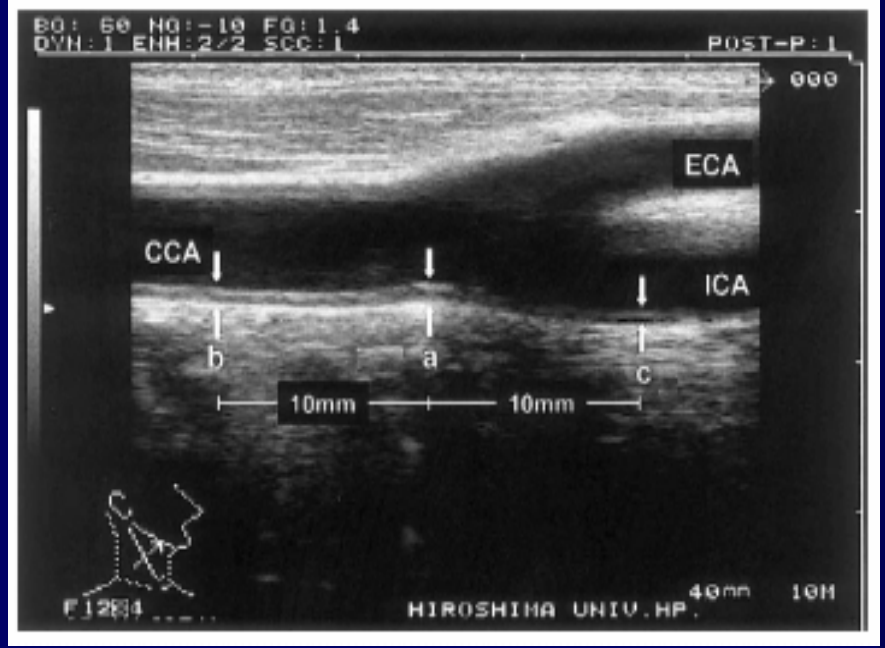
Subjects & methods

IMT measurement

- Neck Duplex Sonography
- B-mode imaging & Color Flow Imaging(CFI)
- SonoAce-9900, Medison Co., Korea
- 4-7 MHz linear probe
- Angle correction (60º)
- Anterior or Anterolateral approach
- Maximal thickness (CCA, carotid bulb, ICA)
- SigmaScan® Pro 5.0

Definition: IMT





Schmidt-Trucksass A. Atherosclerosis 2003;166:57-65

ARIC (Atherosclerosis Risk In Community) study

Definition: Metabolic syndrome

PAPER

Metabolic syndrome and ALT: a community study in adult Koreans

S-K Jeong[1]*, H-S Nam[2], J-A Rhee[3], J-H Shin[3], J-M Kim[4] and K-H Cho[5]

[1]*Department of Neurology, Seonam Un*
Medicine, Seonam University School of
University School of Medicine, Gwangju
Gwangju-city, South Korea; and [5]*Depa*
Korea

OBJECTIVE: To investigate an associatio
ranges.
DESIGN: A population-based cross-secti
SUBJECTS: A total of 1248 men and 21
MEASUREMENTS: Body mass index (BM
RESULTS: ALT and BMI increased with
15 IU/l and the MS was found in both sex
style. The odds ratios for the MS in the h
fold higher in women. The likelihood ra
CONCLUSION: The MS is significantly
sensitive marker of hepatic dysfunction

International Journal of Obesity (2004) 2
Published online 15 June 2004

Keywords: metabolic syndrome; alanin

Definition

The MS was identified by the presence of three or more of the components, according to the Third Adults Treatment Panel (ATP-III) of the National Cholesterol Education Program (NCEP),[18] modified to use different waist circumference cutoffs instead of the original:[19]

(1) abdominal obesity: waist circumference $\geq$90 cm in men and $\geq$80 cm in women;
(2) high triglyceride: $\geq$1.695 mmol/l;
(3) low HDL cholesterol: $<$1.036 mmol/l in men and $<$1.295 mmol/l in women;
(4) high blood pressure: $\geq$130/85 mmHg or subjects using antihypertensives;
(5) high fasting glucose: $\geq$6.1 mmol/l.

Analysis

- Independent t-test
- Analysis of variance (ANOVA)

Results-1

- 2004. 7~8. 전남 두 지역
- 20-74세, 1620명

- Age: mean ± SD, 53.4 ± 14.4 y
  (men, 54.5 ± 14.4 y; women, 52.5 ± 14.3 y)
- Sex: women, 53.7%

Results-2

- MS: 346 (22.1%)

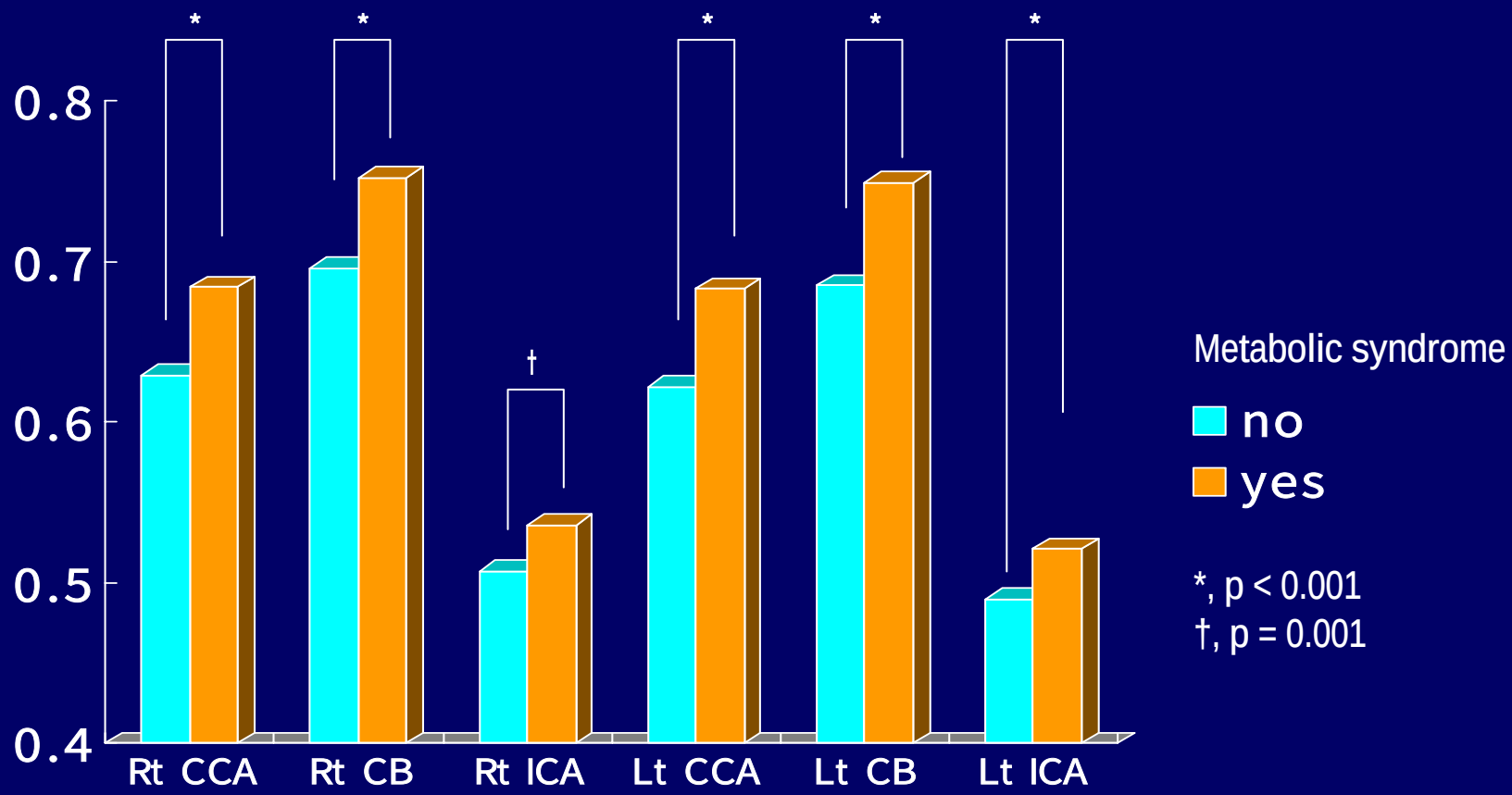
- Its Components:
  1, 338 (21.6%)
  2, 480 (31.3%)
  3, 231 (14.8%)
  4, 91 (5.8%)
  5, 24 (1.5%)

- MS according to age group

- age < 40, 7.4%
- 40 ≤ age < 60, 19.5%
- age ≥ 60, 30.2%

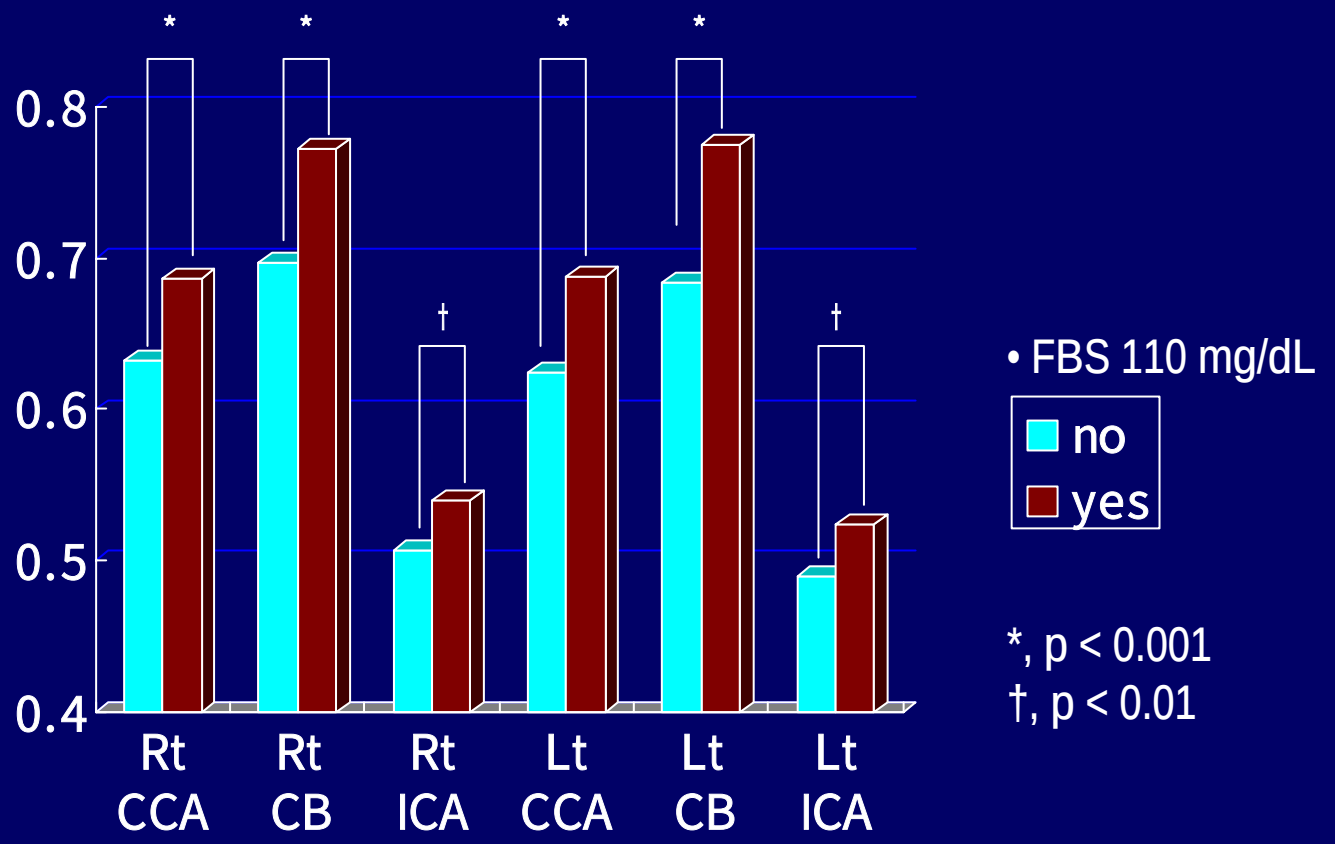
Results-3

Figure 1. IMT and the metabolic syndrome



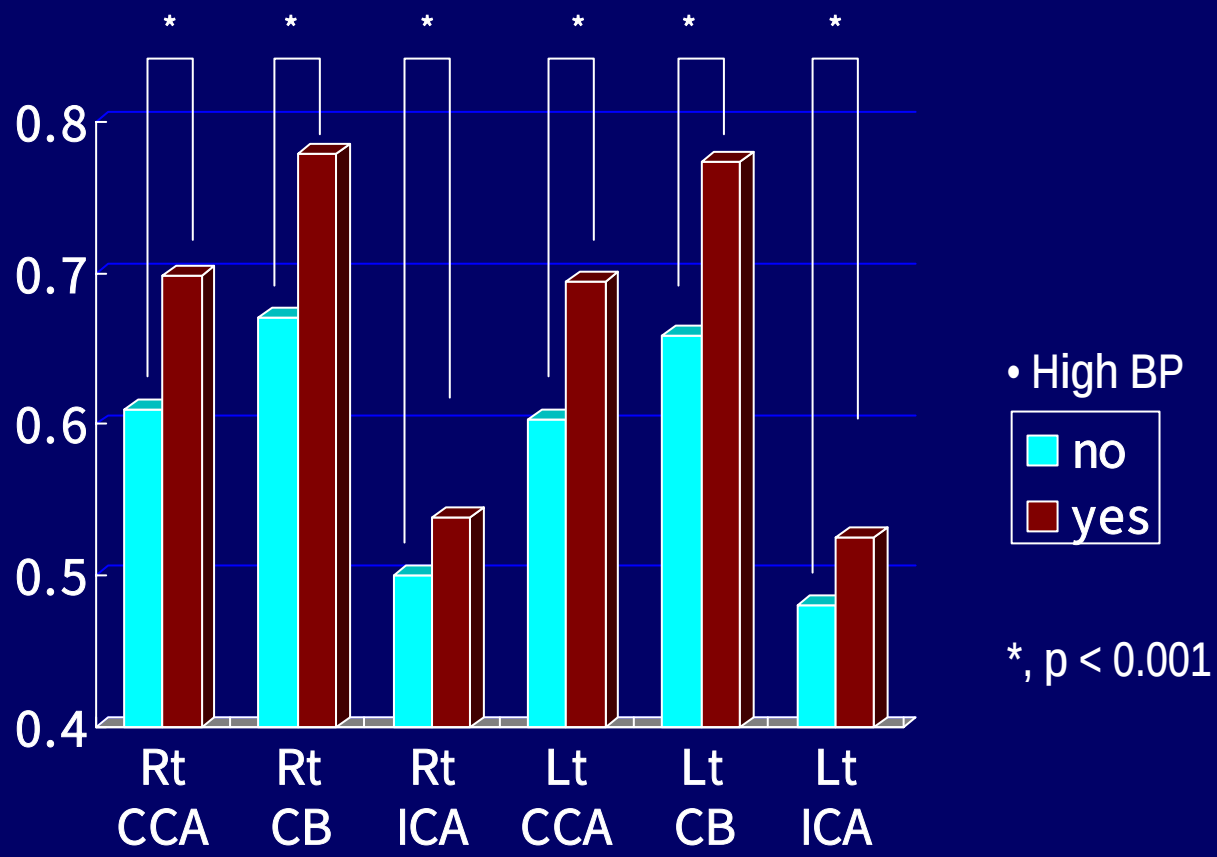
Results-3

Figure 2. IMT and the MS component, FBS 110 mg/dl



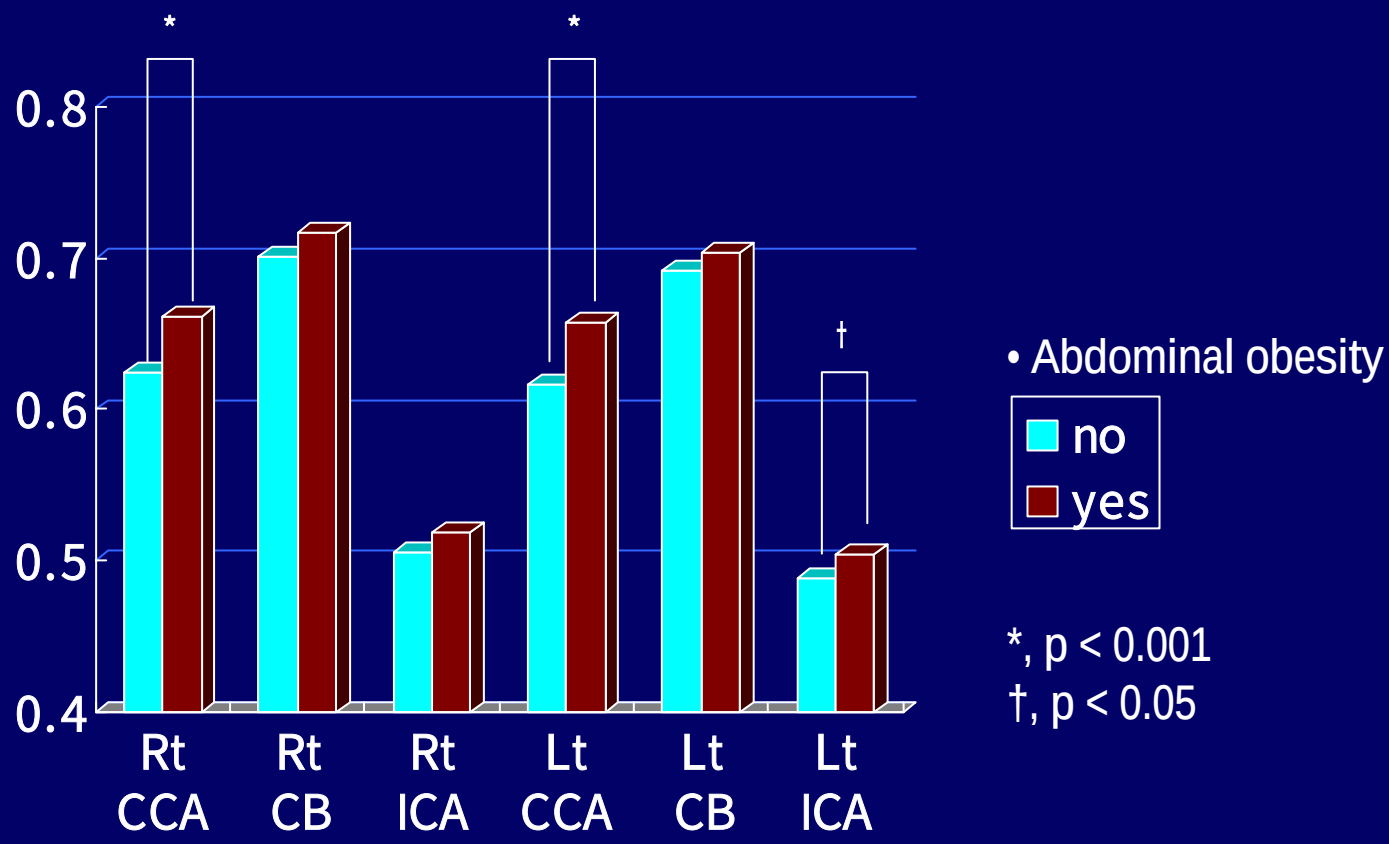
Results-3

Figure 3. IMT and the MS component, high BP



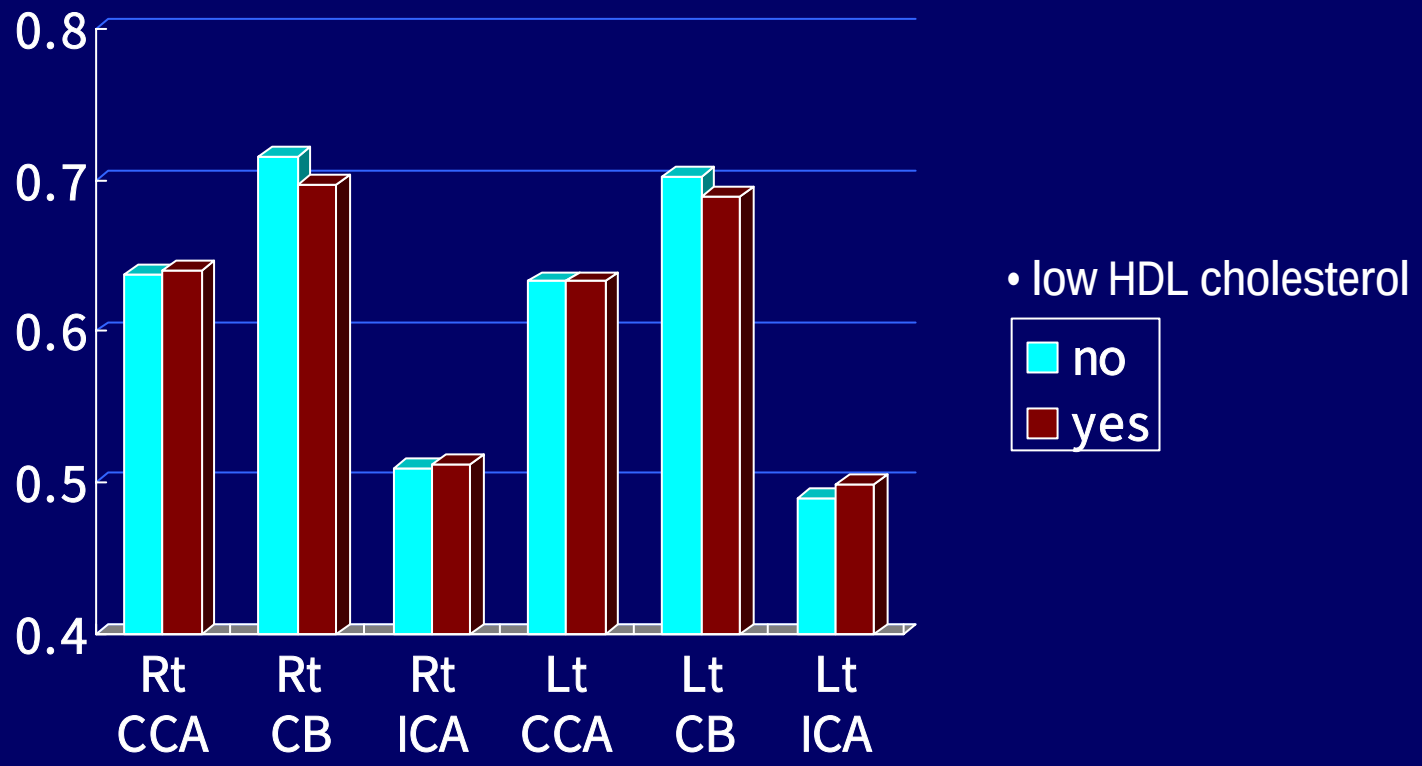
Results-3

Figure 4. IMT and the MS component, abdominal obesity



Results-3

Figure 5. IMT and the MS component, low HDL cholesterol



Results-3

Figure 6. IMT and the MS component, high TG

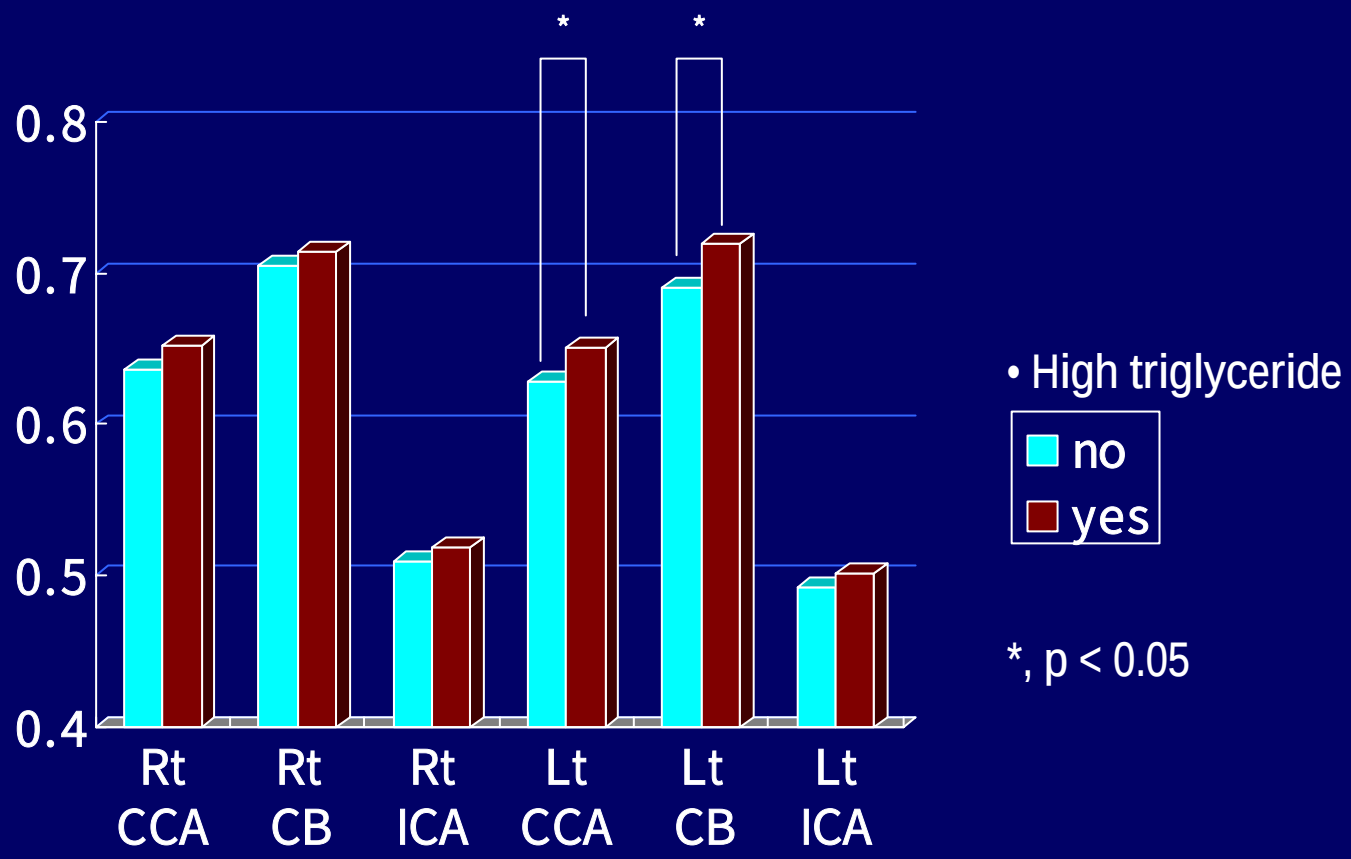
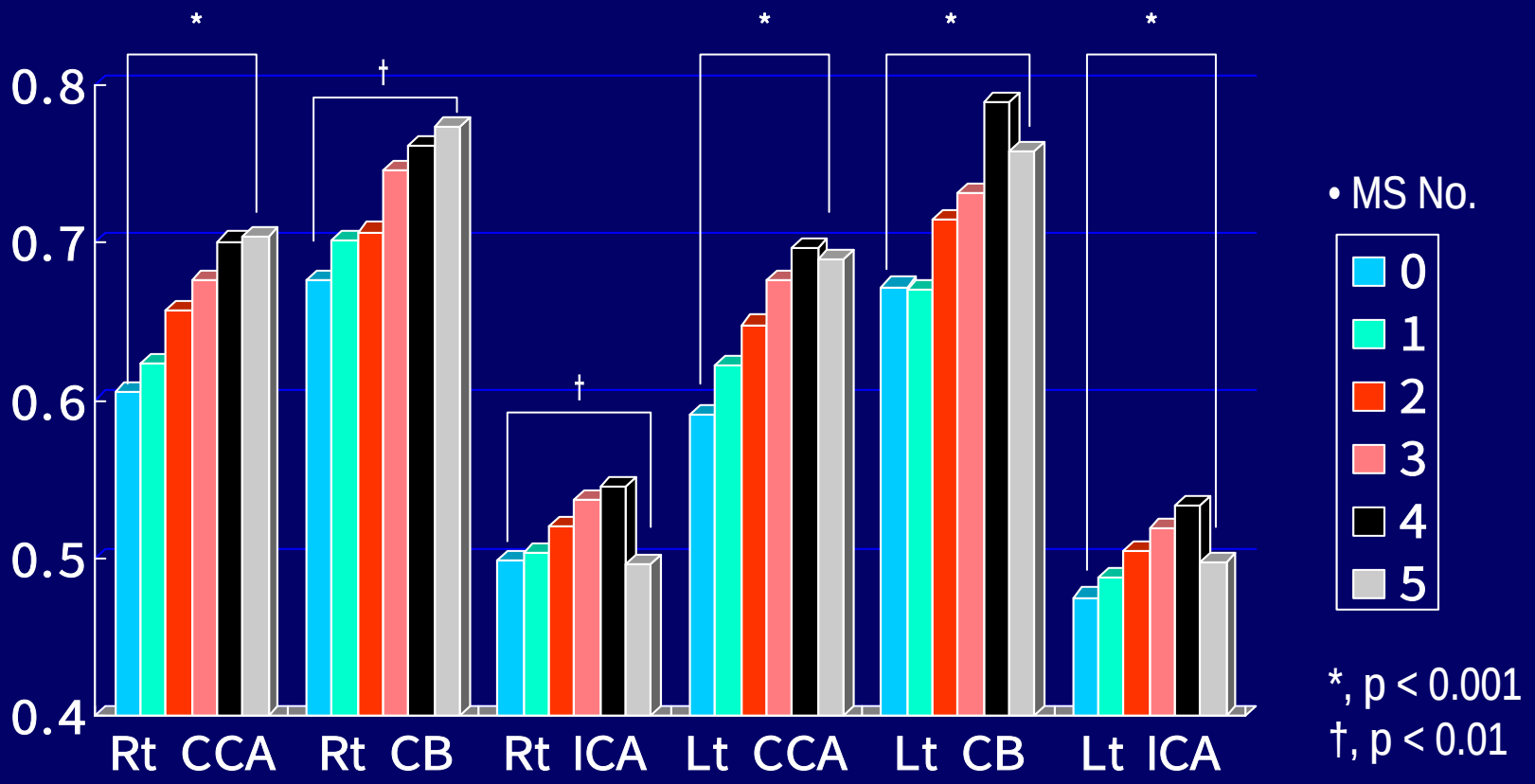


Figure 7. IMT according to summation of MS components



Discussion

- IMT value was significantly higher in the participants with the metabolic syndrome than the normal participants
- Among the components, high BP and FBS were significantly associated with higher IMT values
- According to the summation of the components, IMT values were significantly increased in all the six carotid artery segments

Discussion

- Is IMT a good surrogate marker of atherosclerosis in the metabolic syndrome, a preclinical state of type 2 DM?
  - Biomarker (surrogate ??): a measurement that is indicative of a pharmacodynamic response (PD) to a therapeutic intervention (dose, PK)
  - Five attributes of an ideal biomarker
    - Pathophysiologic relevance
    - Accurately and reproducibly quantified
    - Modified by drug exposure
    - Sensitivity and specificity to drug effects
    - Predictive value

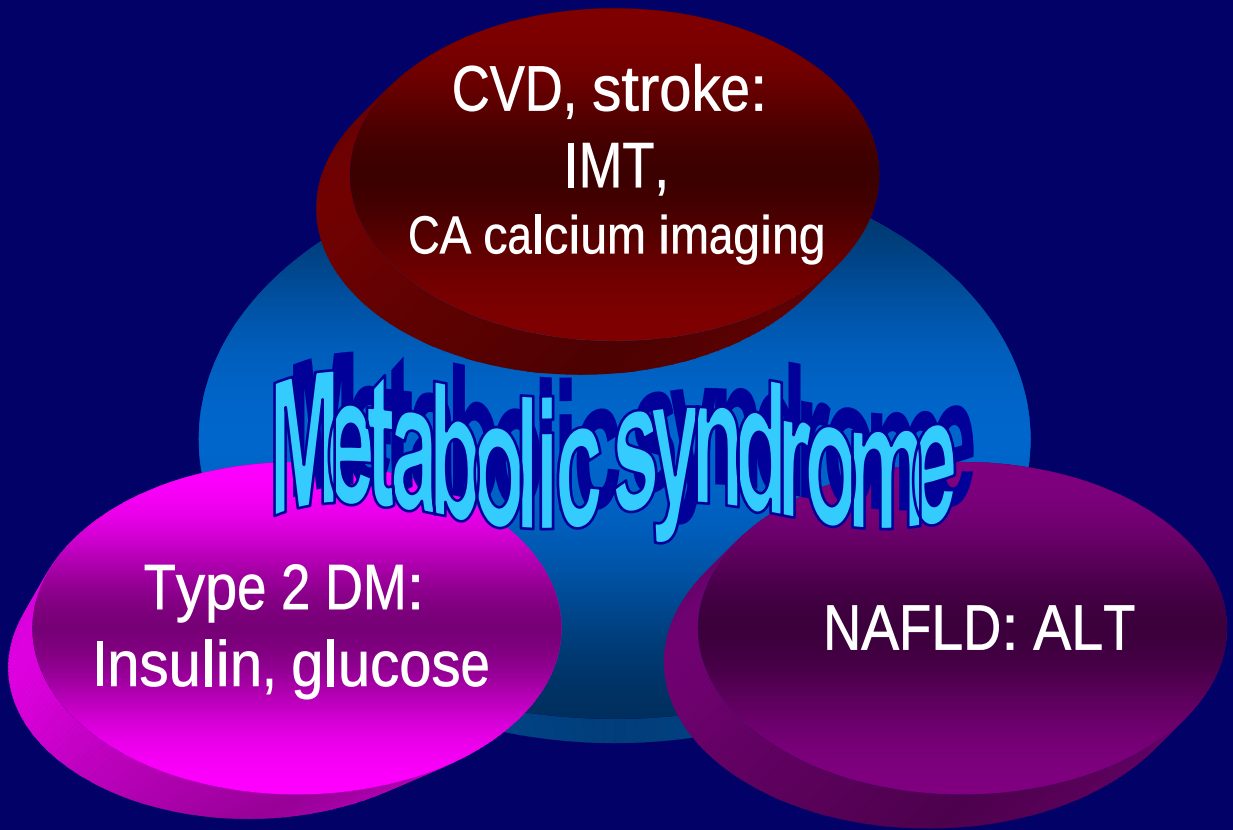
Discussion

- Is IMT a good surrogate marker of atherosclerosis in the metabolic syndrome, a preclinical state of type 2 DM?

  - Surrogate markers in DM and the metabolic syndrome and in evaluating lipid-lowering therapy; conventional and contrast enhanced carotid IMT
    - Rajaram V. et al. Am J Cardiol 2004;93:32C-48C
  - Carotid IMT significantly decreased one year after remission of Cushing's syndrome
    - Faggiano A. et al. J Clin Endocrinol Metab 2003;88:2527-33
  - Endothelial activation do not associate with IMT
    - Leinonen ES. et al. J Intern Med 2004;256:110-27

Discussion

- Surrogate markers of the metabolic syndrome, more!




독도는 우리땅 ~
경청해주셔서 대단히 감사합니다.