Relationship Between Insulin Sensitivity and Carotid Artery Intima-Media Thickness in Healthy Subjects: The RISC Study

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Background

- Experimental and clinical studies have suggested that insulin resistance, or its *in vivo* compensatory equivalent, hyperinsulinaemia, may initiate or sustain cardiovascular disease.
- However, there is currently no evidence for a direct relationship between insulin resistance and atherosclerosis or cardiovascular disease. Previous studies have used surrogate markers of insulin resistance in cohorts of subjects with multiple risk factors.

Objectives

- To test whether there is a direct link between insulin resistance and atherosclerosis in a low-risk Caucasian population.
- To establish whether the development of early atherosclerotic changes over time is accelerated in insulin-resistant healthy subjects.

Design

Relationship Between **I**nsulin **S**ensitivity and **C**ardiovascular Disease Risk: **(RISC)** Study

- Relation of insulin sensitivity to intima-media thickness (IMT) of carotid arteries, a surrogate marker of systemic atherosclerotic load, at baseline and after 3-years of follow-up.
- In this report, baseline, cross-sectional data are presented.
- Over 1 500 subjects were recruited at 19 centres in 14 European countries and are being followed-up.

Participating Centres

Pisa
London
Amsterdam
Newcastle
Lyon
Odense
Dublin
Perugia
Geneva
Frankfurt

Malmö
Rome
Glasgow
Vienna
Madrid
Athens
Milan
Belgrade
Kuopio

Study Population

- 1 569 subjects recruited.

age	30–60 years
blood pressure	<140/<90 mmHg
total cholesterol	<7.8 mmo/L
triglycerides	<4.6 mmo/L
fasting glucose	<7.0 mmo/L
2-hour glucose	<11.1 mmo/L

- Exclusions: cardiovascular disease, chronic illness, significant (>40%) carotid stenosis.

Baseline Examinations

- Lifestyle and medical history questionnaire.
- Anthropometry.
- Biological samples + oral glucose tolerance test.
- Euglycaemic hyperinsulinaemic *(240 pmol.min^{-1}.m^{-2})* clamp.
- Ultrasound (US) examination of extracranial carotid arteries.

B-mode US of Carotid Arteries
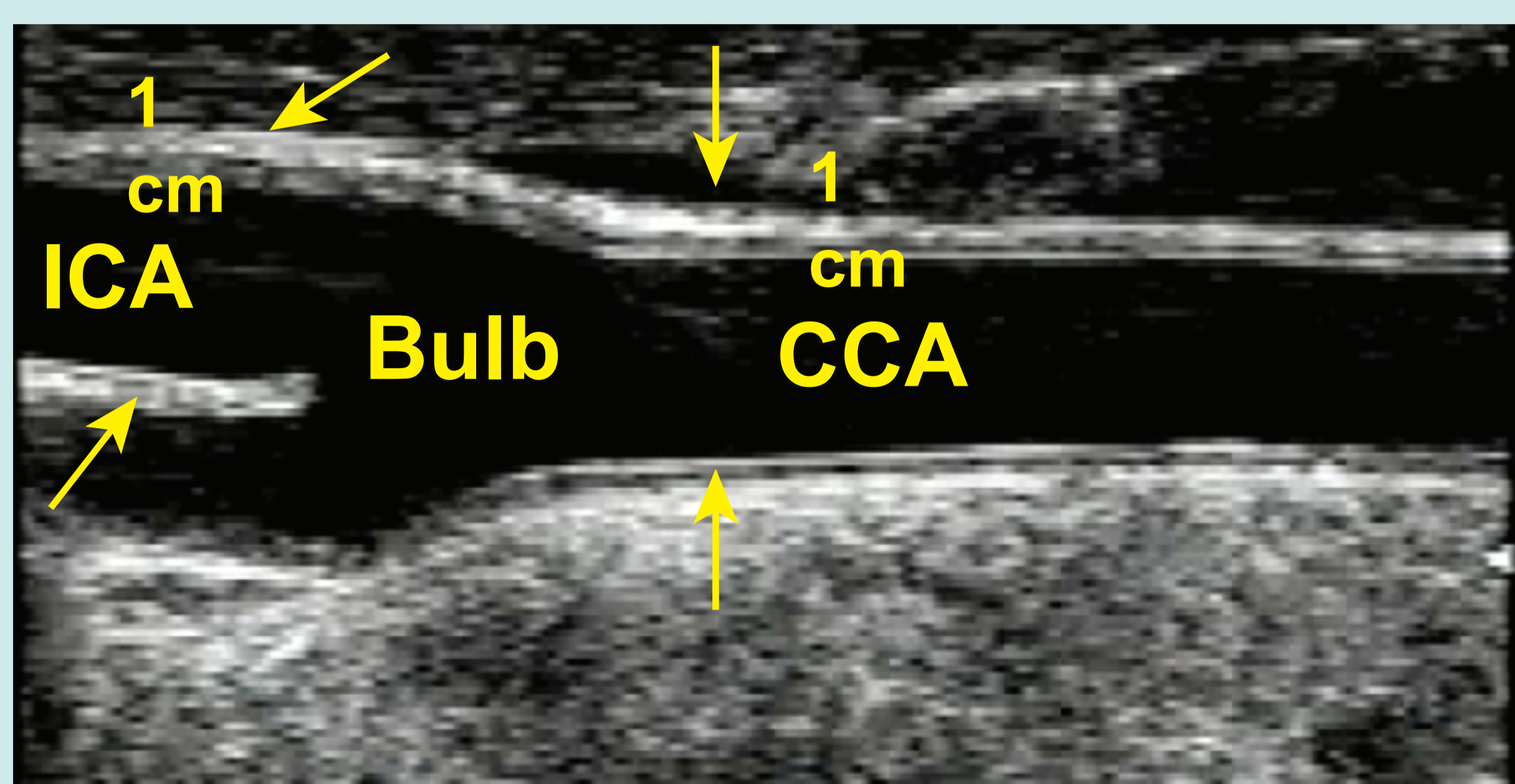
- IMT of the near and far arterial wall was measured off-line in digitised images at the level of
  common carotid artery: IMT$_{CCA}$
  carotid bulb: IMT$_{Bulb}$
  internal carotid artery: IMT$_{ICA}$
- The overall average IMT of all segments was also calculated: IMT$_{AVRG}$

Characteristics of Study Population

- 1 146 subjects satisfying inclusion criteria completed baseline euglycaemic clamp and US examination of carotid arteries.

male/female	503/643
age (years)	44 ± 8
smokers	605

	mean ± SD	range
BMI (kg.m^{-2})	25 ± 4	(17–44)
Waist circ. (cm)	86 ± 13	(49–147)
Total Cholesterol (mmol/L)	4.8 ± 0.9	(2.8–7.7)
LDL-Cholesterol (mmol/L)	2.9 ± 0.8	(0.8–6.1)
HDL-Cholesterol (mmol/L)	1.4 ± 0.4	(0.3–2.9)
Triglycerides (mmol/L)	1.1 ± 0.6	(0.3–4.5)
SBP (mmHg)	117 ± 12	(79–139)
DBP (mmHg)	74 ± 8	(50–89)

Results

|	mean ± SD	range
fasting glucose (mmol/L)	5.1 ± 0.6	(2.7–6.8)
insulin fasting (pmol/L)	34 ± 19	(3–147)
2-hour glucose (mmol/L)	5.7 ± 1.5	(2.2–10.4)
2-hour insulin (pmol/L)	200 ± 207	(10–3332)
M value (μmol.min^{-1}.kg$_{ffm}$$^{-1}$)	57 ± 24	(12–189)
IMT$_{CCA}$ (μm)	599 ± 86	(380–963)
IMT$_{Bulb}$ (μm)	764 ± 143	(328–1568)
IMT$_{ICA}$ (μm)	617 ± 128	(337–1300)
IMT$_{AVRG}$ (μm)	663 ± 102	(444–1182)

Main Determinants of IMT$_{AVRG}$

sex	+40 ± 6 μm for male sex
age	+53 ± 3 μm per 10 years
waist	+24 ± 3 μm per 10 cm
BMI	+5.7 ± 0.7 μm per unit
SBP	+23 ± 2 μm per 10 mmHg
LDL-Cholesterol	+39 ± 4 μm per mmol/L
glucose	+40 ± 5 μm per mmol/L

Relationship Between IMT$_{AVRG}$ and Measures of Insulin Sensitivity

r = +0.08, p<0.01 · r = +0.07, p<0.05 · r = -0.10, p=0.001
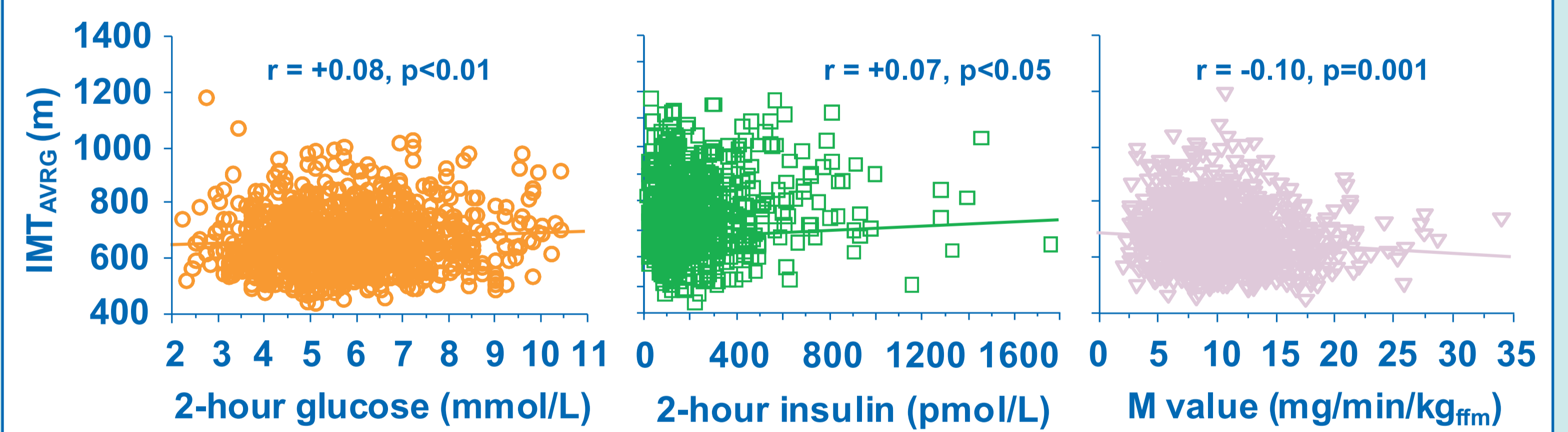
- Associations between IMT and 2-hour glucose or M value were statistically significant but weak and were lost after adjustment for the main determinants of IMT.

Conclusions

- In cross-sectional observations in a low-risk population, insulin resistance is not an independent predictor of carotid artery IMT.
- The follow-up phase of the RISC Study will conclusively test whether insulin resistance *per se* is atherogenic.