

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 Insulin Sensitivity and Cardiovascular 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.

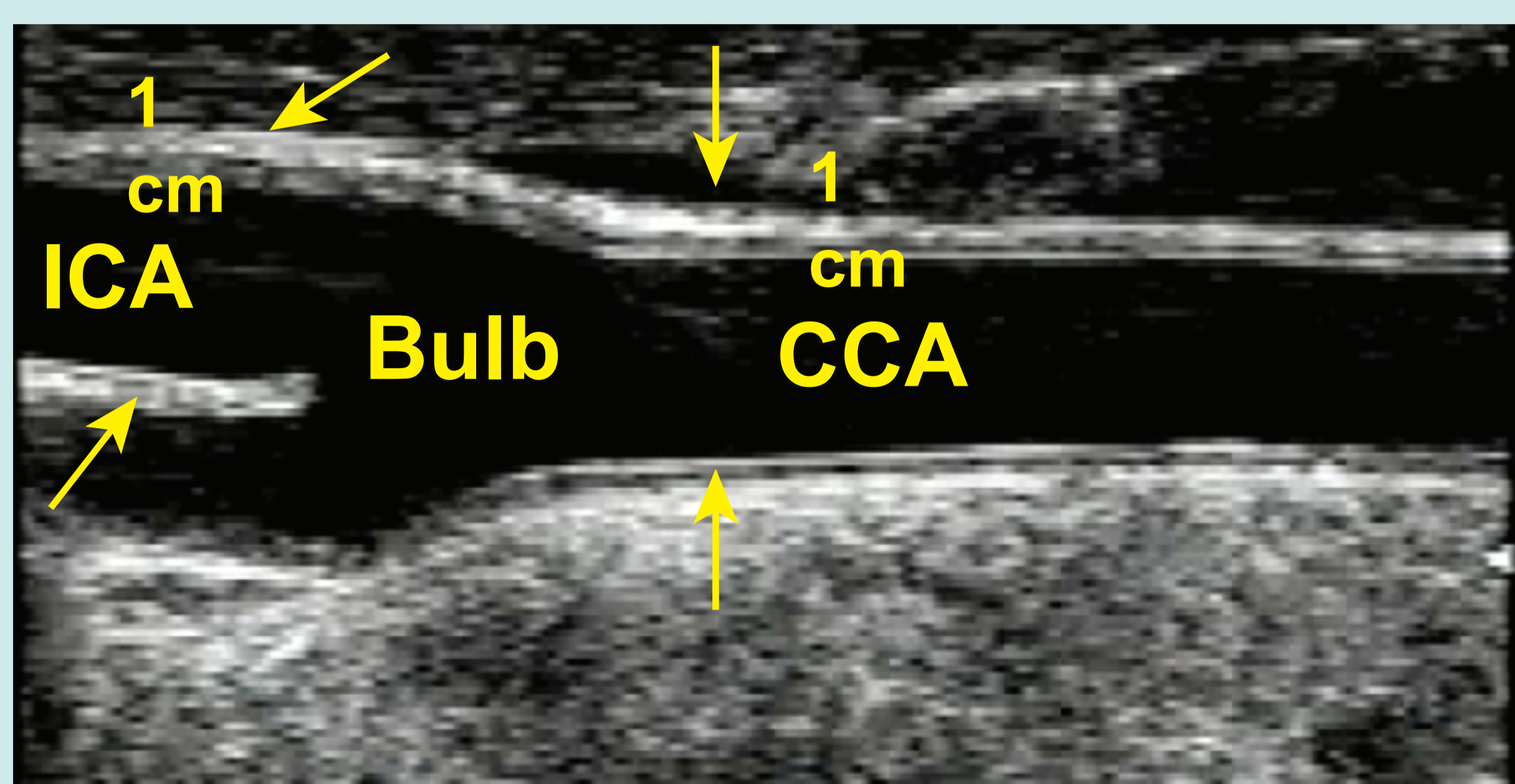
age 30–60 years
blood pressure <140/<90 mmHg
total cholesterol <7.8 mmol/L
triglycerides <4.6 mmol/L
fasting glucose <7.0 mmol/L
2-hour glucose <11.1 mmol/L

- 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

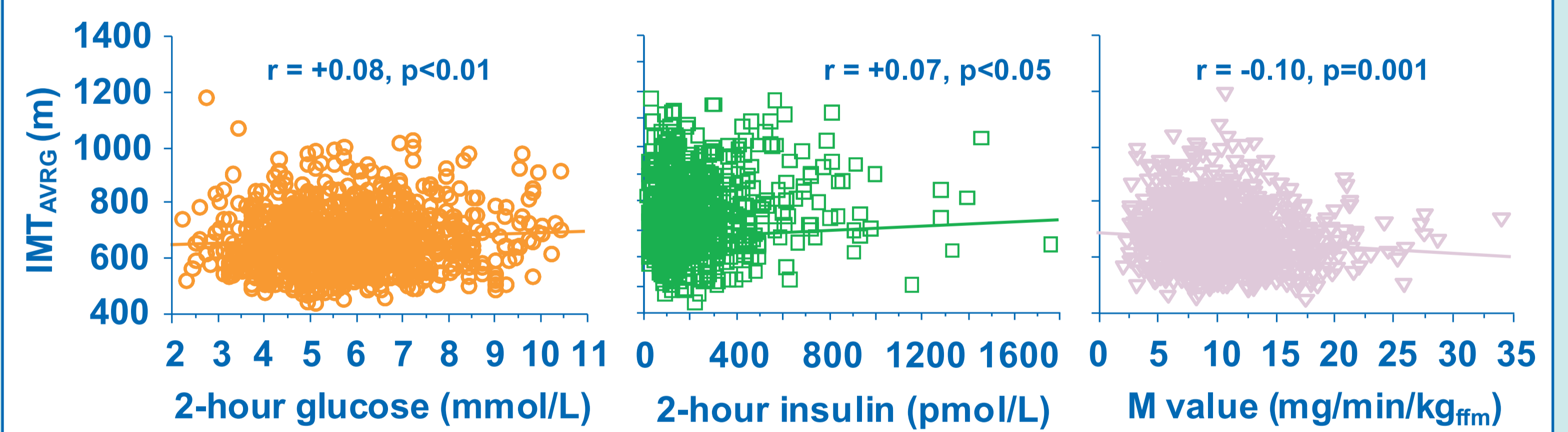
fasting glucose (mmol/L) 5.1 ± 0.6 (2.7–6.8)
insulin fasting (pmol/L) 34 ± 19 (3–147)
2-hour glucose (mmol/L) 5.7 ± 1.5 (2.2–10.4)
2-hour insulin (pmol/L) 200 ± 207 (10–3332)
M value (μmol.min⁻¹.kg_{ffm}⁻¹) 57 ± 24 (12–189)
IMT_{CCA} (μm) 599 ± 86 (380–963)
IMT_{Bulb} (μm) 764 ± 143 (328–1568)
IMT_{ICA} (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



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.

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EGIR-RISC Study Group

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Genetics – Newcastle-upon-Tyne, England: S Patel, M Walker. Stable isotope analysis – Pisa, Italy: A Gastaldelli, D Ciociaro. Ultrasound reading centre – Pisa, Italy: M Kozakova, E Ferrannini. Data Management – Villejuif, France: B Balkau, L Mhamdi. Mathematical modelling and website management – Padova, Italy: A Mari, G Pacini, C Cavaggion. Coordinating office – Pisa, Italy: SA Hills, L Mota, L Landucci.

Further information on the RISC project and participating centres can be found on www.egir.org.

