Key messages

- Only about half of the published randomised controlled trials that could have been double blinded actually were
- Poor reporting of methods used for double blinding raises concerns about how effective blinding was in many of the studies
- Some investigators may have excluded some patients from the analysis but not reported these exclusions in their published paper
- Given the apparent failure to report exclusions, some of the more biased trials may be mistaken as unbiased and vice versa
- Investigators must pay more attention to executing and reporting their approaches to blinding and the handling of exclusions

clusions after randomisation, editors, readers, and those conducting systematic reviews should all be wary of this disquieting paradox.

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Endothelium and inelastic arteries: an early marker of vascular dysfunction in non-insulin dependent diabetes

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Atheroma is the main cause of mortality and morbidity in patients with non-insulin dependent diabetes mellitus. Endothelial dysfunction underlies atheroma formation. Flow mediated vasodilatation is a measure of endothelial function as well as a determinant of arterial distensibility,¹ measurements of which have not previously been reported in patients with non-insulin dependent diabetes.

Subjects, methods, and results

We studied 12 symptom free, non-smoking, healthy patients (six men) with well controlled non-insulin dependent diabetes diagnosed 1-7 (mean 3.8) years previously (mean age 50 (SD 9) years, body mass index 26.9 (4.8) kg/m², serum cholesterol concentration 5.8 (0.5) mmol/l). Patients with known causes of endothelial dysfunction were excluded. All patients had insulin resistance with basal hyperinsulinaemia,² no biochemical evidence of renal impairment, and no

microalbuminuria. A group of 12 normal non-smoking subjects was matched for sex, age, body mass index, blood pressure, and serum cholesterol concentration and served as a control group.

Artery diameter (D) and distensibility were measured by high resolution ultrasonic vessel wall tracking³; blood pressure (P) by finger photoplethysmography; blood flow by ultrasound as the product of mean velocity corrected for Doppler angle and internal brachial artery diameter. Distensibility ($\Delta D/D \cdot \Delta P$) was derived from systolic distension (systolic minus diastolic intravascular diameter, ΔD) and simultaneous pulse pressure (ΔP).

Fasting subjects were studied in a temperature controlled room (21-23°C) after 15 minutes of supine rest. Measurements were made at baseline, during reactive hyperaemia 60 seconds after deflation of a wrist cuff inflated to suprasystolic pressure for five minutes (flow related, endothelium dependent vasodilatation) three minutes after 10 µg (submaximal dose) sublingual glyceryl trinitrate and three minutes after 400 µg (supramaximal dose) sublingual glyceryl trinitrate (endothelium independent vasodilatation). Haemodynamic variables returned to baseline 15 minutes after each intervention.

Groups were compared with unpaired *t* tests, apart from the glyceryl trinitrate distensibility data, which failed a test for normality and were analysed with the Mann-Whitney test. Paired *t* tests were used within groups to assess changes from baseline. *P* < 0.05 was regarded as significant.

Baseline characteristics and resting brachial artery measurements were similar between diabetic and normal subjects (heart rate 61 (SD 4) v 56 (8) per minute; blood pressure 127 (12)/69 (13) v 124 (15)/63

(9) mm Hg; blood flow 45 (28) v 49 (41) ml/min; diastolic diameter 4.82 (0.60) v 4.47 (1.05) mm; distensibility 4.8 (1.4) v 5.9 (1.6) per kPa. During reactive hyperaemia, heart rate, blood pressure, and the increase in brachial artery blood flow (554.8%

(99.5%) v 590% (106.6%)) were similar in diabetic and normal subjects (figure 1) but the increases in brachial artery diastolic diameter (1.2% (2.7%) v 9.1% (4.4%); difference 6.9% (95% confidence interval 4.9% to 11%)) and distensibility (-15.3% (10.4%) v 31% (31.7%); difference 46.3% (25.5% to 67.1%)) were significantly less in diabetic subjects (both $P < 0.001$). After 10 μ g glyceryl trinitrate or 400 μ g glyceryl trinitrate the increase in flow, diameter, and distensibility was similar in diabetic and normal subjects (figure 1).

Fig 1—Mean changes in blood flow, diastolic diameter, and distensibility of brachial artery in 12 diabetic subjects and 12 controls during reactive hyperaemia, 10 μ g glyceryl trinitrate, and 400 μ g glyceryl trinitrate. Bars show 95% confidence intervals

Comment

Endothelium dependent, flow related dilatation and increase in distensibility of the brachial artery are greatly impaired in patients with non-insulin dependent diabetes, but endothelium independent responses induced by glyceryl trinitrate are similar to those in normal subjects. Loss of flow related increase in arterial distensibility will augment systolic pressure, myocardial wall stress, and heart work relative to stroke output, potentially promoting left ventricular hypertrophy and lowering ischaemic threshold. Late systolic pressure will be further augmented by early wave reflection from the periphery³ because pulse wave velocity is increased when distensibility is reduced. Loss of flow mediated vasodilatation reflects endothelial dysfunction and may thus also provide a marker of atherogenic susceptibility. Our data provide evidence of vascular dysfunction in non-insulin dependent diabetes before the appearance of microalbuminuria, previously regarded as its earliest marker.⁴

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Breast feeding and hypertrophic pyloric stenosis: population based case-control study

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Hypertrophic pyloric stenosis is a common infantile disorder characterised by enlarged pyloric musculature and gastric outlet obstruction. Although there is a genetic component,¹ some evidence suggests that postnatal factors may also play an important part. Pyloric stenosis has been associated with birth rank, maternal anxiety and drug use, and feeding practices.² We investigated the association between pyloric

stenosis and infant feeding in a population based case-control study.

Patients, methods, and results

All 102 infants admitted to Santobono Paediatric Hospital, Naples between 1 July 1992 and 31 December 1993 with surgically confirmed pyloric stenosis were recruited for the study. All were born and lived in Campania province. Controls were 204 infants randomly selected from around 600 enrolled from a provincial birth list for a child health survey; all were born in 1993 and were matched to cases of the same sex. Two medical students, unaware of the objectives of the study, interviewed the mothers at around the first birthday of their infants. Sample size was based on the assumption that a 15% difference in the prevalence of breast feeding between the two groups would be clinically significant. Relative risk was estimated by the odds ratio; 95% confidence intervals were calculated by Cornfield's method. The potentially confounding