Key messages

- Epidemiological studies suggest that there is a weakly positive association between coronary heart disease and chronic infection with *Helicobacter pylori*
- A number of reports have also claimed that there are strong correlations between infection with *H pylori* and an increase in vascular risk factors, such as plasma fibrinogen concentrations
- Meta-analysis of 18 studies that involved 10 000 people found no strong correlations between *H pylori* seropositivity and vascular risk factors; previous findings of the existence of such correlations in small studies were largely or wholly due to chance or to the preferential publication of positive results

between *H pylori* seropositivity and these vascular risk factors are largely due to chance, or selective publication, or both. The clinical implication is that if there is any relation between chronic *H pylori* infection and coronary heart disease,¹ then it is not likely to be dependent on the risk factors described here.

Colin Baigent and Rory Collins commented helpfully on this paper; Eric Brunner (Whitehall-2 study), Paul Moayyedi (Leeds angiographic study), Steffen J Rosenstock (Glostrup population study), and Mark Woodward (Glasgow MONICA-3 study) provided unpublished numerical details from their studies.

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Growth hormone as a risk for premature mortality in healthy subjects: data from the Paris prospective study

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continued over

The influence of growth hormone on mortality in adults is well known in conditions such as growth hormone deficiency and acromegaly.^{1,2} In both diseases the excess mortality is principally from cardiovascular disorders, but the occurrence of malignant disorders has also been reported in acromegaly.² To our knowledge the long term effect of physiological growth hormone on mortality in healthy adults has not been reported.

Subjects, methods and results

We studied 864 policemen aged 48 to 52 years who did not have cardiovascular disease, diabetes, or glucose

intolerance and who had complete data in the Paris prospective study.³ They were examined between 1967 and 1973 then followed for mortality until January 1989. The body mass index (weight(kg)/(height(m)²)), ratio of iliac to thigh circumference (a marker of central fat distribution), heart rate, and both diastolic and systolic blood pressures were measured and smoking habits determined. Blood samples were taken at fasting to measure cholesterol and triglyceride concentrations and mean corpuscular volume, and both at fasting and 2 hours after a 75 g oral glucose tolerance test for concentrations of non-esterified fatty acids, glucose, insulin, and growth hormone with a technique described previously.⁴

Hazard ratios (95% confidence intervals) in Paris prospective study cohort (864 men, 48-52 years, 18 year follow up) of factors predictive of death from all causes, from cardiovascular disorders and from malignant disorders from a multivariate Cox model analysis. Variables are presented in order of entry into model using a forward method after adjustment for age

Factors in order of entry into model	Hazard ratios	P value
All causes		
Systolic blood pressure (mm Hg)	1.02 (1.01 to 1.02)	<0.0001
Smoking (cigarettes/day)	1.04 (1.03 to 1.06)	<0.0001
Fasting fatty acids (mg/l)*	2.45 (1.61 to 3.72)	<0.0001
2 hour growth hormone ($\mu\text{g/l}$)†	2.54 (1.51 to 4.27)	0.002
Mean corpuscular volume (fl)‡:		
Mean ν mean+SD	1.21 (0.97 to 1.51)	0.07
Mean ν mean-SD	0.95 (0.76 to 1.18)	
Fasting growth hormone ($\mu\text{g/l}$)‡	1.50 (1.12 to 2.02)	0.009
Cardiovascular disorders		
Diastolic blood pressure (mm Hg)	1.04 (1.02 to 1.05)	<0.0001
Mean corpuscular volume (fl)	1.06 (1.01 to 1.12)	0.02
Fasting growth hormone ($\mu\text{g/l}$)‡	1.79 (1.00 to 3.18)	0.05
Smoking (cigarettes/day)	1.03 (1.00 to 1.06)	0.06
Malignant disorders		
Smoking (cigarettes/day)	1.06 (1.04 to 1.08)	<0.0001
Fasting fatty acids (mg/l)*	2.88 (1.49 to 5.57)	0.002
Mean corpuscular volume (fl)	1.06 (1.01 to 1.10)	0.01
2 hour growth hormone ($\mu\text{g/l}$)‡	2.59 (1.17 to 5.73)	0.04

P values and hazard ratios are adjusted for variables already in the model.

*Log₁₀ transformed.

†Non-linear relation (quadratic), hazard ratio, and P value were calculated for mean (98.7 fl) ν mean+SD (98.7+5.7=104.4 fl) and for mean ν mean-SD (93.0 fl).

‡Above ν below the median at 0 hour (0.5 $\mu\text{g/l}$) and the 95th centile at 2 hours (1.1 $\mu\text{g/l}$).

We excluded from this analysis the three men for whom acromegaly was likely, using the criteria of fasting growth hormone concentration $>10 \mu\text{g/l}$ and 2 hour growth hormone concentration $>5 \mu\text{g/l}$.

We studied deaths from all causes, from cardiovascular disorders, and from cancer. During the 18 years of follow up, 171 men died (64 deaths were due to malignant disorders, 49 to cardiovascular diseases).

Kaplan-Meier survival curves were estimated according to four classes of growth hormone (the limits corresponding to the limit of detection, the median, and the 95th centile) and compared by the Mantel-Cox test. The survival curves showed a significant difference for growth hormone concentration at 2 hours ($P=0.03$) and a trend at fasting ($P=0.11$), with a higher mortality above (ν below) the median of $0.5 \mu\text{g/l}$ at fasting ($P=0.02$) and a higher mortality above (ν below) the 95th centile of $1.1 \mu\text{g/l}$ at 2 hours ($P=0.004$). Growth hormone concentrations were therefore analysed in two classes, chosen after this exploratory data analysis.

Cox proportional hazards models were used to estimate hazard ratios for risk factors for death, after adjustment for age. Variables significant in univariate models were entered into stepwise multivariate analyses. The table shows the hazards ratios of factors that predict death from all causes, from cardiovascular disorders, and from malignant disorders.

Comment

The original finding of this 18 year prospective study is the independent predictive power of higher concentrations of fasting and 2 hour growth hormone for mortality.

We used an old fashioned technique to measure growth hormone concentration, which was the reference at that time.⁴ A lack of assay precision would, however, have increased the variation of growth hormone within individuals, and the association between growth hormone concentration and mortality should be reduced and underestimated, not enhanced.

We could have excluded the 25 men (3%) who had a 2 hour growth hormone concentration $>2 \mu\text{g/l}$, another level accepted for the diagnosis of acromegaly; the trend remained unchanged for fasting growth hormone concentration when they were excluded.

Four other independent risk factors were associated with early mortality, in agreement with a previous analysis of the complete cohort.³ For death from cardiovascular causes, fasting growth hormone—along with the two classic risk factors (arterial blood pressure and cigarette smoking)—seemed to be a risk factor. Indeed, a direct and causal relation between growth hormone and cardiovascular growth and function has previously been suggested.^{2,5} We found a significant relation for 2 hour growth hormone concentrations with death from cancer. Growth hormone is also known to play a role in cancer.²

Since growth hormone treatment is being extended, these disturbing results merit an exploration in other studies of healthy populations.

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Endpiece

A problem often confronting editors

He draweth out the thread of his verbosity finer than the staple of his argument.

Shakespeare, *Love's Labours Lost*, Vi

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