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For debate

Why is insulin *not* a risk factor for coronary heart disease?

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It is commonly stated that insulin is a risk factor for atherosclerosis (or cardiovascular or coronary heart disease (CHD)) and in Reaven's syndrome [1] (otherwise known as the insulin resistance syndrome) hyperinsulinaemia appears to be the motor which drives the other components of the syndrome – hypertension and dyslipidaemia. I have recently rehearsed the arguments against the view that hyperinsulinaemia is a significant factor in causing raised blood pressure [2].

What is the evidence that insulin is a risk factor for CHD? (i.e. that the two variables are statistically significantly associated with one another, irrespective of the nature of the association). It is usual to cite three prospective studies – from Helsinki [3], Paris [4] and Busselton [5].

In the Helsinki study [3] 1059 male police aged 35–59 years underwent an oral glucose tolerance test at baseline and again after 5 years, when fasting and post-load insulin levels were measured. Follow up continued for a further 9.5 years. The combined incidence of CHD deaths and non-fatal myocardial infarction was significantly increased in the upper part of the distribution of 1- and 2-h levels, but not in that of the fasting insulin levels.

The Paris Prospective Study [4] included 6903 men – also police. An oral glucose tolerance test was performed at baseline with measurement of insulin levels at fasting and 2-h post-load. After 11 years follow-up CHD mortality was significantly associated with both fasting and 2-h insulin levels, but after 15 years [6] the associations were attenuated and no longer significant between mortality and the 2-h levels.

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Abbreviations: CHD, coronary heart disease; NIDDM, non-insulin-dependent diabetes mellitus.

The Busselton study [5] involved 91 % of an adult population (n=3390). Blood was sampled 1 h after a glucose load, without reference to time of day or previous food consumption. Six-year CHD morbidity and 12-year mortality were analysed in relation to insulin levels in three age groups and separately by gender. In only one of the six age- and sex-specific groups was there a significant association – in men aged 60–69 years. In a subsequent analysis [7] only multivariate associations were reported for mortality up to 13 years of follow-up. Four age- and sex-specific groups were considered and the only significant associations with serum insulin were all-cause mortality (negative) in men aged 40–59 years and all cancers (positive) in men aged 60–74 years.

Several studies have been reported more recently. From a population sample in Gothenburg 644 men aged 67 years were followed-up for 8 years [8]. Endpoints were fatal and non-fatal myocardial infarction plus other CHD deaths. With 32 diabetic men excluded neither fasting nor 1-h post-load insulin levels were significantly increased in the men who subsequently experienced CHD. In Edinburgh 107 men aged 40 years, randomly selected from the general population, were studied in 1976 and followed-up for 12 years [9]. Clinical evidence of CHD (angina, infarction, coronary bypass or death) occurred in 12 men, whose baseline fasting insulin levels and area under the insulin response curve were similar to and not significantly different from those who were free of CHD.

Pima Indians are a group of Native Americans with relative hyperinsulinaemia and a very high incidence of NIDDM, but with a low incidence of CHD. A prospective study in 605 non-diabetic subjects found no significant association between age-adjusted incidence of electrocardiographic abnormalities and the baseline fasting or 2-h post-load insulin levels [10].

In an unpublished study (A Ferrara, SL Edelstein, E Barrett-Connor: presented to the 28th annual

meeting of the European Diabetes Epidemiology Study Group, Cambridge, 4–7 April, 1993) of 538 men and 706 women aged 50–89 years, without diabetes or heart disease, in Rancho Bernardo, California, USA, deaths from CHD over 5 years were unrelated to baseline fasting insulin levels. In men 2-h levels were significantly *lower* in those who subsequently died from CHD.

In an attempt to discover whether fasting serum insulin was a predictor of CHD in high-risk men in the United States, a nested case-control study was performed in participants in the MRFIT study [11]. During the trial there were 94 CHD deaths occurred (post-trial follow-up) and 114 men suffered non-fatal myocardial infarction; they compared with 414 control subjects matched for age, trial centre, randomisation date and intervention group. Mean serum insulin levels were almost identical in the patients and the control subjects (16.8 vs 16.6 μU/ml).

Three studies have been performed [10, 12, 13] using subjects with glucose intolerance or NIDDM. In the Paris study, a sub-group of men with known diabetes, newly-diagnosed diabetes or impaired glucose tolerance (n=973) were separately analysed [12]. Neither fasting nor 2-h insulin levels were significantly raised in those men who died from CHD during 15 years of follow-up.

In the Bedford study [13] 241 subjects with glucose intolerance were followed-up for 10 years. Post-load insulin levels (2-h) were not significantly different in those subjects who had experienced CHD morbidity or death. The Pima Indian study [10] also reported results in 436 diabetic subjects: as in the non-diabetic population there was no significant association between the incidence of electrocardiographic abnormalities and baseline insulin levels.

Comment

It is stressing the obvious to state that the risk factor status of insulinaemia in terms of subsequent CHD is at best weak (e. g. in the police studies) or at worst non-existent. Even the two studies in policemen were not mutually consistent, with univariate associations between CHD and both fasting and post-load insulin levels in the Paris study, but with post-load levels only in the Helsinki study. Further, the associations became attenuated with the longer duration of follow-up in the Paris study. Yet this unimpressive evidence of risk factor status is surprising when one specifically considers univariate associations, i. e. where confounding variables are not accounted for, because there is ample evidence of significant associations between insulinaemia and several well-documented risk factors for CHD – raised blood pressure and VLDL-triglyceride levels, reduced HDL-cholesterol levels, obesity per se and visceral fat specifically [13–15]. Why then do univariate analyses not consistently associate insulinaemia with the risk of developing CHD? Could it be that high insulin levels in the presence of other associated risk factors in some way *protect* against their malign effects? Or that insulin levels are associated with factors which are themselves protective? Either of these possibilities could explain the association of hyperinsulinaemia with prevalent CHD [16].

Insulin and not insulin

As we now know the insulin assays used in all the studies quoted above have measured what Davies et al. [17] call "total insulin-like molecules". Of these the proportion attributable to insulin itself diminishes with increasing glucose intolerance [17]. There is evidence that associations with cardiovascular risk factors are stronger for insulin-like molecules rather than insulin itself [17–19]. Such data are clearly open to various interpretations. For my part the currently most attractive hypothesis is that of Hales and Barker [20] which suggests a fetal origin for associations seen in later life, including those between insulin-like molecules and undoubted cardiovascular risk factors.

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