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Lp(a) lipoprotein and impaired glucose tolerance

Association poorly investigated

EDITOR,—M Farrer and colleagues recently investigated the association between impaired glucose tolerance and Lp(a) lipoprotein concentration in relation to coronary artery disease.¹ Although the subject was reasonable to investigate, we were disturbed by the statistical methods they used and by the conclusions they drew. In particular, the study design did not directly address the specific objective of assessing the relation between glucose tolerance and raised Lp(a) lipoprotein concentrations in subjects with coronary artery disease. We wonder why they included a group of 517 apparently healthy subjects. We are concerned that the majority of subjects were lost because of the matching of cases and controls, resulting in a primary analysis of some 39 asymptomatic subjects and 102 patients whose representation of the target population was questionable when selection bias is taken into account. Furthermore, the use of *t* tests and analyses of variance to analyse the data assumes a causal relation between the factors, which is not the same as the hypothesis of an association. We suggest that it would have been more appropriate to compute and test Pearson's correlation coefficient for all subjects to assess the association of interest without matching subjects or assuming a specific relation.

Further issues include the use of a geometric mean rather than a more common statistic to summarise the transformed variables. Farrer and colleagues state that the study had 95% power to detect an effect in subjects with coronary artery disease (without specifying the size of the effect), implying that an effect rather than an association was the objective. In addition, since 23% of asymptomatic subjects with normal glucose tolerance had high concentrations of Lp(a) lipoprotein the power to detect a fivefold higher prevalence was not meaningful. Finally, even with the appropriate statistics and more confident data, retrospective case-control studies such as this should at best generate hypotheses: they should not be the basis on which to draw definitive conclusions.

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Authors' reply

EDITOR,—Andrew C G Uprichard and Linda Shurzinske are correct to point out potential limitations in epidemiological studies of performing analyses that were not prospectively identified when subjects were recruited. The information from such analyses in the Framingham study and others shows, however, that their argument should not deter epidemiologists when the population(s) studied can provide useful insights into testing as well as generating hypotheses.

Our study was in response to a previous study of subjects with no known coronary artery disease which found a fivefold increase in the proportion

of subjects with impaired glucose tolerance who had concentrations of Lp(a) lipoprotein above 300 mg/l (25% of those with impaired glucose tolerance v 5% of those with normal glucose tolerance).¹ The null hypothesis was that impaired glucose tolerance was not associated with high concentrations of Lp(a) lipoprotein (as a postulated mechanism for the association between impaired glucose tolerance and coronary artery disease in British studies).^{2,3} The size of the effect observed by Davies *et al* would be clinically important and we therefore examined this hypothesis in our study populations. In patients with established coronary artery disease, however, high Lp(a) lipoprotein concentrations could theoretically be caused by atherosclerotic disease rather than be a cause of atherosclerosis. If the high concentrations were caused by the disease the effect of impaired glucose tolerance may be overwhelmed by it. A control group free of coronary artery disease was therefore essential. It also allowed the hypothesis of Davies *et al* to be tested in a similar population to theirs.

We showed that the population samples used are representative, and far from losing data we have analysed all subjects as well as subgroups, appropriately selected to test the size of effect suggested by Davies *et al* with the stated power. We showed that subgroups of impaired glucose tolerance had the expected characteristics with respect to the metabolic syndrome (syndrome X) but no difference in Lp(a) lipoprotein concentration. The prevalence of high Lp(a) lipoprotein concentrations (>300 mg/l) in subjects with normal glucose tolerance was 23% in our study of 504 asymptomatic subjects compared with 5% of 36 subjects studied previously. This finding leads to the different conclusions from the two studies.

We used geometric means because Lp(a) lipoprotein concentration is highly positively skewed and log transformation normalised the distribution. The use of parametric statistics to examine differences between geometric mean values is therefore appropriate for the stated hypothesis testing. Two paragraphs are devoted to Pearson correlation coefficient data, but we were concerned that there might be a threshold effect (analogous to the relation between microangiopathy and diabetes mellitus but not impaired glucose tolerance), and this has also been sought. To show a lack of association with certainty is difficult, but in our study the null hypothesis stands; if a real association has been missed we suggest that it is small and unlikely to be important.

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Potassium depletion and rhabdomyolysis

EDITOR,—In his report of rhabdomyolysis complicating the diabetic hyperosmolar state G M Lord discusses the possible causes of muscle cell injury and concludes that hypophosphataemia, though relevant, is insufficient by itself to cause rhabdomyolysis.¹ Deficiency of total body potassium—a frequent complication of hyperosmolar and hyperglycaemic states—may also be implicated in the pathogenesis of rhabdomyolysis; it has been suspected in diabetic patients with rhabdomyolysis and hyperosmolality.

Further evidence for the pathogenetic relevance of potassium depletion comes from occasional reports of rhabdomyolysis complicating hypernatraemic hyperosmolar states in non-diabetic patients.^{2,5} Tuller reported inappropriate urinary loss of potassium and phosphate in patients who did not develop oliguria;² Ulvila and Nesson pointed out the similarities of myoglobinuria due to potassium depletion and that due to hypernatraemia;³ and two of the children reported on by Opas *et al* were hypokalaemic at presentation,⁴ as was the patient of Bateman *et al* with probable lithium induced nephrogenic diabetes insipidus.⁵ Concurrently, low phosphate concentrations were also found in some of these patients.^{2,5}

Hypokalaemia, like hypophosphataemia, has been shown experimentally to reduce muscle cell transmembrane voltage (as predicted by the Nernst equation) and to cause muscle cell damage. Hence a combination of hypokalaemia and hypophosphataemia, although often masked by muscle cell lysis, may be the key biochemical derangement leading to muscle cell injury in hyperosmolar states.

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Imaging methods used in aortic dissection

EDITOR,—In the second of their articles on chest radiographs in emergency radiology D W Hodgkinson and colleagues state that the diagnosis of aortic dissection depends ultimately on arteriography.¹ This traditional view has become outdated with the introduction of quicker, less invasive methods that provide more detailed images. These include transoesophageal echocardiography, computed tomography, and magnetic resonance imaging. Arteriography is slow and invasive, carries considerable risk, and may be non-diagnostic.²

The optimal imaging technique has been the subject of much interest recently.^{3,5} The plain radiographic signs are non-specific and unreliable. The most impressive of the modern imaging techniques for diagnosing either acute or chronic dissection is magnetic resonance imaging.⁴ Its accuracy in diagnosis and in defining the morphological and haemodynamic features of the aortic dissection is unsurpassed.⁵ However, its limited availability, the fact that it cannot be used at the bedside, and the time that it takes make it inappropriate for use in acute cases. Transoeso-