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Triacylglycerol and coronary heart disease

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The importance of elevated plasma cholesterol, and specifically LDL-cholesterol, as risk factors for CHD is indisputable (Levine *et al.* 1995), especially considering the recent evidence from intervention trials such as the Scandinavian Simvastatin Survival Study (Scandinavian Simvastatin Survival Study Group, 1994) and the West of Scotland study (Shepherd *et al.* 1995). Although the role of triacylglycerol (TAG) as a risk factor has been controversial for over three decades (Austin, 1991; NIH Consensus Development Panel on Triglyceride, High Density Lipoprotein and Coronary Heart Disease, 1993), accumulating epidemiological evidence is now demonstrating that TAG is associated with increased risk, probably in combination with decreased levels of HDL-cholesterol and the presence of small, dense LDL.

For example, we recently performed a meta-analysis of all population-based prospective studies of TAG and cardiovascular disease (CVD) available from the literature to determine whether TAG is a risk factor for CVD, independent of HDL-cholesterol (Hokanson & Austin, 1996). The analysis included seventeen studies published between 1965 and 1994, sixteen in men and five in women. A total of 46 413 men were included in these studies and 10 864 women, with average follow-up times of 8·4 and 11·4 years respectively. Applying the standard statistical approaches for meta-analysis resulted in weighted, summary relative risks (RR; standardized for a 1 mmol/l or 880 mg/l increase in plasma TAG). The univariate RR values for men ranged from 1·07 to 1·98, and were statistically significant for thirteen of the sixteen studies. The summary RR was 1·32 with a 95 % CI of 1·26–1·39. For women, RR values were higher and ranged from 1·69 to 2·05, with a summary RR of 1·76 (95 % CI of 1·50–2·07). Thus, a 30 % increase in risk is seen for men and a 75 % increase in risk for women. Interestingly, the summary RR values varied by geographic location, with the highest values in Scandinavian countries for both men and women (1·49 and 2·02 respectively).

Of the seventeen studies included in the analysis, only six reported TAG RR adjusted for HDL-cholesterol, including six studies in men and two in women. As expected due to the inverse correlation between TAG and HDL-cholesterol, the RR for TAG were attenuated to 1·14 (95 % CI 1·05–1·28) and 1·37 (95 % CI 1·13–1·66) in men and women respectively, although these values were still statistically significant. These analyses clearly demonstrate that taken together, TAG is a risk factor for CVD, independent of HDL-cholesterol.

SMALL, DENSE LDL AND CHD

Similarly, there is growing body of evidence to support the role of small, dense LDL as a risk factor for CHD. Beginning in the early 1980s, at least nine case–control studies have demonstrated that a predominance of small, dense LDL particles is more common in cases than in controls (Austin *et al.* 1994). The cases in these studies were either myocardial infarction (MI) survivors or patients with coronary artery disease documented by angiography. Importantly, even though a variety of laboratory approaches were used in

these studies to characterize LDL subclasses either by size or density, the results uniformly showed a relationship between small, dense LDL and risk of CHD. The RR in these studies range from 3·0 (Austin *et al.* 1988) to 6·9 (Griffin *et al.* 1994).

Despite these consistent cross-sectional data, prospective studies examining small, dense LDL as a risk factor were lacking until very recently. Results of nested case–controls analyses from the Stanford Five City Project (Gardner *et al.* 1996) and from the Physicians' Health Study (Stampfer *et al.* 1996) have now made important contributions to our understanding of both TAG and LDL size as risk factors.

The Stanford Five City Project (Gardner *et al.* 1996) was based on incident cases of CHD, both fatal and non-fatal, identified through community surveillance from 1979 to 1992. Controls were selected based on matching criteria for age, sex, ethnicity, treatment of control city, and time of surveillance. The laboratory analyses were based on non-fasting baseline blood samples obtained from these study subjects. A total of 124 case–control pairs were identified, ninety pairs of men and thirty-four pairs of women, and the analyses were based on the case–control difference in LDL size. For all subjects, a highly significant case–control mean difference was found ($-5{\cdot}1$ Å, $P < 0{\cdot}001$), demonstrating that smaller LDL size predicted incident CHD in this population. Importantly, this difference in LDL size was independent of TAG, HDL-cholesterol, smoking, systolic blood pressure and BMI in multivariate analyses.

The findings from the Physicians' Health Study (Stampfer *et al.* 1996) were based on a 7-year follow-up of 266 men with incident non-fatal MI or fatal CHD. Controls were matched for age, smoking, and time of randomization. Similar to the Stanford Five City Project (Gardner *et al.* 1996), study participants were 'not specifically instructed to provide fasting specimens'. In this study mean baseline TAG levels were significantly increased in cases compared with controls (2030 *v.* 1550 mg/l respectively, $P = 0{\cdot}001$) and baseline LDL diameter values were smaller in cases compared with controls (256 Å *v.* 259 Å respectively, $P < 0{\cdot}001$; Stampfer *et al.* 1996). The resulting RR values were 1·43 (95 % CI 1·22–1·68) for a 1000 mg/l increase in TAG, similar to the value noted previously for men in the meta-analysis. The RR was 1·38 (95 % CI 1·18–1·62) for an 8 Å decrease in LDL size. Thus, both TAG and LDL size were significant predictors of future CHD in this study. However, in contrast with the Stanford Five City Project (Gardner *et al.* 1996) the TAG relationship was independent of both LDL size and HDL-cholesterol (RR 1·3, $P = 0{\cdot}009$), while the LDL size relationship was not independent of TAG and HDL-cholesterol (RR 1·09, $P = 0{\cdot}46$).

As valuable as the results are from these two studies, the subjects were all middle-aged Caucasian men and women. Two other ongoing collaborative studies, using similar case–control prospective designs, are currently in progress. The first of these involves a 12-year follow-up of older Japanese American men participating in the Honolulu Heart Program. The second study is an ancillary study of the Multicenter Cardiovascular Health Study, examining men and women over 65 years of age. The results of these studies will be available within the next year and will provide important new information about the role of small, dense LDL as a risk factor in these different populations.

INTERRELATIONSHIPS OF LIPOPROTEIN RISK FACTORS

The apparently contradictory results described previously in the recent prospective studies, that LDL is an independent risk factor in the Stanford Five City Project (Gardner *et al.* 1996), but not in the Physicians' Health Study (Stampfer *et al.* 1996) are not surprising given the well-established correlations between LDL size and TAG and HDL-cholesterol

concentrations (Austin *et al.* 1990). Even in the Physicians' Health Study (Stampfer *et al.* 1996), the correlations for each possible pair of these variables were highly statistically significant: −0·71 for TAG and LDL size, −0·57 for TAG and HDL-cholesterol, and +0·61 for LDL size and HDL-cholesterol. Similar correlations have been seen in many other studies, including a recent prospective study of small, dense LDL and non-insulin-dependent diabetes (Austin *et al.* 1995). These consistent interrelationships suggest that small, dense LDL and TAG and HDL-cholesterol concentrations may actually represent a composite lipoprotein risk factor with a common, underlying atherogenic mechanism.

One such potential mechanism may relate to the insulin resistance syndrome (IRS; Reaven, 1988; Defronzo & Ferrannini, 1991; Ferrannini *et al.* 1991). In addition to studies demonstrating that LDL subclass phenotype B is an integral feature of the syndrome (Reaven *et al.* 1993; Selby *et al.* 1993), multivariate analyses have demonstrated that ten of the inter-related risk factors of the IRS can be reduced to three uncorrelated factors (Edwards *et al.* 1994). One of these factors, accounting for over 20 % of the total variance in the data was a factor characterized by LDL size and TAG and HDL-cholesterol concentrations. These results in women have subsequently been confirmed in post-menopausal women (K. L. Edwards, M. A. Austin and E. Barrett-Connor, unpublished results), elderly Japanese American men (Edwards *et al.* 1996) and Finnish men and women (Austin *et al.* 1995).

Based on studies that include only TAG and HDL-cholesterol, other investigators have also proposed that the combination of high TAG and low HDL-cholesterol levels comprises an inherited 'conjoint trait' associated with familial risk of CHD (Sprecher *et al.* 1994). Stratified epidemiological analyses based on data from the PROCAM study (Assmann *et al.* 1996) and from the Honolulu Heart Program (Burchfiel *et al.* 1995) also demonstrate high risk of CHD among subgroups with combined high TAG and low HDL-cholesterol concentrations.

Using a multivariate genetic approach, Mahaney *et al.* (1995) have applied a quantitative genetic test of the 'conjoint trait' hypothesis based on data from the San Antonio Heart Study. These findings demonstrate significant univariate heritability for both TAG and HDL-cholesterol levels (0·53 and 0·55 respectively, both $P < 0·001$), as well as significant inverse genetic and environmental correlations for these two variables. These investigators conclude that approximately 25 % of the genetic variance in these two variables is attributable to common polygenic effects (i.e. pleiotropy). Taken together, these epidemiological and genetic observations to date show that TAG and HDL-cholesterol concentrations are jointly involved in genetic susceptibility to CHD.

SUMMARY

Based on meta-analysis of prospective studies from the epidemiological literature, TAG is a risk factor for CVD, independent of HDL-cholesterol. The RR values were 1·3 and 1·8 for a 1 mmol/l increase in TAG among men and women respectively. Adjustment for HDL-cholesterol and other risk factors attenuated these estimates, but they remained statistically significant. Recent prospective findings from the Stanford Five City Project (Gardner *et al.* 1996) and the Physicians' Health Study (Stampfer *et al.* 1996) further demonstrate that TAG and LDL size are highly inter-related risk factors for CHD. Quantitative genetic analysis from large-scale family studies show that these correlations reflect common genetic influences that may be important for understanding genetic susceptibility to CHD.

REFERENCES

Assmann, G., Schulte, H. & von Eckardstein, A. (1996). Hypertriglyceridemia and elevated lipoprotein(a) are risk factors for major coronary events in middle-aged men. *American Journal of Cardiology* **77**, 1179–1184.

Austin, M. A. (1991). Triglycerides and coronary heart disease. *Arteriosclerosis & Thrombosis* **11**, 2–14.

Austin, M. A., Breslow, J. L., Hennekens, C. H., Buring, J. E., Willett, W. S. & Krauss, R. M. (1988). Low-density lipoprotein subclass patterns and risk of myocardial infarction. *Journal of the American Medical Association* **260**, 1917–1921.

Austin, M. A., Hokanson, J. E. & Brunzell, J. D. (1994). Characterization of low-density lipoprotein subclasses: methodologic approaches and clinical relevance. *Current Opinion in Lipidology* **5**, 395–403.

Austin, M. A., King, M.-C., Vranizan, K. M. & Krauss, R. M. (1990). Atherogenic lipoprotein phenotype: A proposed genetic marker for coronary heart disease risk. *Circulation* **82**, 495–506.

Austin, M. A., Mykkänen, L., Kuusisto, J., Edwards, K. L., Nelson, C., Haffner, S. M., Pyörälä, K. & Laakso, M. (1995). Prospective study of small LDLs as a risk factor for non-insulin dependent diabetes. *Circulation* **92**, 1770–1778.

Burchfiel, C. M., Laws, A., Benfante, R., Goldberg, R. J., Hwang, I.-J., Chiu, D., Rodriguez, B. L., Curb, J. D. & Sharp, D. S. (1995) . Combined effects of HDL cholesterol, triglyceride and total cholesterol concentrations on 18-year risk of atherosclerotic disease. *Circulation* **92**, 1430–1436.

Defronzo, R. A. & Ferrannini, E. (1991). Insulin resistance: a multifaceted syndrome responsible for NIDDM, obesity, hypertension, dyslipidemia and atherosclerotic cardiovascular disease. *Diabetes Care* **14**, 173–194.

Edwards, K. L., Austin, M. A., Newman, B., Mayer, E., Krauss, R. M. & Selby, J. V. (1994). Multivariate analysis of the insulin resistance syndrome in women. *Arteriosclerosis & Thrombosis* **14**, 1940–1945.

Edwards, K. L., Burchfiel, C. M., Sharp, D. S., Curb, J. D., Rodriguez, B. L., LaCroix, A. Z., Vitiello, M. V. & Austin, M. A. (1996). Multivariate factors of the insulin resistance syndrome (IRS) in elderly Japanese American men. *Diabetes* **45**, Suppl. 2, 280A.

Ferrannini, E., Haffner, S. M., Mitchell, B. D. & Stern, M. P. (1991). Hyperinsulinaemia: the key feature of a cardiovascular and metabolic syndrome. *Diabetologia* **34**, 416–422.

Gardner, C. D., Fortmann, S. P. & Krauss, R. M. (1996). Association of small low-density lipoprotein particles with the incidence of coronary artery disease in men and women. *Journal of the American Medical Association* **276**, 875–881.

Griffin, B. A., Freeman, D. J., Tait, G. W., Thomson, J., Caslake, M. J., Packard, C. J. & Shepherd, J. (1994). Role of plasma triglyceride in the regulation of plasma low density lipoprotein (LDL) subfractions: relative contribution of small, dense LDL to coronary heart disease risk. *Atherosclerosis* **106**, 241–253.

Hokanson, J. E. & Austin, M. A. (1996). Plasma triglyceride level is an independent risk factor for cardiovascular disease: a meta-analysis of population-based prospective studies. *Journal of Cardiovascular Risk* **3**, 213–219.

Levine, G. N., Keaney, J. F. & Vita, J. A. (1995). Cholesterol reduction in cardiovascular disease. Clinical benefits and possible mechanisms. *New England Journal of Medicine* **332**, 512–521.

Mahaney, M. C., Blangero, J., Comuzzie, A. G., Vandeberg, J. L., Stern, M. P. & MacCluer, J. W. (1995). Plasma HDL cholesterol, triglyceride and adiposity. A quantitative genetic test of the conjoint trait hypothesis in the San Antonio Heart Study. *Circulation* **92**, 3240–3248.

NIH Consensus Development Panel on Triglyceride, High Density Lipoprotein and Coronary Heart Disease (1993). Triglyceride, high density lipoprotein and coronary heart disease. *Journal of the American Medical Association* **269**, 505–510.

Reaven, G. M. (1988). Role of insulin resistance in human disease. *Diabetes* **37**, 1595–1607.

Reaven, G. M., Chen, I. Y.-D., Jeppesen, J., Maheux, P. & Krauss, R. M. (1993). Insulin resistance and hyperinsulinemia in individuals with small, dense, low density lipoprotein particles. *Journal of Clinical Investigation* **92**, 141–146.

Scandinavian Simvastatin Survival Study Group (1994). Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). *Lancet* **344**, 1383–1389.

Selby, J. V., Austin, M. A., Newman, B., Zhang, D., Quesenberry, C. P., Mayer, E. J. & Krauss, R. M. (1993). LDL subclass phenotypes and the insulin resistance syndrome in women. *Circulation* **88**, 381–387.

Shepherd, J., Cobbe, S. M., Ford, I., Isles, C. G., Lorimer, A. R., MacFarlane, P. W., McKillop, J. H. & Packard, C. J. for the West of Scotland Coronary Prevention Study Group (1995). Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. *New England Journal of Medicine* **333**, 1301–1307.

Sprecher, D. L., Hein, M. J. & Laskarzewski, P. M. (1994). Conjoint high triglycerides and low HDL cholesterol across generations. Analysis of proband hypertriglyceridemia and lipid/lipoprotein disorders in first-degree family members. *Circulation* **90**, 1177–1184.

Stampfer, M. J., Krauss, R. M., Blance, P. J., Holl, L.G., Sacks, F. M. & Hennekens, C. H. (1996). A prospective study of triglyceride level, low-density lipoprotein particle diameter and risk of myocardial infarction. *Journal of the American Medical Association* **276**, 882–915.