

## Diabetes journals

### What drives atherosclerosis in diabetes and IFG?



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**E**pidemiological data indicate the risk of cardiovascular (CV) death to be increased by two- to four-fold in people with type 2 diabetes (T2D). In the United Kingdom Prospective Diabetes Study, levels of plasma LDL cholesterol (LDL-C) and HDL cholesterol (HDL-C) were strong predictors of CV events. The typical dyslipidaemia of T2D is characterised by hypertriglyceridaemia and low HDL-C; LDL-C levels have been reported as normal, above normal or below normal in people without T2D. Intervention studies have demonstrated outcome benefits for both reducing LDL-C and increasing HDL-C in people with T2D. It is not clear, however, which lipoprotein abnormality primarily contributes to the vascular risk associated with T2D.

This study investigated a large cohort of angiographically characterised patients with T2D, normal fasting glucose (NFG) or impaired fasting glucose (IFG) in an attempt to answer the following primary questions. Which lipid factors distinguish individuals with T2D from those with IFG and NFG? Which lipid factors are associated with coronary atherosclerosis? And, most importantly, which lipid factors are predictive of future vascular events? Lipid

analysis, the presence of coronary artery disease and the incidence of vascular events over 2.3 years were recorded in 750 patients undergoing angiography.

Triglycerides increased, HDL-C decreased and LDL particle size decreased from NFG (<5.6 mmol/l) to IFG (≥5.6 mmol/l) to frank T2D. In patients with T2D, the lipid profile of low HDL-C, low apolipoprotein A1, elevated triglycerides and reduced LDL particle size was associated with coronary atherosclerosis and proved predictive of vascular events. This lipid profile correlated with increasing insulin resistance and glycaemic status. Of note, this study illustrates that the new American Diabetes Association definition of IFG (that is, ≥5.6 mmol/l) may be of relevance in assessing vascular risk since it is associated with an atherogenic lipid profile and progressive insulin resistance. These data thus reflect a pathophysiological association of impaired glucose homeostasis, insulin resistance and dyslipidaemia resulting in atherogenesis.

Thus, in an era of widespread statin therapy, specific treatments for diabetic dyslipidaemia may provide further reduction in CV events in patients with T2D. Furthermore, the observations of this study provide additional support for the concept that insulin sensitiser therapy may produce CV benefits in patients with T2D, an issue that is the focus of numerous large outcome studies.

### DIABETES CARE



### Vascular events and hyperglycaemia correlate with lipid profile

Readability	✓✓✓✓✓
Applicability to practice	✓✓✓✓
WOW! factor	✓✓✓✓

- The main focus of cardiovascular risk intervention for patients with diabetes is lipid levels, but it has not been determined which lipoprotein abnormality is most important.
- This study aimed to establish the atherogenicity of lipids in patients undergoing coronary angiography.
- Patients were divided into three sub-groups: those with normal fasting glucose (NFG; <5.6 mmol/l; n=272); those with impaired fasting glucose (IFG; 5.6–6.9 mmol/l; n=314); and those with diabetes by World Health Organization criteria (n=164).
- Triglyceride levels significantly increased ( $P<0.001$ ) from patients with NFG, through patients with IFG to patients with type 2 diabetes.

**5** In patients with diabetes, an HDL-related factor – determined by factor analysis – was a significant predictor of vascular events (odds ratio [OR], 0.708; 95 % confidence interval [CI], 0.506–0.990;  $P=0.044$ ), but an LDL-related factor was not (OR, 1.362; 95 % CI, 0.985–1.883;  $P=0.061$ ).

**6** The pattern was similar for the prevalence of coronary artery disease.

**7** Based on their results, the authors suggest that among people with type 2 diabetes, treating diabetic dyslipidaemia is the most promising approach to reducing cardiovascular events.

Drexel H, Aczel S, Marte T, Benzer W, Langer P, Moll W, Saely CH (2005) Is atherosclerosis in diabetes and impaired fasting glucose driven by elevated LDL cholesterol or by decreased HDL cholesterol. *Diabetes Care* **28**(1): 101–7

### DIABETES CARE

### Wide 24-hour PP predicts CV events

Readability	✓✓✓
Applicability to practice	✓✓✓
WOW! factor	✓✓✓

**1** The evidence base for wide pulse pressure (PP) as an independent predictor of cardiovascular (CV) disease in elderly people is growing; a prognostic role for this indicator has been applied to younger people too, though.

**2** This study aimed to assess the validity of this prognostic role on vascular events in younger people (<60 years old) with type 2 diabetes.

**3** Patients with a study-defined wide 24-hour PP had a significantly greater incidence of CV events (20.7 %) than those with a narrow 24-hour PP (4.1 %;  $P<0.001$ ).

**4** A wide 24-hour PP was shown to be better predictively than systolic and diastolic blood pressure.

**5** Cerebrovascular events were also assessed, but the only risk factor for these was duration of diabetes.

**6** The results support the prognostic role of wide 24-hour PP and its use in risk-stratifying non-elderly patients.

Nakano S, Konishi K, Furuya K, Uehara K, Nishizawa M, Nakagawa A et al (2005) A prognostic role of mean 24-h pulse pressure level for cardiovascular events in type 2 diabetic subjects under 60 years of age. *Diabetes Care* **28**(1): 95–100

## DIABETES CARE

### The metabolic syndrome and CVD

Readability	✓✓✓✓
Applicability to practice	✓✓✓✓✓
WOW! factor	✓✓✓✓

1 Several prospective analyses have linked the metabolic syndrome to an approximately two-fold cardiovascular disease (CVD) risk increase; limitations of the make-up of study populations, however, mean that these results are not generalisable to US populations.

2 The population-based sample of the Atherosclerosis Risk in Communities (ARIC) study was used by this study to examine the applicability of the link.

3 For people without CVD or diabetes, having the metabolic syndrome increased the risk of having long-term cardiovascular outcomes, although most of that increase was accounted for by the Framingham Risk Score, according to statistical models.

McNeill AM, Rosamond WD, Girman CJ, Hill Golden S, Schmidt ML, East E et al (2005) The metabolic syndrome and 11-year risk of incident cardiovascular disease in the Atherosclerosis Risk in Communities study. *Diabetes Care* 28(2): 385–390

## DIABETOLOGIA

### Including glucose levels in CV risk

Readability	✓✓✓✓✓
Applicability to practice	✓✓✓✓
WOW! factor	✓✓✓✓

1 Most risk scores for cardiovascular (CV) mortality have included diabetes status, but results from a number of trials, including the DECODE Study, have pointed to glucose concentrations below threshold levels for diabetes diagnosis as an additional factor.

2 This article used the DECODE cohort (16 506 men and 8907

women from Europe) to develop CV mortality risk scores over 5 and 10 years' follow-up, adding non-diabetic glucose levels (either at fasting or after 2 hours) to well-established risk factors.

3 Glucose concentrations were predictive of 5- and 10-year CV mortality in men and women – after adjustment for study centre and age – both in single-factor and multiple-factor models.

4 Quantitative information for the prediction of CV risk is given by using glucose concentration as well as the status of diabetes.

Balkau B, Hu G, Qiao Q, Tuomilehto J, Borch-Johnsen K, Pyörälä K et al (2004) Prediction of the risk of cardiovascular mortality using a score that includes glucose as a risk factor. *The Decode Study. Diabetologia* 47(12): 2118–28

## DIABETES

### High adiponectin levels reduce CHD risk in men with type 2 diabetes

Readability	✓✓✓✓
Applicability to practice	✓✓✓
WOW! factor	✓✓✓

1 Adiponectin has anti-inflammatory properties and modulates insulin resistance and dyslipidaemia, which are both associated with elevated atherosclerosis in people with diabetes.

2 There is little evidence, though, for an association between high adiponectin levels and reduced coronary heart disease (CHD) risk in individuals with diabetes.

3 This association was investigated in 745 men with type 2 diabetes from the Health Professionals Follow-up Study.

4 The investigation suggested that there was a modest decrease in CHD risk with raised adiponectin levels, after adjusting for age, body mass index, diabetes duration and lifestyle factors; the association may be partially attributable to adiponectin's effect on HDL cholesterol.

Schulze MB, Shai I, Rimm EB, Li T, Rifai N, Hu FB (2005) Adiponectin and future coronary heart disease events among men with type 2 diabetes. *Diabetes* 54(2): 534–9

## DIABETOLOGIA

### Subclinical diabetic heart disease: prevalence and determinants

Readability	✓✓✓✓
Applicability to practice	✓✓✓
WOW! factor	✓✓✓

1 The stages of diabetic heart disease run from a normal heart, through preclinical left ventricular (LV) diastolic and systolic dysfunction and then clinically apparent LV dysfunction, to symptomatic heart failure.

2 Several compensatory mechanisms conceal the early stages of diabetic heart disease, and although there are new echocardiographic techniques with higher sensitivity (such as tissue Doppler and strain imaging), prevalence and determinants had not previously been established.

3 In this study, the 120 patients who met the inclusion criteria (an absence of both coronary artery disease and LV hypertrophy) underwent tissue Doppler imaging for systolic strain of each wall and diastolic and systolic velocity of each basal segment.

4 Twenty-seven per cent of patients with diabetes had significant subclinical LV dysfunction.

5 Myocardial systolic dysfunction (by peak strain) was independently predicted by HbA<sub>1c</sub> levels ( $P < 0.001$ ) and absence of angiotensin-converting enzyme (ACE) inhibitors ( $P = 0.003$ ).

6 Myocardial diastolic dysfunction was independently associated with hypertension ( $P = 0.001$ ), insulin ( $P = 0.008$ ), metformin treatment ( $P = 0.01$ ) and age ( $P = 0.013$ ).

7 ACE inhibitors and insulin therapy thus appear to be protective, while hypertension, metformin, age and poor glycaemic control are all linked to the relatively common condition of subclinical LV dysfunction.

Fang ZY, Schull-Meade R, Downey M, Prins J, Marwick TH (2005) Determinants of subclinical diabetic heart disease. *Diabetologia* 48(2): 394–402

**‘Several compensatory mechanisms conceal the early stages of diabetic heart disease, and although there are new echocardiographic techniques with higher sensitivity [...] prevalence and determinants had not previously been established.’**

**‘ACE inhibitors and insulin therapy thus appear to be protective, while hypertension, metformin, age and poor glycaemic control are all linked to the relatively common condition of subclinical LV dysfunction.’**

## DIABETOLOGIA

### Lipid lowering and glycaemic control reduce CHD risk

Readability	✓✓✓✓
Applicability to practice	✓✓✓✓
WOW! factor	✓✓✓

- 1 VLDL and intermediate-density lipoprotein (IDL) contribute to atherogenic cholesterol, particularly in people with high triglyceride levels.
- 2 Levels of non-HDL cholesterol (the sum of LDL, VLDL and IDL cholesterol) have thus been identified as a valuable measurement for managing dyslipidaemia in people with diabetes who have elevated triglycerides.
- 3 It is not certain, though, whether the relationship between non-HDL cholesterol and cardiovascular risk is dependent on hyperglycaemic status.
- 4 This prospective study followed 921 women with diabetes in the Nurses' Health Study, none of whom reported a diagnosis of cardiovascular disease before blood was first collected.
- 5 After adjusting for age, body mass index and major lifestyle risk factors, non-HDL cholesterol appeared to strongly predict the relative risk of coronary heart disease (CHD), especially in women with elevated fasting triglycerides.
- 6 There was a strong association between HbA<sub>1c</sub> and CHD risk, and non-HDL cholesterol and HbA<sub>1c</sub> additively predicted this risk.
- 7 The study suggests that therapies to reduce CHD risk in people with diabetes should take into account both the lowering of lipid levels and glycaemic control.

Schulze MB, Shai I, Manson JE, Li T, Rifai N, Jiang R, Hu FB (2004) Joint role of non-HDL cholesterol and glycated haemoglobin in predicting future coronary heart disease events among women with type 2 diabetes. *Diabetologia* 47(12): 2129–36

## DIABETES

### Cardiac insulin sensitivity linked to cardioprotection

Readability	✓✓✓
Applicability to practice	✓✓✓
WOW! factor	✓✓✓

- 1 The mechanism behind the increased risk of ischaemia-induced myocardial injury associated with type 2 diabetes is not clear.
- 2 This study investigated the effect on this risk of cardiac insulin sensitisation resulting from rosiglitazone treatment.
- 3 Rosiglitazone 3 mg/kg/day was administered to male Zucker diabetic fatty (ZDF) rats for 8 days.
- 4 This treatment was associated with a 58% reduction in the number of apoptotic cardiomyocytes and a 46% reduction in myocardial infarct size; this suggests that long-term rosiglitazone treatment in ZDF rats reduces the myocardial injury risk from ischaemia and reperfusion.
- 5 There was a relative lack of insulin sensitisation in ZDF rats treated for 2 days compared with those treated for 8 days.
- 6 Also, experimentally blocking the insulin–AKT signalling pathway with wortmannin in the ZDF rats treated for 8 days led to a markedly reduced cardioprotective effect.
- 7 Taken together, these last two findings suggest that the improvements seen in cardiac protection might be partly due to increased cardiac insulin sensitivity.
- 8 Further studies are suggested by the authors to help determine the extent to which cardioprotection comes from insulin-related and non-insulin-related mechanisms.

Yue TL, Bao W, Gu JL, Cui J, Tao L, Ma XL et al (2005) Rosiglitazone treatment in Zucker diabetic fatty rats is associated with ameliorated cardiac insulin resistance and protection from ischemia/reperfusion-induced myocardial injury. *Diabetes* 54(2): 554–62