Double diabetes: the cardiovascular implications of combining type 1 with type 2 diabetes

The current prevalence of double diabetes is 25% but this is projected to rise over the next few years. As Dr Steve Cleland here describes, we may need to widen our horizons and learn to spot patients with double diabetes in order to address cardiovascular risk at an earlier stage, and be prepared to use concurrent therapeutic strategies normally reserved for patients with type 2 diabetes.

The cardiovascular epidemiology of double diabetes
Type 1 diabetes (T1D) is associated with premature cardiovascular (CV) morbidity and mortality. Analysis of the Scottish Care Information-Diabetes database, involving 21,789 people with T1D vs 3,966 million non-diabetic population, revealed age-adjusted incidence rate ratios for first CV event of 3.0 in women and 2.3 in men. While there is a growing consensus that increased CV risk in type 2 diabetes (T2D) is driven largely by features of the metabolic syndrome with a much smaller component of risk, conferred by chronic hyperglycaemia, it is generally assumed that hyperglycaemia is the main CV risk factor in T1D, supported by demonstration of the long-term benefit (albeit modest) of a period of intensive glucose-lowering on CV outcome in the DCCT/EDIC study. However, closer inspection of epidemiological data from published T1D prospective cohorts reveals a more complex picture. Modelling predictive factors for major outcomes including coronary heart disease (CHD), stroke, end-stage renal failure, amputation, blindness and all-cause death in the EURODIAB study (n=1973), the Pittsburgh EDC study (n=2999), the FinnDiane study (n=2999) and the CACTI study (n=580) demonstrated that age, waist:hip ratio, HDL-cholesterol (HDL-C) and urinary albumin:creatinine were significant prognostic factors in addition to HbA1c, implying that some factors more usually associated with CV risk in T2D are also contributing to risk in T1D. Translating these findings to a clinical setting, it might be predicted that patients with T1D who also had risk factors for T2D by virtue of positive family history or unhealthy lifestyle (sedentary, central obesity) are at accelerated risk of CV complications. They might be described as having ‘double diabetes’.

Risk markers for surrogate features of CVD in type 1 diabetes
In T1D, coronary artery calcification (CAC) measured by computerised tomography (CT) is highly prevalent and strongly correlated with clinical and obstructive coronary disease. In a subgroup of the CACTI study, 40 patients with T1D and age-, BMI- and sex-matched control individuals underwent hyperinsulinaemic-euglycaemic clamp studies to measure a variety of metabolic parameters. In agreement with many other studies, patients with T1D had markedly lower whole-body insulin-mediated glucose uptake (insulin sensitivity less than 50% control values). They also exhibited reduced insulin-mediated non-esterified fatty acid suppression. Both measurements correlated (p<0.0001 within the T1D group) with CAC – the more insulin resistant, the higher the burden of coronary disease. Of additional interest, HbA1c did not correlate with either insulin resistance or CAC. Furthermore, 652 patients with T1D were re-examined after six years, as part of the prospective CACTI study. Baseline estimated insulin resistance predicted not only progression of CAC, but also albuminuria and retinopathy. Therefore, it appears that insulin resistance, a CV risk marker usually associated with T2D, is strongly predictive of coronary burden in T1D.

Another surrogate measure of atherosclerosis is carotid intima-media thickness (cIMT). In a study of 127 patients with T1D vs 125 matched controls, not only was cIMT significantly higher in T1D, but also in multivariate regression analysis, significant associations included BMI and positive family history of T2D. An emerging surrogate for coronary disease is epicardial adipose tissue (EAT). EAT thickness measured by cardiac magnetic resonance has been demonstrated to be an indicator for coronary artery stenosis in T2D. In T1D, EAT thickness measured by echocardiogram was increased (p<0.0001) in 36 patients compared with 43 matched controls, and within the patient group there were significant correlations of EAT with both waist:hip ratio (p=0.003) and estimated insulin resistance (p=0.0004). Furthermore, EAT volume was measured by cardiac CT in 100 patients with T1D who were part of the DCCT/EDIC study. After adjusting for age and gender, significant predictors of EAT volume were BMI, waist:hip ratio, HbA1c, triglyceride level and nephropathy.

Pathophysiological similarities between types 1 and 2 diabetes
The most obvious similarity between T1D and T2D is chronic hyperglycaemia but, as mentioned above, while HbA1c is important and likely to play a role in the development of macrovascular complications in T1D, it does not, in itself, predict clinical CV outcomes or surrogate atherosclerotic markers in prospective cohort studies. Perhaps surprisingly, insulin resistance is a consistent feature of T1D, irrespective of glycaemic control. When studied in more detail, physiological patterns share features found in T2D; for example: (1) there is resistance to insulin-mediated suppression of hepatic glucose output as well as to insulin-mediated glucose uptake in skeletal muscle; (2) peripheral carbohydrate oxidation and
muscle glycogen storage are reduced; and (3) there is a metabolic shift in mitochondria favouring fat oxidation over carbohydrate oxidation – i.e. decreased respiratory quotient.22

Linked to peripheral insulin resistance in T1D is another feature shared with T2D – increased skeletal muscle lipid content. When a group of slim T1D patients with good glycaemic control were compared with a matched control group, significantly higher levels of intramyocellular triglyceride (assessed by magnetic resonance spectroscopy) were demonstrated in the patients.23

Taken together with the EAT findings described above, it appears that T1D is characterised by increased ectopic fat deposition in a similar pattern to T2D, except that, of course, BMI tends to be much lower in T1D compared with classic T2D/metabolic syndrome. Therefore, it might be hypothesised that the threshold for ectopic fat deposition (and subsequently CV risk) for any given BMI or waist:hip ratio is much lower in T1D than in T2D, meaning that even subtle features of the metabolic syndrome could drive accelerated atherosclerosis in T1D. To understand why this might be, we need to focus on the liver, where there are several markedly contrasting features between T1D and T2D.

### Contrasting features of types 1 and 2 diabetes

The most striking difference between T1D and T2D is portal vein insulin level (Figure 1). Seventy-five percent of blood supply to the liver is via the portal vein and 50–80% of portal vein insulin is cleared by first-pass hepatic metabolism.24 T1D is characterised by portal insulinopenia secondary to beta-cell failure, while T2D is characterised by portal hyperinsulinaemia, secondary to hepatic and peripheral insulin resistance. Insulin promotes the deposition of hepatic fat by stimulating sterol regulatory element-binding protein 1c, which plays a crucial role in the regulation of triacylglycerol accumulation in the liver.25–27 It follows, therefore, that in T1D lack of portal insulin would result in a shift from fat storage in the liver to fat oxidation. While T2D is often associated with non-alcoholic fatty liver disease, it might be predicted that T1D would demonstrate the opposite phenotype. This has now been confirmed in several studies using magnetic resonance imaging and spectroscopy: reduced liver fat was demonstrated in lean patients with T1D compared with matched controls28 and also in children with T1D.29 Of particular interest is a study in overweight (BMI 28.9kg/m²) patients with T1D compared with a matched control group. This demonstrated a marked reduction in liver fat in the patients (0.6%) compared with controls (9%).30 In the context of these findings, it is tempting to speculate a mechanism for increased CV risk in T1D. Chronic basal under-insulinaemia will lead to increased lipolysis in visceral adipose stores. Excess circulating non-esterified fatty acids will not be ‘mopped up’ and stored in the liver so effectively due to portal insulinopenia. Therefore, ectopic fat distribution is promoted in other sites including skeletal muscle (exacerbating insulin resistance) and intrathoracic sites (including epicardial and perivascular fat, with implications for local pro-inflammatory adipokine delivery to crucial vascular beds, e.g. coronary).

Another difference between T1D and T2D is the pattern of lipoproteins. T2D and metabolic syndrome are generally characterised by low HDL-C and high triglycerides. In T1D, the opposite pattern is seen. For example, in the study of overweight T1D patients referred to above, HDL-C was higher (1.7) than in matched controls (1.2) and triglycerides were lower (0.9 vs 1.4).31 Several mechanisms, again linked with portal insulinopenia, have been suggested to explain this phenomenon.31 High HDL-C levels are likely to be atheroprotective32 and patients with T1D who have CHD events have been shown to have lower HDL-C and higher triglycerides.32 Therefore, it is possible that via this mechanism T1D could actually confer a cardioprotective state, as long as ectopic fat redistribution and chronic hyperglycaemia were minimised – the Golden Years cohort may be a living testimony to this combination.21

### Prevalence of double diabetes

The largest cross-sectional study of double diabetes to date involves over 31 000 T1D patients from 392 clinics in Germany and Austria.33 Patients were labelled as having double diabetes if they fulfilled at least two out of three of the NCEP criteria for metabolic syndrome. The prevalence of double diabetes according to this definition was 25.5% – patients in this group were older (45 vs 36...
years), had longer duration of T1D (18 vs 15 years) and were diagnosed with T1D at an older age (27 vs 21 years). Patients with double diabetes had significantly more coronary disease (8% vs 3%) and cerebrovascular disease (3.6% vs 1.6%); they also had more retinopathy (32% vs 22%) and nephropathy (28% vs 18%) consistent with findings across the prospective cohort studies.33–35 Furthermore, total daily insulin requirement per kg bodyweight was significantly higher in patients with double diabetes (0.865 vs 0.801U/kg) despite poorer HbA1c (69 vs 64mmol/mol), indicating insulin resistance.33

It seems likely that incidence and prevalence will rise over the next decade, mainly driven by socio-cultural trends in BMI. For example, in the Pittsburgh EDC prospective cohort between 1987 and 2007 the prevalence of obesity rose sevenfold (to 22.7%) and overweight increased by 47% (to 42%).36 Also contributing to weight gain in T1D is improvement in glycaemic control through intensive insulin regimens and encouragement of ‘normal eating’ with carbohydrate counting. In the EURODIAB study, in which 1800 patients were followed up for seven years, those who gained more than 5kg over this time had slightly better HbA1c (2mmol/mol) than those with less or no weight gain, but had higher BP, LDL-C and triglycerides in association with lower HDL-C.37 Therefore, some patients with T1D may be at increased risk of double diabetes by virtue of environmental obesogenic influences combined with intensive insulin regimens and the drive for improved HbA1c, possibly conferring increased CV risk.

**Double diabetes: clinical implications**

The mainstay of treatment for T1D is optimisation of glycaemic control through multiple-dose intensive insulin regimens or insulin pump therapy with a view to minimising future microvascular complications, especially retinopathy. This approach also has a significant effect on CV risk reduction, as demonstrated in the DCCT/EDIC study, although, as described above, the predictive power of HbA1c on CV outcome is relatively small and other factors more traditionally associated with T2D (central obesity, HDL-C and BP) appear to be important. Therefore, as diabetes health care professionals, we may need to widen our horizons and learn to spot patients with double diabetes in order to address CV risk at an earlier stage and be prepared to use concurrent therapeutic strategies normally reserved for patients with T2D.

For example, a 35-year-old man with T1D (diagnosed aged 14) may present at clinic with excellent HbA1c and no history of microvascular complications. We might congratulate him and spend time talking about hypoglycaemia and potential loss of awareness with tight control; we might discuss new technologies and lifestyle issues such as driving and alcohol intake. We might not notice that he has been gaining a significant amount of weight over the past five years, predominantly in a central distribution (BMI rising from 26 to 29kg/m²), and we may never have asked him about his strong family history of T2D. It is unlikely that we would have noticed a fall in HDL-C from 1.7 to 1.2mmol/L over the past 10 years or a subtle rise in systolic BP over the same period from 125 to 139mmHg. We probably haven’t discussed aerobic exercise in the context of healthy lifestyle and weight maintenance, although we may have discussed the interaction of exercise and hypoglycaemia. This patient is likely to be developing double diabetes.

How could we expand our approach? We could explain to him that he is displaying features of the metabolic syndrome, and that, if he hadn’t already been diagnosed with T1D, he might have been at higher risk of developing T2D in his 40s or 50s. We could explain that there is increasing evidence that double diabetes is associated with a higher risk of future CV complications, which might partly explain why men with T1D have a three-fold incidence of CV events irrespective of chronic glycaemic control – this might be due to exaggeration of an atherogenic T2D phenotype in T1D patients secondary to altered liver physiology. We might go on to spend some time talking

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**Features of double diabetes**

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<td>• Soedamah-Muthu SS, et al.²¹</td>
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**Evidence**

- Long-term survivors of T1D typically exhibit a phenotype that is ‘opposite’ to that of T2D
- For a given degree of metabolic syndrome, T1D may have a lower threshold for developing shared T2D pathological features, e.g. insulin resistance, ectopic fat deposition, shift to fat oxidation
- The liver phenotype in T1D is ‘opposite’ to that in T2D in terms of liver fat and lipoprotein output. Imposing T2D features on this may result in adverse CV consequences via ectopic fat deposition and a more atherogenic lipid profile
- Prevalence of double diabetes is 25% of T1D, but may vary depending on how it is defined. It is likely that the incidence will continue to rise due to the combination of an obesogenic environment and tightening of glycaemic targets

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about weight loss strategies and promotion of aerobic exercise, and we might even consider adding metformin for insulin-sparing and weight-maintenance benefits. We could consider lower thresholds for introduction of lipid-lowering and BP-lowering drugs.

**Summary and conclusions**

The incidence of CV disease in T1D is up to three-fold that in the background population. Prospective cohort studies have revealed that chronic glycemic control is not the predominant predictive factor for CV disease – in fact, risk factors more commonly associated with T2D (e.g. waist:hip ratio, HDL-C) appear to be more predictive of CV outcome in T1D. Long-term survivors of T1D (low CV risk) exhibit a phenotype ‘opposite’ to T2D (low BMI, high HDL-C, insulin sensitive). Therefore, it appears that there is an interaction between T1D and a T2D phenotype which accelerates macrovascular complications – so-called double diabetes. Surrogate markers of atherosclerosis such as CAC, cIMT and epicardial fat have been shown to be increased in T1D compared with matched controls, and these are strongly correlated with either direct or indirect measurement of insulin resistance. Despite having entirely different aetiologies, T1D and T2D share a number of pathophysiological features including insulin resistance, reduced respiratory quotient and increased muscle and epicardial fat stores. However, liver phenotypes are markedly different, mainly due to contrasting levels of portal vein insulin between T1D and T2D. This could account for the paucity of liver fat in T1D as well as the ‘anti-atherogenic’ lipid profile (which includes relatively high HDL-C levels), both of which are likely to have implications for circulating lipids, ectopic fat storage and atherogenesis in T1D.

The current prevalence of double diabetes is 25% but this is likely to rise over the next few years due to cultural and societal influences on population BMI as well as improvements in glycaemic control with intensive insulin regimens and improved use of technologies. Awareness of double diabetes will hopefully allow patients to be spotted early, with lower thresholds for advice on caloric reduction and aerobic exercise, consideration of metformin and introduction of primary preventative drugs such as statins and antihypertensives.

Further research is required in double diabetes, especially to assess the impact of lifestyle and drug interventions on CV outcomes and surrogate measures. In this context, the results of the REMOVAL trial were announced in June 2017 – this is a multicentre RCT of metformin vs placebo in T1D patients with carotid IMT as the primary outcome measure.  

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