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Biomarkers of vascular complications in type 2 diabetes

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ABSTRACT

People with T2D are at substantially increased risk of developing severe complications, (coronary heart disease, stroke, retinopathy and nephropathy). Clinicians have an important responsibility to identify those patients who, because they are at high risk, will benefit more from a preventive program or intensified therapy. However, due to the limited accuracy of the predictive tests, and limited effectiveness of preventive measures, clinicians and their patients show a suboptimal compliance to such programs. An improved risk assessment will positively impact cost/benefit ratios, opening the door for new intervention. Research involving human genetic or genomic information becomes increasingly powerful and, in conjunction with other novel biomarkers, together with personal or health data, will offer new tools for harnessing risk factors underlying complex (multi-factorial) diseases such as T2D and its complications. Altogether, there is a rationale to develop early biomarkers with improved predictive value for vascular complications of T2D by integrating patients' genetic information with traditional and emerging biomarkers.

1. Introduction

The International Diabetes Federation reports that 382 million people worldwide are estimated to have had diabetes, mainly T2 diabetes in 2013.This number was 194 million in 2003 and if these trends continue, some 592 million people, (a 55% increase from 2013), will have diabetes by 2035 [1] People with T2D are at substantially increased risk of developing complications, both macrovascular (coronary heart disease and stroke) and microvascular (retinopathy and nephropathy). In spite of highly encouraging capacity to improve morbidity/mortality of T2D (by intensifying blood pressure and glucose control, such as accomplished in the ADVANCE trial [2,3] about 40% of T2D patients will develop complications which may ultimately lead to death. Likewise, while intensive multifactorial interventions can reduce the incidence of complications, the costs of such strategies exceed the resources of healthcare systems in even the most affluent countries particularly in the light of ever increasing numbers of diabetic patients [4] with complications. Moreover recent literature

Abbreviations: ACS, Acute coronary syndrome; ADVANCE, Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation; AHA, American Heart Association; CVD, cardiovascular diseases; CKD, chronic kidney disease; CKDGEn, Chronic kidney disease genetics; CAD, coronary artery disease; CK-MB, creatine kinase-MB; DN, Diabetic nephropathy; eGFR, Estimated glomerular filtration rate; GWAS, Genome-Wide Association Studies; LD, high-linkage disequilibrium; hsCRP, high-sensitivity CRP; IL-6, interleukin-6; KCNE2, potassium voltage-gated channel, Isk-related family, member2; LDL, low-density lipoprotein; miRNAs, microRNAs; MRPS6, mitochondrial ribosomal protein S6; MIGEN, Myocardial Infarction Genetics Consortium; PHACTR1, phosphatase and actin regulator 1; PCSK9, proprotein convertase subtilisin/kexin type 9; ST, ST segment; cTnt, connects the QRS complex and the T wave in an electrocardiogram, cTroponin test; NT-proBNP, N-terminal pro-BNP; UKPDS, U.K. Prospective Diabetes Study; WDR12, WD repeat domain 12; WTCCC, Wellcome Trust Case Control Consortium.

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points towards increasing incidence of T2D at younger age [5] and, even more importantly, with earlier penetrance of complications including hypertension and kidney function impairment [6,7]. There is, therefore, a need to identify those patients at higher risk of developing complications earlier, since the cost increases with the severity and early, presymptomatic stage interventions are usually more efficient as well as less costly. It is relevant for the discussion here, that genomic influences preponderate over environmental ones at younger age, we may focus on discoveries in that young stratum of patients.

1.1. *Biomarkers of coronary artery disease in T2D*

Acute coronary syndrome (ACS) is a category of coronary artery disease (CAD). For example, CAD can be asymptomatic, but ACS almost always presents a symptom such as unstable angina or myocardial infarction though in diabetics the severity and type of symptoms are often attenuated and *silent* myocardial infarct is diagnosed only *a posteriori*. ACS is a significant cause of morbidity and mortality worldwide. ACS results from a sudden blockage in a coronary artery. This blockage causes unstable angina or myocardial infarction depending on the location and amount of blockage. ACS types are currently classified according to ST elevation (ST segment connects the QRS complex with the T wave in an electrocardiogram) myocardial infarction (STMI, 30%), non ST elevation myocardial infarction (NSTEMI, 25%), or unstable angina (38%). The term acute myocardial infarction (MI) should be used when there is evidence of myocardial necrosis in a clinical setting attention consistent with acute myocardial ischaemia. Currently, troponin is the gold standard biomarker for myocardial injury and is used commonly in conjunction with creatine kinase and myoglobin (CK-MB) and myoglobin to enable a more rapid diagnosis of ACS. Other markers of myocardial necrosis, inflammation and neurohormonal activity have also been shown to have either diagnostic or prognostic utility, but none of them have been shown to be superior to troponin. The measurement of multiple biomarkers and the use of point of care markers may accelerate current diagnostic protocols for the assessment of such patients.

As a prognostic tool, C-reactive protein (CRP) may be useful in patients with ACS in which high CRP levels (10–15 mg/L) are a strong indicator of long-term future cardiac events, while the evidence for CRP as a predictor of short-term events is conflicting. In another study of patients with MI treated with thrombolysis, high CRP levels (226 mg/L) were associated with an increased risk of death within the first 6 months of the infarct event. It has also been shown that CRP is raised in patients with unstable coronary syndromes, but specificity and sensitivity are not sufficient for use as a reliable diagnostic marker. It is, however, a significant predictor of poor outcome. In 2003, the American Heart Association (AHA) and the Centre for Disease Control and Prevention issued a scientific statement that suggested the use of high-sensitivity CRP (hsCRP, from 0.5 to 10 mg/L) as an optional risk factor measurement in patients with ACS [8]. The future of biomarkers in the outcome prediction and/or detection of myocardial injury may call for a multimarker approach for diagnosis and prognosis. A study using cTnT, CRP, and NT-proBNP showed that elevations in 2 or 3 of these biomarkers predicted worse outcomes than those with 1 biomarker alone [8].

While risk factors for cardiovascular diseases (CVD) in general have been extensively studied in the general population, such studies in T2D are relatively limited. Adler [9] developed a UKPDS risk engine, available online, providing a risk probability that a patient will develop angina, myocardial infarction, stroke, peripheral vascular disease or will die from cardiovascular complications, in the next 10 years. A more contemporary model for predicting cardiovascular risk in people with T2D has been developed based on the ADVANCE trial [10,11]. Age at diagnosis, known duration of diabetes, sex, pulse pressure, treated hypertension, atrial fibrillation, retinopathy, HbA1c, urinary albumin/creatinine ratio and non-HDL cholesterol at baseline were the most significant predictors of cardiovascular events. However, these risk factors, although useful, are generally of limited predictive value (usually below 70%) as recently evaluated [10] and they do not take into account patients genomic background. Noticeably, almost half of these outcome predictors are actually surrogates or markers of existing target organ damage rather than predictors. The challenge here is to replace these markers of target organ damage by real predictors (Fig. 1).

People with diabetes have higher levels of hsCRP [12] and fibrinogen [13] compared to those without diabetes. A recent case-cohort study composed of 3865 patients with T2D who participated in the ADVANCE trial, showed that three biomarkers of inflammation (IL-6, hsCRP and fibrinogen) were associated with an increased risk of macrovascular events and death in analyses adjusted for age, sex, and treatment groups. However, after further adjustment, only IL-6 was shown to be an independent predictor of macrovascular events (hazard ratio per SD increase 1.37 [95% CI 1.24-1.51]) and death (1.35 [1.23-1.49]). It has to be noted that none of these three markers predicted microvascular complications [14].

1.2. *Genomic markers of coronary artery disease*

Recent technological progress, allowing routine determination of over a million markers on a single chip, has paved the way to Genome-Wide Association Studies (GWAS). These studies allow the determination of genomic contributions in a variety of diseases including CVD. More than 580 genomic variants have been associated to CAD in several GWAS according to PheGenI database. Although most of the cohorts included T2D patients (from 10 to 50%), none of the GWAS reported genomic variants associated to CAD in T2D patients only. Variants at the 9p21.3 locus have been established as the strongest common genetic factors associated with the risk of CAD in people of European ancestry and even in some non-European populations (e.g., East-Asians). [15]. In addition to 9p21, several other loci have been mapped and replicated in independent populations. The Wellcome Trust Case Control Consortium (WTCCC) identified a SNP (rs2943634) located in a non-coding region of chromosome 2q36.3, to be associated with CAD and further reports suggest that this SNP is associated also with ischemic stroke risk and with plasma levels of HDL-cholesterol and adiponectin [16]. Three other