Biomarkers and prediction models for type 2 diabetes and diabetes related outcomes

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Chapter 1

Biomarkers for prediction of type 2 diabetes: clinical and methodological views

Introduction

Type 2 diabetes (T2D) is a multi-factorial disease which can be diagnosed by levels of plasma glucose (≥7 mmol/l) or HbA1c (≥6.5%) in the circulation [1, 2]. In fact, glucose and HbA1c are two major biological clues of which variation below the diagnostic threshold is strongly predictive of future risk of T2D, particularly within a time frame of 5 to 10 years before the actual diagnosis of T2D [3]. In clinical practice, all measurable biological clues are called "biomarkers", irrespective of whether the biological clue is obtained from physical examination of the body (i.e. blood pressure or blood tests) or anywhere else from medical history [4]. From a public health perspective, T2D has become an increasing global health burden, with an increase in the number of people with diabetes by 2-3 fold between 1985 and 2008 [5]. In 2008, age-standardised (to the WHO reference population) prevalence of T2D was 9.8% in men and 9.2% in women worldwide. The majority of people with diabetes worldwide (40%) come from India and China. For china, this estimate was 9.6% in men and 9.4% in women. For The Netherlands, this estimate was 6.1% in men and 4.1% in women, while, for Iran, these estimates were 9.3% and 10.5%, respectively [5]. The emerging pandemic is presumably driven by the combined effects of population ageing, rising rates of obesity and unhealthy lifestyle related to prosperity [6]. Meanwhile, the prevalence of obesity and T2D is shifting to younger ages, increasing the lifetime burden of T2D and diabetes-associated co-morbidities, including cardiovascular disease (CVD) and renal disease [7].

Good news is that T2D and most likely its complications are preventable [8, 9]. To reverse future projections on the increasing prevalence of T2D, early identification of individuals at high risk for T2D is essential for early implementation of targeted prevention strategies [10, 11]. Of course, such a targeted strategy should be complementary to a general population strategy of reducing well-known risk factors for T2D, such as smoking, sedentary lifestyle and a high-calorie diet [9]. However, given limited healthcare resources, risk classification of the population will aid in avoiding implementation of interventions in a very large number of individuals who are at low-risk for T2D [10, 11].

What makes prediction different from etiologic research?

From an epidemiological perspective, we can investigate risk factors that might be causally related to disease. In this type of research, the strength of the association is usually expressed in a relative sense: a relative risk, or, if time of onset of disease is known, a hazard ratio [12]. This type of study, called "etiologic research" is performed to investigate the risk of disease by levels of risk factors such as biomarkers [13]. For example, parental history of T2D is known to be associated with an increased risk of T2D (2.9 fold higher risk of T2D) [14, 15]. A relative risk of two or three tells us that a person with parental diabetes has 2-3 fold higher risk of T2D when compared to another person, of similar age, gender and possibly other characteristics, but without

parental history of diabetes. Those factors that are etiologically linked to the outcome of disease are good candidates to include in prediction models (or risk scores) [16-19]. Clearly, also factors that are a consequence of the disease may be good predictors, since they may reflect the early stages of a pathological process. Importantly, in prediction modelling it does not matter whether markers are causally related to the development of T2D, or a consequence of disease, as long as the marker has the capacity to distinguish between those who will develop the disease or the complication and those who will not [18, 20]. The product of "prediction research" is a prediction tool providing absolute estimates of disease risk in the future [16]. To estimate risk of future T2D, the use of a reliable and practical scoring tool/questionnaire is recommended. Of course, a valid tool can also help to inform patients about the future – expected –course of their illness, and can guide doctors and patients in decisions on further treatment.

How to assess performance of prediction models?

For early identification of individuals at high risk for T2D, accurate prediction of future T2D is of utmost importance. To date, many prediction models for T2D have been developed in different settings and populations [10, 11, 19, 21]. In general, prediction models perform less well in other populations than the population in which it was developed. The poor performance is because of inherent deficiencies in the development of prediction models, like an over-fitted model or lack of important predictor(s) [22]. Therefore, external validation of such models in independent populations and datasets is an essential step to broadly evaluate the performance of such models [11]. External validation is also relevant because treatment and characteristics of populations may change over time.

To assess the performance of a prediction model, epidemiologists and statisticians propose two essential measures; discrimination and calibration [11, 22-24]. Discrimination describes the ability of the model to distinguish those at high risk of developing T2D (or those who will get the disease) from those at low risk (those who will not get the disease) [11, 12]. It is evaluated using the area under the curve (AUC) of a receiver operating characteristic curve (ROC curve) (Figure 1). For a binary outcome, the AUC is identical to the C-statistic [13]. This ROC-curve is derived from the specificity and sensitivity of the model. For a certain cut-off point (a score), sensitivity and specificity can be determined. Sensitivity is the percentage of individuals who are correctly identified as cases. Specificity is the percentage of individuals who are correctly identified as non-cases. A ROC-curve plots the sensitivity against 1-specificity for a large number of possible cut-off points, and is thereby a general measure for overall predictability [13]. Calibration addresses whether the estimated absolute risk is in agreement with the observed risk (e.g. incident T2D) [13]. This can be visualized by calibration plots (Figure 2). In a calibration plot, the estimated risk is plotted against the observed incidence of the outcome. Ideally the estimated risk equals the observed incidence throughout the entire risk spectrum and the calibration plot follows the 45° line [11, 13, 25]. Calibration is also tested using the Hosmer–

Lemeshow (H-L) goodness-of-fit statistic (or Chi²-test). A lack of significant difference is then interpreted no difference between observed and estimated risks, and indicates a good 'model fit' [13]. Even with good discrimination, calibration may be insufficient in an external validation, since the absolute risk strongly depends on the incidence of the disease in the development population and on population characteristics like age [11, 26]. In order to overcome such differences between a development and validation population, a first step is recalibration of prediction model by adjusting for the difference in incidence of the disease [11, 23]. In this step, the intercept (for logistic regression models) or the baseline survival function (for survival regression models) of the original prediction model will be updated or adjusted to the new circumstance [11, 23, 27, 28].

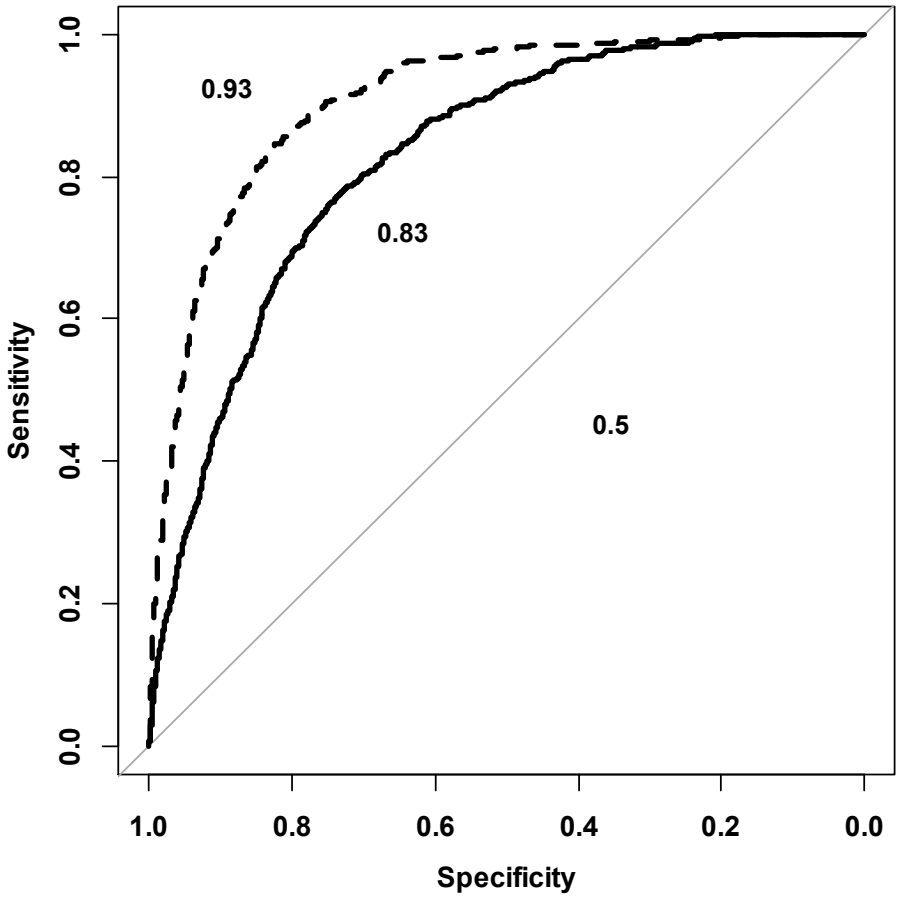

Figure 1. Hypothetical receiver operating characteristic (ROC) curves for prediction of type 2 diabetes. The C-statistics for models were 0.83 and 0.93, indicating good to excellent discrimination. A C-statistic of 0.5 is considered as threshed of random chance, indicating discrimination not better than tossing a coin.

Other prognostic measures such as the net reclassification improvement (NRI) or the integrated discrimination improvement (IDI) will be calculated to address the improvement in prediction of disease by adding a (bio)marker to a validated model [12, 13]. For the NRI, it is necessary to have a validated prediction model that uses risk

categories, such as 'low', 'intermediate' or 'high' risk. The NRI "measures" to what extent the new model that incorporates new biomarker(s) leads to improvement in classification. Improved classification is determined by upward movement in categories for individuals who will get the disease, and downward movement for individuals who will not get the disease. The IDI is a continuous version of the NRI without a priori defined risk categories [12, 29].

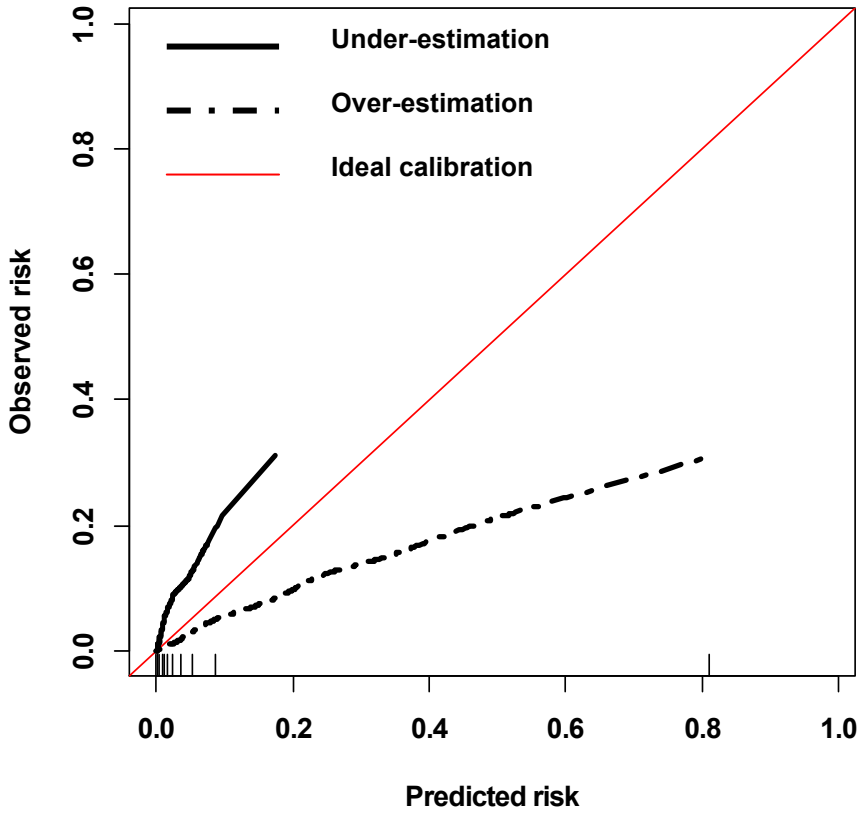

Figure 2. Hypothetical calibration plot depicting predicted risk against observed risk of type 2 diabete. The red line (the 45° line) from zero denotes ideal calibration line (slope=1, intercept=0), the solid line denotes smooth calibration curve for a model with under- estimation of the risk and the dotted line for a model with over-estimation of risk.

To what extent biomarkers could improve prediction of T2D?

Observational epidemiological studies have identified associations of many well-known or emerging biomarkers with risk of development of T2D and its associated complications [20, 30-37]. In principle, prior studies suggest that the risk of future T2D can differ by levels of a given biomarker. Whether intervention at the level of a given biomarker is useful will depend on whether the biomarker is "causal" to T2D or not.

If the biomarker is not causally related, the process of developing T2D may cause an increase or decrease in the levels of biomarker, as one of the consequences of T2D. Etiologic research for causal biomarkers provides better insights into mechanism of T2D and perhaps introduces targets for (pharmacological) intervention and treatment. Moreover, research for prognostic biomarkers might improve prediction of T2D and have implications for early prevention of T2D. From clinical perspectives, the main application of a biomarker lies within risk stratification and guided preventive strategies for the outcome [12, 34, 38]. In this phase, candidate biomarkers, either causal or not, are added to the validated prediction models to examine which biomarkers have incremental predictive value on top of the models. For example, in the Framingham Offspring Study, several risk scores have been developed for the prediction of T2D [39]. A simple model, incorporating data on age, sex, parental diabetes and body mass index, correctly classified 72% of cases and non-cases. Addition of well-known biomarkers, including fasting glucose, blood pressure, high-density lipoprotein cholesterol (HDL-C) level and triglyceride level yielded a significant improvement in discrimination to a level of 85% of correct classification. Next, addition of C-reactive protein, insulin sensitivity and resistance indices showed no further improvement. In the Data from an Epidemiological Study on the Insulin Resistance Syndrome (DESIR) cohort [40], the clinical prediction model that included waist circumference, hypertension, family history of diabetes (in women) and smoking (in men) showed C statistics of 71.3% and 82.7% for men and for women, respectively. The addition of known biomarkers such as fasting glucose, triglycerides and gamma-glutamyl transferase considerably increased the discriminative power (up to 85% for men and 91.7% for women). Further addition of genetic risk factors added little to the prediction of diabetes in the DESIR study. This is consistent with another study in which a genotype score provided slightly better prediction for risk of T2D on top of common diabetes risk factors [41]. One explanation is that the contribution of some genetic variants on T2D risk are effectuated through the intermediate risk factors [41]. So far, the incremental predictive value of most known and novel biomarkers above validated model(s) for T2D is still unclear. Independent studies evaluating utility of the measured markers when incorporated in validated prediction model(s) are needed to answer this question [20, 38, 42].

Outline and aims of the thesis

This thesis is conducted within the framework of the Center for Translational Molecular Medicine (CTMM), a public-private consortium dedicated to the development of medical technologies that enable the design of new and "personalized" treatments for the main causes of mortality and diminished quality of life and the rapid translation of these treatments to the patient. The aim of the PREDICCt project, a CTMM project, entitled 'Biomarkers for the PREdiction and early diagnosis of DIabetes and diabetes-related Cardiovascular Complications', is to identify biomarker for the prediction and early detection of diabetes and its

complications. The aim of work package 7 of Predicct is "the validation of biomarkers in large prospective cohorts". The aim of this thesis, within the work package 7 of the PREDICCt project, is to identify biomarkers with added predictive value for risk of future T2D.

The first part is aimed at validating and updating existing prediction models for the risk of T2D in Dutch population-based cohorts. In **Chapter 2**, we will systematically search the literature to identify existing prediction models for the risk of future T2D and to externally validate the retrieved models in the Dutch contribution of the large European Prospective Investigation Into Cancer and Nutrition cohort study (EPIC-NL). **Chapter 3** describes the validation and update of the prediction models (from the KORA S4/F4 study) for T2D in the Prevention of Renal and Vascular Endstage Disease (PREVEND) study. **Chapter 4** will focus on incremental predictive value of liver function tests compared with the KORA models in EPIC-NL and PREVEND, separately.

The second part of thesis focuses on associations of conventional risk factors with risk of T2D and investigation of novel biomarkers for risk of T2D (etiologic research). Next, we evaluate incremental predictive value of novel biomarkers for risk of T2D and CVD (prediction research). In **Chapters 5** and **6**, we will investigate the associations of parental history of diabetes– specified to maternal and/or paternal transmission– with risk of incident T2D and cardio-metabolic biomarkers. We also explore associations of novel risk factors, such as inflammatory biomarkers, lipid markers, CRP and procalcitonin with the determinants of obesity, the metabolic syndrome, insulin resistance, kidney function and risk of incident T2D in **Chapters 7, 9** and **10**. In **Chapter 8**, we aim to test whether the association of a novel stress system biomarker, named copeptin, with T2D is independent of other predictors including clinical variables and more established biomarkers like glucose, CRP and urine albumin excretion. **Chapter 9** describes the associations of HDL-cholesterol, apolipoproteins and HDL particle composition with risk of incident T2D in the PREVEND study. In **Chapter 11**, we will study, a novel circulating biomarker with antioxidant properties, to be associated with the common risk factors of CVD and risk of incident CVD and all-cause mortality. We also examine the incremental predictive value of the marker compared with the Framingham risk score in terms of discriminative ability and net reclassification. In general discussion chapter, we provide an overview of concepts around screening and prediction of T2D, validation of prediction models and the incremental value of known and novel biomarkers for mid-term risk of T2D and CVD. Future perspectives focus on direction of observational studies for the estimated risk of T2D and its complications over the lifetime.

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