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

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Chapter 12

Prediction of type 2 diabetes and diabetes-related outcomes

Diabetes mellitus is a common disease with a large health burden. The prevalence of diabetes is increasing worldwide. Over four decades, prevalence of diagnosed diabetes increased from 1-2% (in 1970s) to 8-12% (in 2010s) in European adults ^{1, 2}. One reason for this rise is that definitions of diabetes varied over time ²⁻⁴, with a reduction of the diagnostic threshold of fasting plasma glucose concentration from 7.8 mmol/l to 7.0 mmol/l as largest step in 1997 ^{5, 6}. Another reason lies in the rising rates of obesity, unhealthy lifestyle and aging of populations ⁷. Yet another reason is the increase in intensity of screening for diabetes that has occurred during the past decades ⁷. In 1975, dr F. Gerritzen stated that only half of patients with diabetes are aware of their disease and that the other half should be identified by screening ¹, but this is not true anymore. Nowadays, the American Diabetes Association recommends screening of asymptomatic adults of any age who are overweight or obese, and who have one or more additional risk factors for diabetes ^{4, 8}. This has resulted in a sharp decline in prevalence of undiagnosed diabetes in individuals with obesity ⁹. Also in Europe, the prevalence of undiagnosed diabetes has decreased over time. It is likely that the low prevalence of undiagnosed diabetes (< 20%) reported in recent studies ¹⁰⁻¹², is actually an overestimation of the current state. Importantly, recent evidence shows that this early screening has benefits in terms of reduction of diabetes-related complications, morbidity and quality of life ^{8, 13, 14}.

Although type 2 diabetes has a heterogeneous, multi-factorial nature and is caused by interplay of genetic and environmental factors ¹⁵, current evidence shows that the disease can undoubtedly be prevented or delayed by lifestyle modification ¹⁶⁻¹⁹. European evidence based guidelines ²⁰ and the International Diabetes Federation ²¹ recommend the use of a reliable, simple, and practical risk scoring system or questionnaire to identify people at high risk of future diabetes. In the past 20 years, many studies have described risk scores or predictive value of traditional risk factors (such as metabolic syndrome) for type 2 diabetes over a wide range of populations ²²⁻²⁶. These risk scores generally are presumed to leave much room for improvement. Therefore, interest has grown in the prospect of addition of novel biomarkers to existing models to improve prediction of diabetes and diabetes-related outcomes. More accurate estimation of risk is critical to allocating resources and planning preventive strategies.

Here, we aim to first describe the current knowledge of prediction of type 2 diabetes. The second part focuses on traditional risk factors of diabetes and predictive value of novel biomarkers for type 2 diabetes and diabetes-related outcomes. The last part describes future perspectives on study of biomarkers and modelling for type 2 diabetes.

Existing prediction models for type 2 diabetes

While population-based screening for undiagnosed diabetes in population remains hotly debated ^{27, 28}, early identification of people at high-risk for future development

of type 2 diabetes is essential for timely initiation of targeted prevention programs at different ages. Age itself is a strong predictor of diabetes and diabetes-related outcomes^{23,24}, although the worldwide epidemic is shifting prevalence of diabetes to younger ages²⁹. This will increase the burden of disease, as the duration of diabetes is elongated.

Since the last decade, major efforts were aimed at developing risk scores or prediction models to estimate absolute risk of future type 2 diabetes at a 5-10 year (short-term) horizon. First, recent systematic reviews have found that the existing prediction models differ considerably in terms of characteristics of population, type and number of predictors, age ranges, duration of follow-up and outcome measure; but only few studies have validated and compared diabetes risk scores²²⁻²⁵. The performance of a prediction model is generally overestimated in the population in which it was developed^{25, 30, 31}. This overestimation is inherent to the process of development of a risk score^{23,30,31}. However, many studies do not assess the amount of optimism in the development dataset. The first step that can be taken is to adjust for this overestimation, by a process called internal validation³⁰⁻³². At the development level, this approach involves splitting the dataset into two parts, using one of the portions for the development of a model and another one for the validation of it. Other methods such as cross-validation or bootstrapping can be used at this stage^{30,31}. The next step is external validation of prediction models in an independent population. This is essential to evaluate the performance of such models^{25, 26, 30, 31}. Consequently, prediction models to identify those at high risk of diabetes cannot be recommended for more general use when external validity is unknown²⁵. A direct comparison of the performance of existing models in the same (external) validation cohort can bridge the gap between the development of models and the conduct of studies for clinical utility^{22, 24-26}.

In **Chapter 2**, we applied a more comprehensive approach by first conducting a recent systematic review to retrieve the most relevant existing models for predicting the risk of future type 2 diabetes^{25,26}. Then, we used various analytical measures for validating and comparing their predictive performance^{25, 32}. We have shown that most of current risk scores are valid tools to discriminate between high-risk and low-risk individuals within this time frame^{25,33}. In other words, the discriminative ability of basic risk scores (based on non-invasive variables) was good and ranged from 74% to 84%. These results were in line with the discrimination observed in other population-based cohorts^{24, 25, 33}. Among the basic risk scores, we found that those scores including 4-6 predictors performed similar to the more extensive scores in terms of discrimination²⁵. For instance, two basic risk scores – KORA basic (derived from the Cooperative Health Research in the Region of Augsburg study) and DESIR clinical equation (derived from the Data from the Epidemiological Study on the Insulin Resistance Syndrome) – approximated discrimination performance of the basic risk scores including more predictors, such as the FINDRISC full model and the Atherosclerosis Risk in Communities (ARIC) model^{34, 35}. In our external validation, the discriminative power of these four risk scores ranged from 81% to 83%²⁵. This

suggests that a basic model which uses a limited set of non-invasive predictors, already provides good discrimination to predict mid-term risk of future type 2 diabetes ²⁵.

Another important aspect of prediction performance is the ability of a risk score to quantify absolute risk. Current risk scores have been developed in different settings, for instance primary care data versus population-based cohorts, and usually include only middle-aged and older subjects ^{22, 23}. Therefore, they might not sufficiently quantify absolute risk of diabetes when one applies those risk scores to younger age groups or to a clinical setting if the original risk score has been developed in public health setting with a lower background risk ^{25, 32, 36}. There are various potential explanations for the deviation of predicted risks from observed absolute risks – ‘mis’calibration. First, the calibration performance of a risk score is generally overestimated in the development population ^{25, 37, 38}. Second, mis-calibration happens because of differences in the incidence of diabetes or background risk between development and validation populations ^{25, 37}. In our validation study, we adjusted the models for these differences in the incidence of diabetes, resulting in much better calibration. However, mis-calibration was still present after recalibrating for most models, except for the KORA basic model ²⁵. Third, mis-calibration can be due to the difference in how certain predictors, the outcome variable, or baseline characteristics of the study populations are measured, which can lead to different predictive effects ^{36, 39}. We illustrated differences in the effect sizes of the predictors of the German Diabetes Risk Score from our validation cohort, showing significant differences for important predictors like age ^{25, 40}. Therefore, such risk scores need to be calibrated before use in practice. Finally, a model developed in one setting (such as public health data) or in a particular country does not necessarily need to be useful in another setting (such as secondary care) or country ²⁵.

Conventional risk factors and novel biomarkers

A number of studies developed or extended a risk score by incorporating conventional biomarkers to potentially improve prediction of risk of future type 2 diabetes ^{22, 23}. In our validation study, we showed that addition of conventional biomarkers, such as glucose, HbA1c and lipids to the basic scores can improve discrimination performance up to 90% or more ^{25, 41, 42}. At mid-term horizon, variation of glycaemia indices below the threshold for diagnosis of diabetes are very good predictors of incident diabetes in adult populations ⁴³, because high levels more or less automatically translate into an earlier future diagnosis of diabetes ^{4, 44}. Consistently, evidence has shown that individuals at pre-diabetes stage are more likely to develop diabetes than those who are at normal glycaemia state ⁴⁵.

Recently, much attention has been paid to the exploration of the predictive value of lipids, liver function tests, inflammatory markers and novel biomarkers for risk of diabetes and diabetes-related outcomes ^{22, 41, 44, 46-58}. In **Chapter 4**, we describe significant associations of some components of liver function tests with the risk of type 2 diabetes. However, despite these significant associations, addition of liver

function tests to an extended risk score such as the KORA clinical model appeared to only minimally improve the risk prediction of disease ^{58, 59}. This was also found by other investigators ^{41, 60}. We found an only 1% increase in discriminative power and 3.6% to 8.8% improvement in overall reclassification ⁵⁸. Also, biomarkers of chronic low-grade inflammation, such as C-reactive protein (CRP), interleukin-6 and procalcitonin and a stress marker such as the C-terminal portion of the precursor of vasopressin (copeptin), have been proposed as interesting additions to existing prediction models ^{44, 56, 61}. In **Chapters 7, 9 and 10**, we have evaluated CRP, lipids and procalcitonin for their association with the metabolic syndrome and risk of incident type 2 diabetes after adjustment for conventional diabetes risk factors ^{62, 63}. In **Chapter 8**, we examined the association of copeptin with risk of incident type 2 diabetes and the incremental predictive value of copeptin for the risk of incident type 2 diabetes when compared with the DESIR model ⁴⁴. Similarly, these studies showed that a single biomarker had only limited predictive value when added on top of a basic model (i.e. DESIR) or an extended risk score ^{55, 61, 63}. After addition of procalcitonin to the DESIR clinical equation, we observed 1% increase in discriminative power to predict type 2 diabetes ⁶³, while this was not significant for CRP ^{55, 63}.

Similar results were observed for diabetes-related outcomes, such as cardiovascular disease. Prior studies showed that addition of some novel biomarkers such as fibrinogen, CRP, mid-regional pro-adrenomedullin, mid-regional pro-atrial natriuretic peptide, and N-terminal pro-B-type natriuretic peptide, produced minimal to modest improvement of prediction ^{48, 49, 64, 65}. Indeed, the addition of different biomarkers to the model of conventional risk factors increased the discriminative power by 0.5% to 2%, and led to 1% to 7.6% net reclassification improvement ^{48, 49, 64}. In **Chapter 11**, we describe our findings concerning the relation of peroxiredoxin 4 (Prx4), a novel circulating biomarker for oxidative stress, with future risk of cardiovascular disease on top of classic risk factors included in the Framingham risk score (FRS) ⁵⁷. In a Cox-regression model adjusted for the Framingham risk factors, the marker seemed promising, but, after addition of Prx4 to the FRS, the incremental predictive value for 10-year risk of cardiovascular disease ⁵⁷ was marginal (2.7% net reclassification improvement). Studies on how this marker adds to prediction of diabetes are underway.

There are some potential explanations for the limited additive value of biomarkers that have been studied so far. First, biomarker levels overlap between cases and non-cases, limiting its incremental predictive value ^{58, 64}. Second, most testable biomarkers are in the causal biological pathways leading to disease or are a consequence of the disease and share associations with cardiometabolic disorders such as adiposity, hypertension and diabetes ^{61, 64}. For example, in **Chapter 6**, we showed that liver markers were associated with family history of diabetes; and adiposity substantially contributed to these associations. Family history of diabetes is itself an strong predictor for risk of future type 2 diabetes ^{43, 66} (**Chapter 5**). Because of the resulting correlations between diabetes risk factors such as family history of diabetes and biomarkers, addition of inflammatory or stress biomarkers to

conventional risk factors will only provide small improvement in prediction for risk of diabetes ^{44, 55, 56}. Correlated biomarkers are less likely to provide additional prognostic information ^{64, 67-69}.

Third, if biomarker levels are differently distributed by sex, the analysis of the total sample might hamper the association between biomarkers and outcome ⁴⁴. In **Chapters 3, 4 and 8**, we performed analyses in sex-stratified subgroups to account for potential sex differences in the prediction performance of models and incremental predictive value of biomarkers ^{44, 58, 70}. We and others have shown that existing prediction models might have a slightly better discrimination performance to identify women than men at high risk for type 2 diabetes ^{44, 58, 70, 71}. When we added liver function tests to an extended model incorporating glucose, uric acid plus HbA1c, we found a statistically significant improvement in prediction only in men ⁵⁸. However, for the association between copeptin and the risk of developing type 2 diabetes we found that it was stronger in women than in men. In fact, addition of copeptin to the DESIR model significantly improved prediction of diabetes only in women ⁴⁴. Finally, most traditional analyses, to date, assume a linear or log-linear relationship between biomarker levels and an outcome. This assumption might limit incremental predictive value of a certain biomarker if the association is not truly linear ⁵⁷. To deal with the potential non-linearity, it is recommended to do sensitivity analyses, examining other functional forms for continuous predictors such as biomarkers in the process of model building ^{72, 73}.

Future perspectives on better “prediction models” and better “biomarkers”

Despite of this good discrimination, one of major shortcomings in predicting diabetes risk and its complications is that all risk scores have been developed and validated for a shorter time period, while long term projection is necessary before the establishment of conventional risk factors of diabetes and later complications. Evidence shows that most of changes in glycaemia control happen 5 to 10 years closely preceding the diagnosis of diabetes ^{45, 74}. Previous studies have observed gradual increases in fasting glucose as early as 10 years before diagnosis of type 2 diabetes. These changes were followed by a rapid increase in glucose levels 3 to 6 years before diagnosis of the disease ⁷⁴. One would, therefore, expect that modelling of age, sex with conventional clinical risk factors (e.g. glucose) can accurately classify non-cases versus future cases who are close to developing of diabetes.

In actual clinical practice, the application of current risk scores and novel biomarkers to predict diabetes and diabetes-related outcomes presents some challenges. For instance, if one would like to predict one’s future risk of diabetes or cardiovascular disease, gathering important predictive data such as age, sex, smoking history, family history of diabetes or cardiovascular disease only require a small interview and assessment of (central) obesity and blood pressure only require additional measurements with standard and readily available equipment. Glucose

and cholesterol testing already requires additional equipment which is less widespread and readily available than a weighing scale, a tape-measure, and a blood pressure meter. Typically, one would first come to an impression based on the interview and the simple measurements and decide based on that whether glucose and cholesterol will be measured. If the picture then still is not clear one would proceed with assessment of additional biomarkers, typically from blood or urine collected during a next visit. This differs markedly from how prediction rules including biomarkers are currently evaluated and envisioned for clinical use. Current evaluation is being done as if all data are available at the same time. Better mimicking of actual practice in primary or secondary care could be an important next step to be made in generating prediction rules and implementation of biomarkers. Next, for both diabetes and cardiovascular disease, most risk scores have been developed only in middle-aged and older populations for short-term prediction horizon ^{22-25, 75}. However, a number of adults who are considered to be at low risk for type 2 diabetes and cardiovascular disease, e.g. over 5 to 10 years, are actually at high risk in later adult life ⁷⁶. Additionally, current estimates for diabetes risk do not account for potential variation of the relation between risk factors and outcome with age. Therefore, younger individuals are commonly classified as low-risk groups in the short-term horizon, but of course several of these subjects would be at high risk if one considers it from a long-term perspective. This is because later life risk factors such as hypertension are less informative at younger ages when such phenotypes are not yet established ⁷⁷. Thus, existing risk scores do not adequately perform to predict risk of diabetes and cardiovascular disease across the lifespan. To date, it is unclear whether performance of these risk scores differ by age or birth cohort, since large studies are necessary for these subgroup analyses ^{25, 76}. Moreover, all risk scores are based on incorporation of baseline data and do not include more information than that of one single time point from which prediction started ^{22, 24}. Indeed, current estimates do not account for longitudinal changes of risk factors and inter-relationships between biomarkers and modifiers, i.e., environmental exposures ^{15, 77, 78}. Consequently, the contribution of risk factors and novel biomarkers to diabetes risk has been assumed to be constant over life course. Furthermore, “age at onset” of risk factors may change their effects on disease risk for long term ^{79, 80}. For example, the inter-relationship between biomarkers and changes in lifestyle may be important for implementation of specific preventive strategies for individuals at high risk. Studies are warranted to uncover life course burden of diabetes in the future ^{79, 80}. This approach may also elucidate new insights into the aetiology of diabetes. Finally, the clinical utility of validated risk scores need to be critically assessed in terms of changes in health care management, improvements in health outcome and cost of screening ⁸¹⁻⁸³. This requires implementation of these risk scores in long-term clinical trials and application of health technology assessment to determine the long-term clinical and health economic consequences ^{81, 82}.

Two strategies can be useful for the application of relevant biomarkers to clinical practice. First, to improve prediction of diabetes and diabetes-related

outcomes, we need to account for “changes” of available biomarkers, because, for example, varying lifestyle can modify biomarker concentrations. It is worthy to mention that the absolute risk of a given outcome for levels of biomarkers will change over the lifetime. For example, the estimates of risk may differ between puberty and middle age ⁷⁹. Statistical models have to be developed to take both the changes in levels of biomarkers and the changes in risk into account. Indeed, prediction should obviously contain longitudinal information (or trajectories) available from multiple time-points rather than that of a single time-point. This approach provides full use of biomarkers which are indicating “flow” of life. Second, genetic data, but also less correlated proteomics and metabolomics other than glycaemia indices, may have a more important contribution to prediction of diabetes and cardiovascular disease in more specific target populations such as age subgroups ^{81, 84}. In the future, use of high-throughput data analysis will be more available in parallel with novel technological platforms. Before this, an integrative approach to gene-protein-metabolite data can be analyzed to find relevant biomarkers as potential screening clues in clinical practice. Finally, interactions with lifestyle over time and multiple measurements have to be taken into consideration.

In summary, existing prediction models which include traditional risk factors perform well to identify individuals at high risk for type 2 diabetes and cardiovascular disease at 5-10 year horizon. To quantify absolute risk of future disease, prediction models need to be updated and adjusted for differences between the development and validation settings. In the next step, addition of biomarkers to validated models can lead to marginal or modest improvement in prediction of type 2 diabetes and cardiovascular disease at 5-10 year horizon. So far, there is lack of data and evidence to critically assess the clinical utility of prediction models and value of biomarkers in real practice. For lifetime projections, a challenging journey is beginning with analysis of longitudinal and high-throughput data.

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