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Prediction of treatment response in patients with newly diagnosed type 2 diabetes: the Skaraborg diabetes register

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ABSTRACT

Aims: Type 2 diabetes is associated with cardiovascular complications. It is largely unknown which patients have poor treatment response and high complication risk; biomarkers are studied for this purpose. The aim of the study was to investigate the association between clinical factors such as HbA1c, level of biomarkers (C-peptide, copeptin) at diagnosis and changes in HbA1c, blood pressure or body mass index (BMI) after five years.

Methods: Clinical data and blood samples from 460 newly diagnosed type 2 diabetes patients from the Skaraborg diabetes register (SDR) at diagnosis and after 5 years and were analyzed with linear and logistic regressions.

Results: High BMI at diagnosis and smoking were associated with less reduction of HbA1c i.e. poorer treatment outcome after 5 years. A high HbA1c at baseline predicted a greater reduction of HbA1c and need for insulin treatment. High systolic blood pressure and BMI at baseline were associated with greater reduction.
The biomarkers were not associated with increase of blood pressure, HbA1c, BMI or need for insulin treatment.

Conclusions: Smokers and patients with high HbA1c at diagnosis respond poorer to treatment over 5 years. This highlights the importance of advice for non-smoking and weight reduction and more intensive treatment over time.

1. Introduction

The prevalence of type 2 diabetes has been rising during the last decades[1] and at the same time the average age of diagnosis has decreased.[2] Type 2 diabetes is associated with severe and increasing micro- and macrovascular complications[3] leading to a higher incidence of cardiovascular diseases and risk of cardiovascular death compared to the background population.[4] To lower the risk of complications it is important to treat not only the glucose level but also other risk factors such as hypertension, hyperlipidemia and obesity.[5,6] Even if cardiovascular risk factors in diabetes have been extensively studied it is still not yet known which individuals have the highest risk for complications. Several studies have been performed to increase the knowledge on how to identify persons with diabetes and high risk early[7] as this would be of great value for tailored treatment to avoid or postpone complications. Studies in patients with newly diagnosed diabetes are scarce.

Biomarkers have attracted increased attention for early identification of patients at risk. In earlier studies of newly diagnosed type 2 diabetes patients we found that an increase in C-peptide concentration was associated with a higher all-cause mortality and specifically cardiovascular death.[8] In the same cohort there was also an association between copeptin at diagnosis and the development of chronic kidney disease.[9]

C-peptide estimates the insulin secretion[10] and elevated concentrations are associated with insulin resistance.[11] There is limited data that C-peptide concentration is associated to cardiovascular and total mortality in non-diabetic patients.[12] Prospective studies of the association between C-peptide concentrations and diabetic complications are scarce and demonstrate contradictory results.[13–15] None of these studies included patients with newly diagnosed diabetes.

Copeptin is the C-terminal fragment of the arginine vasopressin (AVP) pro-hormone. AVP influences glucose metabolism by stimulating gluconeogenesis and glycogenolysis in the liver.[16] It is short-lived and difficult to use as a biomarker. On the other hand, copeptin is considered to be a reliable surrogate marker for AVP.[16]

Conflicts of interest: There is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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High copeptin levels have been associated with the metabolic syndrome, development of diabetes mellitus and nephropathy.[16,17] Two recent studies have shown association between copeptin and cardiovascular disease and death in patients with and without diabetes.[7,18]

It would be of great value to detect diabetes patients with high complication risk and reduced treatment effect already at diagnosis. Their treatment could thereby be more intense and tailored to prevent complications and premature death. It has previously been shown that glycemic control became better in patients with ongoing type 2 diabetes with a higher BMI[19] but as far as we know there are no studies on treatment response in patients with newly diagnosed diabetes patients.

To gain a better understanding about responders and non-responders to treatment we analyzed the associations between clinical factors such as current smoking, HbA1c, blood pressure, body mass index (BMI) and previous blood pressure treatment and their influence to changes in HbA1c, blood pressure or BMI or need of insulin treatment five years after diagnosis. We also analyzed the association between levels of C-peptide and copeptin at diagnosis and treatment response after five years.

2. Materials and Methods

2.1. Patients and Laboratory Analyses

The participants in this study were all patients newly diagnosed with type 2 diabetes registered in the Skaraborg diabetes register (SDR), which was established in 1991. In the SDR height, weight and blood pressure were registered and during 1996 and 1998 in addition, blood samples were taken from people aged <65 years. The cohort for this study consisted of the patients younger than 65 diagnosed during 1996–1998 (n = 460), in detail described elsewhere.[8,20]

SDR includes date of diabetes diagnosis and clinical data such as BMI and blood pressure.[21] Plasma and serum were sampled at the time of diagnosis and after 5 years, C-peptide, and HbA1c were analyzed and a biobank was established. In 2012 we completed laboratory analysis with creatinine, CRP and cystatin C. We calculated estimated glomerular filtration rate (eGFR) as the arithmetic mean of the two estimates, eGFR based on Cystatin C ($GFR = 86.49^{*}\ pCy^{-1.686*}$ 0.948 (if female)) and eGFR based on creatinine concentrations ($GFR = e^{X\ 0.0124\ *age\ +0.339\ *\ ln(age)\ 0.226\ if\ female}$); $X = 4.62–0.0112^{*}$ pCr (if pCr < 150 μmol/L); $X = 8.17 + 0.0005^{*}$ pCr 1.07^{*} ln(pCr) (if pCr ≥ 150 μmol/L) according to Grubb.[22]

Copeptin concentrations were measured in available samples from 382 individuals using a commercially available assay in the chemiluminescence/coated tube format (B.R.A.H.M.S. AG, Hennigsdorf, Germany) as described previously.[23,24] The lower detection limit was 0.9 pmol/liter and the functional assay sensitivity (<20% interassay coefficient of variation) was less than 2 pmol/liter.

As some clinical data and laboratory values were missing in the SDR, we completed information on HbA1c, blood pressure and BMI using the computerized patients' medical charts from primary care. Information on possible treatment with insulin 5 years after diagnosis was also extracted from the patients' charts and defined as a prescription of insulin, which are automatically registered in the charts when prescribing.

2.2. Statistics

The levels of the two biomarkers copeptin and C-peptide at diagnosis were analyzed with descriptive statistics. The characteristics of the study cohort at baseline and after 5 years including the clinical parameters and the levels of the two biomarkers copeptin and C-peptide were analyzed with descriptive statistics for the whole study group and for the group of individuals with complete data at both baseline and follow up.

The association between the biomarkers and the baseline clinical parameters on the one hand and the change in HbA1c, systolic blood pressure and BMI after 5 years on the other hand was tested with linear regressions. The association between the biomarkers and the baseline clinical parameters and treatment with insulin 5 years after diagnosis was tested with logistic regressions.

In a first step we used a univariate model. In a second step we performed multivariate analysis using the factors that turned out significant in the first model.

SPSS version 21 (IBM corporation®) was used for all statistical analyses. A two-sided p-value of <0.05 was considered statistically significant.

3. Results

3.1. Description of the Study Cohort at Baseline and After 5 years

The study cohort consisted of 460 participants with newly diagnosed type 2 diabetes. Of the 460 persons 270 individuals had complete data (Table 1). The mean age was 53.0 ± 8.6 years, 41.7% were women, 24.8% were smokers and 31.5% had hypertensive treatment at diabetes diagnosis. Five years after diagnosis data were available for 333 participants of whom 169 individuals had complete data (Table 1). The mean HbA1c value at baseline was 51 ± 20 mmol/mol (6.80 ± 1.8%) and was after 5 years not at a significantly different level. The mean systolic blood pressure at baseline was 140.7 ± 19.2 mm Hg and after 5 years 141.8 ± l7.1 mm Hg. The mean BMI value at baseline was 31.2 ± 5.6 kg/m^2 and after 5 years at almost same level with 31.2 ± 5.8 kg/m^2. The mean eGFR was 104.0 ± 38.3 ml/min/1.73m^2 and decreased after 5 years to 87.1 ± 27.2 ml/min/1.73m^2. Fifty-three patients had been prescribed insulin 5 years after diagnosis (11.5%), Table 1.

The group with complete data at both baseline and follow-up showed modest differences with less hypertensive treatment and fewer women than the patients who were excluded due to missing data, otherwise there was no difference between the groups, Table 1.

3.2. Association Between Clinical Parameters/Biomarkers and the Development of HbA1c, Systolic Blood Pressure, BMI and Need for Insulin: Univariate Analysis

3.2.1. HbA1c

In the univariate analysis there was a statistical significant association between higher C-peptide at diagnosis and greater increase of HbA1c level after 5 years (Table 2). We could not show a significant association between copeptin at baseline and a change in HbA1c after 5 years.

Furthermore in the univariate model HbA1c increase after 5 years was significantly associated with a high BMI, smoking and current hypertensive treatment (Table 2). On the other hand, a high HbA1c at diagnosis was associated with a greater decrease of HbA1c after 5 years (Table 2).

3.2.2. Systolic Blood Pressure

We found a significant association between a high systolic blood pressure at diagnosis and a decrease in blood pressure after 5 years (Table 2). No other clinical marker was associated with a change in blood pressure.

There was no significant association between C-peptide or copeptin concentration and change of blood pressure (Table 2).

3.2.3. BMI

A high BMI at baseline was associated to a decrease in BMI after 5 years, (Table 2). No other clinical marker was associated with a change in BMI.

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