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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.

Keywords: Type 2 Diabetes Mellitus, prognosis, Treatment Outcome, biomarkers, Primary Health Care

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 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, 14, 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]. 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

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 was 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.

Association between clinical parameters / biomarkers and the development of HbA1c, systolic blood pressure, BMI and need for insulin. Univariate analysis.

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).

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).

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.

There was no significant association between C-peptide or copeptin concentration and change in BMI (Table 2).

Need of insulin treatment

A high HbA1c value at diagnosis was associated with an increased prescription of insulin after 5 years (Table 2). No other clinical marker was associated with need for insulin after 5 years.

Neither C-peptide nor copeptin concentrations at diagnosis were significantly associated with prescription of insulin after 5 years (Table 2).

Association between clinical parameters / biomarkers and the development of HbA1c. Multivariate analysis.

High HbA1c at baseline predicted a greater reduction of HbA1c after five years whereas smoking and high BMI at baseline turned out to be an independent risk factor for poor treatment response regarding HbA1c reduction over five years (Table 3).

The association between current hypertensive treatment and HbA1c increase was not significant in the multivariate model (Table 3).

Further, the C-peptide level did not remain significantly related to treatment response in the multivariate model (Table 3).

4. Discussion

The key findings in our study were that a high BMI at diagnosis and smoking predicted a poor treatment outcome regarding HbA1c development. On the other hand a high HbA1c at baseline was related to a better treatment response. High systolic blood pressure and BMI at baseline were associated with greater reduction over time. The biomarkers were not associated with the development of systolic blood pressure, HbA1c or BMI or the need for treatment with insulin over time.

Smoking has earlier shown to be associated with insulin resistance [25] as smokers might have an increased decline in beta cell function compared to non-smokers [26, 27] and it has been shown that an improvement of insulin sensitivity after smoking cessation [28]. Therefore it is possible that the poorer treatment result in smokers in our study is related to insulin resistance. Another possibility is that smokers have less compliance to lifestyle

changes than non-smokers. In any case, our data underline the importance of smoking cessation, not only to decrease cardiovascular and cancer risk but also to improve control of diabetes early after diagnosis.

Regarding the individuals with a high BMI a first thought could be that their worse outcome concerning HbA1c could be explained by the fact that obese people have a higher insulin resistance [29]. In contrast, our study shows that the association between a high BMI and less decline of HbA1c is independent of the C-peptide level, a proxy for insulin concentrations and consequently for insulin resistance [10]. Another explanation could be that obese adults are often less physically active than normal-weight adults [30] and it is well known that physical activity improves HbA1c in people with diabetes [31]. This emphasizes the importance of motivating persons with diabetes and a high BMI to start exercising.

Aside from a high baseline value we could in our study not see other associations with changes in the systolic blood pressure and the BMI. Further studies are needed to understand which persons are more likely to have difficulties in reaching treatment target of blood pressure and BMI.

The biomarkers we studied were not associated with treatment response of the metabolic risk factors. This was surprising since previous studies of the same cohort showed an association between C-peptide and increased mortality and between copeptin and a deterioration of the kidney function [8, 9]. As those complications are the results of a combination of high levels of risk factors with for instance both elevated blood pressure, HbA1c, BMI and lipids an explanation could be that the individual effects on risk factors are small and therefore difficult to show in a small sized study like this one, while cardiovascular complications and death are the final result of several risk factors acting together and therefore easier to detect. Moreover, we might see a combination of both treatment effect and natural development of the disease and complications. This makes it difficult to detect significant associations. Due to the observational nature of the study, we cannot disentangle these factors from each other. On the other hand, despite only a part of the relationship of the change of risk factors over time can be explained by the baseline parameters, it represents the natural course in newly diagnosed diabetes that will encounter the patient. We could therefore not explain the elevated risk for complications and death we earlier showed as to be associated with elevated levels of C-peptide and copeptin. There could also be other unknown factors making these biomarkers predictors of risk independent from the studied treatment effect.

For the individuals with a high HbA1c at diagnosis it was more likely to lower their levels over time. This was the same for individuals with a high systolic blood pressure, lowering their blood pressure and those with a high baseline BMI, lowering their BMI over time. These findings were not surprising, as often very high levels elicit more forceful treatment actions compared to only slightly elevated levels. This was also probably why for patients with high HbA1c at diagnosis it was more probably to have insulin treatment after five years.

A particular strength of our study is that the study cohort consists of patients with newly diagnosed diabetes only, in contrary to other studies as far as we have experienced. The cohort is population based, which makes it similar to the persons we usually meet in primary care. The data from the SDR we have been using has a very good capture rate, the completeness was 88.4% in 1995 [21] and the bias was low. Moreover the additional data we used was from the persons' medical charts which means that we studied the treatment in clinical practice and not in a clinical study.
The limited time from 1996 to 1998 as well as including only patients less than 65 years where blood samples were taken at diagnosis reduced the sample size of our cohort to 460 individuals which means a limitation of power. There was also a rather great loss to follow-up. This could lead to undetected associations in the calculations and should lead to cautious interpretation of the results. Another limitation is that only patients younger than 65 years at diagnosis are included whereas many patients with type 2 diabetes mellitus are diagnosed in older age.

5. Conclusion

In conclusion, in patients with newly diagnosed type 2 diabetes individuals with high levels of HbA1c, systolic blood pressure and BMI have a good chance in lowering their levels over time. It is though important to know that both smokers and individuals with a high BMI at diabetes diagnosis have a worse prognosis for the development of their HbA1c. As both smokers and individuals with high HbA1c at diabetes diagnosis respond significantly poorer to treatment of metabolic control over five years it is important to follow up and treat them more intensively over time. Analyzing biomarkers such as C-peptide and copeptin were not useful in this context to predict treatment response and to understand the mechanism behind the development of complications and higher risk for death.

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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Author Contribution statement

Kristina Boström contributed with the design of the research questions, assistance with the data collection, the analysis and interpretation of the data and a critical review of the manuscript.

Olle Melander contributed with the design of the research questions, assistance with the analysis and interpretation of the data and a critical review of the manuscript.

Per Hjerpe contributed with assistance with the data collection, the analysis and interpretation of the data and a critical review of the manuscript.

7. References

1. Chen L, Magliano DJ, Zimmet PZ. The worldwide epidemiology of type 2 diabetes mellitus--present and future perspectives. *Nature reviews Endocrinology* 2012; **8**:228-236.
2. Koopman RJ, Mainous AG, 3rd, Diaz VA, Geesey ME. Changes in age at diagnosis of type 2 diabetes mellitus in the United States, 1988 to 2000. *Annals of family medicine* 2005; **3**:60-63.
3. Lam DW, LeRoith D. The worldwide diabetes epidemic. *Current opinion in endocrinology, diabetes, and obesity* 2012; **19**:93-96.
4. Chiha M, Njeim M, Chedrawy EG. Diabetes and coronary heart disease: a risk factor for the global epidemic. *International journal of hypertension* 2012; **2012**:697240.
5. UKPDS. UKPS study group. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. UK Prospective Diabetes Study Group. *Bmj* 1998; **317**:703-713.
6. Krentz AJ. Lipoprotein abnormalities and their consequences for patients with type 2 diabetes. *Diabetes, obesity & metabolism* 2003; **5 Suppl 1**:S19-27.
7. Enhorning S, Hedblad B, Nilsson PM, Engstrom G, Melander O. Copeptin is an independent predictor of diabetic heart disease and death. *American heart journal* 2015; **169**:549-556 e541.
8. Pikkemaat M, Melander O, Molstad S, Garberg G, Bostrom KB. C-peptide concentration, mortality and vascular complications in people with Type 2 diabetes. The Skaraborg Diabetes Register. *Diabetic medicine: a journal of the British Diabetic Association* 2015; **32**:85-89.
9. Pikkemaat M, Melander O, Bengtsson Bostrom K. Association between copeptin and declining glomerular filtration rate in people with newly diagnosed diabetes. The Skaraborg Diabetes Register. *Journal of diabetes and its complications* 2015; **29**:1062-1065.
10. Van Cauter E, Mestrez F, Sturis J, Polonsky KS. Estimation of insulin secretion rates from C-peptide levels. Comparison of individual and standard kinetic parameters for C-peptide clearance. *Diabetes* 1992; **41**:368-377.
11. Banu S, Jabir NR, Manjunath CN, Shakil S, Kamal MA. C-peptide and its correlation to parameters of insulin resistance in the metabolic syndrome. *CNS & neurological disorders drug targets* 2011; **10**:921-927.
12. Patel N, Taveira TH, Choudhary G, Whitlatch H, Wu WC. Fasting serum C-peptide levels predict cardiovascular and overall death in nondiabetic adults. *Journal of the American Heart Association* 2012; **1**:e003152.
13. Marx N, Silbernagel G, Brandenburg V, Burgmaier M, Kleber ME, Grammer TB, *et al.* C-peptide levels are associated with mortality and cardiovascular mortality in patients undergoing angiography: the LURIC study. *Diabetes care* 2013; **36**:708-714.
14. Sari R, Balci MK. Relationship between C peptide and chronic complications in type-2 diabetes mellitus. *Journal of the National Medical Association* 2005; **97**:1113-1118.
15. Mavrakanas T, Frachebois C, Soualah A, Aloui F, Julier I, Bastide D. C-peptide and chronic complications in patients with type-2 diabetes and the metabolic syndrome. *Presse medicale* 2009; **38**:1399-1403.
16. Enhorning S, Bankir L, Bouby N, Struck J, Hedblad B, Persson M, *et al.* Copeptin, a marker of vasopressin, in abdominal obesity, diabetes and microalbuminuria: the prospective Malmo Diet and Cancer Study cardiovascular cohort. *International journal of obesity* 2013; **37**:598-603.

17. Enhorning S, Struck J, Wirfalt E, Hedblad B, Morgenthaler NG, Melander O. Plasma copeptin, a unifying factor behind the metabolic syndrome. *The Journal of clinical endocrinology and metabolism* 2011; **96**:E1065-1072.
18. Tasevska I, Enhorning S, Persson M, Nilsson PM, Melander O. Copeptin predicts coronary artery disease cardiovascular and total mortality. *Heart* 2016; **102**:127-132.
19. Koro CE, Bowlin SJ, Bourgeois N, Fedder DO. Glycemic control from 1988 to 2000 among U.S. adults diagnosed with type 2 diabetes: a preliminary report. *Diabetes care* 2004; **27**:17-20.
20. Berger B, Borg H, Fernlund P, Stenström G, Sundkvist G. Islet antibodies associated with pancreatic B-cell dysfunction at and 3 years after diagnosis of diabetes in subjects aged 35-64 years old: degree of impairment less severe than in those aged 0-34 years old. *Diabet Med.* 2006: **23**:1180-5.
21. Berger B, Stenstrom G, Sundkvist G. Incidence, prevalence, and mortality of diabetes in a large population. A report from the Skaraborg Diabetes Registry. *Diabetes care* 1999; **22**:773-778.
22. Grubb A, Nyman U, Bjork J. Improved estimation of glomerular filtration rate (GFR) by comparison of eGFRcystatin C and eGFRcreatinine. *Scandinavian journal of clinical and laboratory investigation* 2012; **72**:73-77.
23. Fenske W, Stork S, Blechschmidt A, Maier SG, Morgenthaler NG, Allolio B. Copeptin in the differential diagnosis of hyponatremia. *The Journal of clinical endocrinology and metabolism* 2009; **94**:123-129.
24. Morgenthaler NG, Struck J, Alonso C, Bergmann A. Assay for the measurement of copeptin, a stable peptide derived from the precursor of vasopressin. *Clinical chemistry* 2006; **52**:112-119.
25. Targher G, Alberiche M, Zenere MB, Bonadonna RC, Muggeo M, Bonora E. Cigarette smoking and insulin resistance in patients with noninsulin-dependent diabetes mellitus. *The Journal of clinical endocrinology and metabolism* 1997; **82**:3619-3624.
26. Ostgren CJ, Lindblad U, Ranstam J, Melander A, Rastam L, Skaraborg H, *et al.* Associations between smoking and beta-cell function in a non-hypertensive and non-diabetic population. Skaraborg Hypertension and Diabetes Project. *Diabetic medicine : a journal of the British Diabetic Association* 2000; **17**:445-450.
27. Xu M, Zhou Y, Xu B, Sun J, Wang T, Lu J, *et al.* Associations of smoking and alcohol consumption with impaired beta-cell function in Chinese men. *Journal of diabetes* 2016; **8**:434-441.
28. Eliasson B, Attvall S, Taskinen MR, Smith U. Smoking cessation improves insulin sensitivity in healthy middle-aged men. *European journal of clinical investigation* 1997; **27**:450-456.
29. Riserus U, Arnlov J, Berglund L. Long-term predictors of insulin resistance: role of lifestyle and metabolic factors in middle-aged men. *Diabetes care* 2007; **30**:2928-2933.
30. Pietilainen KH, Kaprio J, Borg P, Plasqui G, Yki-Jarvinen H, Kujala UM, *et al.* Physical inactivity and obesity: a vicious circle. *Obesity* 2008; **16**:409-414.
31. Peirce NS. Diabetes and exercise. *British journal of sports medicine* 1999; **33**:161-172; quiz 172-163, 222.

8. Tables

Table 1: Population description – baseline characteristics and characteristics 5 years after diagnosis

	Baseline Total studycohort (n=460)	Baseline Individuals with complete data (n=270)	After 5 years Total studycohort (n=333)	After 5 years Individuals with complete data (n=169)
Age (years)	53.0 ± 8.6	52.8 ± 8.2	58.0 ± 8.6	57.8 ± 8.2
Sex (% women)	41.7	38.9	41.7	38.9
Smoking (%)	24.8	25.9	21.1	20.7
Current hypertensive treatment (%)	31.5	27.4	40.0	38.9
eGFR (ml/ min/1.73m^2)	104.0 ± 38.3	105.4 ± 39.6	87.1 ± 27.2	89.1 ± 26.8
HbA1c (mmol/mol ; %)	51 ± 20 (6.8 ± 1.8)	52 ± 20 (6.9 ± 1.8)	51 ± 16 (6.8 ± 1.5	52 ± 16 (6.9 ± 1.5)
SBP (mm Hg)	140.7 ± 19.2	141.2 ± 19.5	141.8 ± 17.1	142.3 ± 17.2
BMI (kg/m^2)	31.2±5.6	31.3 ± 5.5	31.2 ± 5.8	31.1 ± 5.4
C-peptide (nmol/l)	0.95 ± 0.48	0.94 ± 0.48	0.88 ± 0.46	0.89 ± 0.49
Copeptin (pmol/l)	4.10 ± 2.66	4.00 ± 2.50	NA	NA
Need of insuline treatment (%)	0	0	11.5	18.1

SBP = systolic blood pressure, BMI = Body Mass Index, NA = not analyzed

Table 2. Association between clinical parameters /biomarkers and the development of HbA1c, SBP, BMI and need for insulin. Univariate analysis.

	Delta HbA1c (%)*			**Delta SBP (mmgHg)***			**Delta BMI (kg/m^2)***			**Need for insulin 5 years after diagnosis**		
	p	unst. B	st. beta	p	unst. B	st. beta	p	unst. B	st. beta	p	unst. B	OR
Age (years)	0.06	-0.03 (-0.05–0.00)	-0.11	0.14	-0,18 (-0.42–0.06)	-0.09	0.59	0.01 (-0.03–0.05)	0.03	0.80	0.01	1.00 (0.97–1.04)
Sex	0.88	0.04 (-0.43–0.50)	0.01	0.79	0.56 (-3.55–4.66)	0.02	0.33	0.31 (-0.32–0.94)	0.05	0.97	0.01	1.01 (0.57–1.81)
HbA1c (%)	**0.00**	**-0.77** (-0.85–0.68)	-0.71	0.37	0.50 (-0.59–1.60)	0.05	0.18	0.12 (-0.05–0.29)	0.08	**0.00**	**0.26**	1.30 (1.13–1.49)
SBP (mmHg)	0.30	-0.01 (-0.02–0.01)	-0.06	**0.00**	**-0.53** (-0.61–0.45)	-0.59	0.62	-0.01 (-0.02–0.01)	-0.03	0.21	-0.01	0.99 (0.98–1.01)
BMI (kg/m^2)	**0.00**	**0.06** (0.02–0.10)	0.18	0.50	-0.12 (-0.48–0.23)	-0.04	**0.00**	**-0.10** (-0.15–-0.05)	-0.21	0.86	-0.01	1.00 (0.95–1.05)
Smoking	**0.03**	**0.57** (0.06–1.09)	0.12	0.32	2.39 (-2.30–7.07)	0.06	0.73	0.13 (-0.58–0.83)	0.02	0.40	0.27	1.31 (0.70–2.46)
Current HT	**0.00**	**1.01** (0.51–1.50)	0.22	0.48	1.61 (-2.85–6.07)	0.04	0.67	0.15 (-0.53–0.83)	0.02	0.93	0.03	1.03 (0.56–1.90)
C-peptide (per SD)	**0.04**	**0.25** (0.02–0.48)	0.12	0.91	-0.12 (-2.18–1.94)	-0.01	0.91	-0.12 (-2.18–1.94)	-0.01	0.06	0.24	1.28 (0.99–1.65)
Copeptin (per SD)	0.16	-0.18 (-0.43–0.07)	-0.08	0.06	-2.02 (-4.10–0.06)	-0.01	0.06	-2.02 (-4.10–0.06)	-0.11	0.40	0.12	1.12 (0.86–1.47)

*Difference between baseline value at diagnosis and value 5 years after diagnosis
C-peptide and copeptin as Zscore
SBP = systolic blood pressure, BMI = Body Mass Index, Current HT = Current hypertensive treatment
p = p value, st. beta = standardized coefficient Beta,
unst. B = unstandardized coefficient B, 95 % Confidence Interval
OR = Odds Ratio, 95% CI

Table 3. Association between clinical parameters/biomarkers and the development of HbA1c. Multivariate analysis.

	Delta HbA1c (%)*		
	p	unst. B	st. beta
HbA1c (%)	**0.00**	**-0.72** (-0.80–0.63)	-0.67
BMI	**0.01**	**0.04** (0.01–0.07)	0.12
Smoking	**0.00**	**0.55** (0.18–0.92)	0.12
Current HT	0.09	0.32 (-0.05–0.69)	0.07
C-peptide (per SD)	0.66	-0.04 (-0.22–0.14)	-0.02

*Difference between baseline value at diagnosis and value 5 years after diagnosis
C-peptide as Zscore
Current HT = Current hypertensive treatment
p = p value, st. beta = standardized coefficient Beta,
unst. B = unstandardized coefficient B, 95 % Confidence Interval