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ORIGINAL ARTICLE

Agonistic autoantibodies against B2-adrenergic receptors correlating with macrovascular disease in longstanding diabetes type 2

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Abstract

Aims Agonistic autoantibodies directed against adrenergic, endothelin, and angiotensin receptors are known as pathogenic factors in disease-causing vascular impairments such as Buergers' disease, dilatative cardiomyopathy, dementia, and preeclampsia. Diabetes mellitus also causes micro- and macrovascular damages, but pathogenesis is still not fully understood. Following indications for a pathogenic role of the mentioned antibodies from our preliminary investigations, we investigated the prevalence in a bigger cohort of patients with longstanding diabetes with or without diabetic complications.

Methods We included 200 patients in four groups (grouping due to duration of diabetes and presence of complications) from our university polyclinic with longstanding diabetes mellitus type 2 and evaluated the prevalence of the agonistic autoantibodies using ELISA technique.

Results Antibodies directed against the alpha1-(39%), the first extracellular loop of the beta2-(34,5%), and the first extracellular loop of the beta1-adrenergic receptor (29,0%) were the most often detectable. With progression of diabetes and its complications, we found a decrease in the prevalence of the antibodies. Regression analyses revealed a positive association of antibodies against the first loop of the beta2-receptor and the presence of macrovascular complications.

Conclusions This investigation found mid frequent prevalence of agonistic autoantibodies in patients with longstanding diabetes mellitus type 2. The association between an antibody against one epitope and the presence of macrovascular complications may indicates a pathogenic linkage. This finding is inconsistent with our preliminary data and needs further evaluation, maybe by follow-up.

Keywords Agonistic autoantibodies · Diabetes type 2 · Diabetic complications

Introduction

Diabetic complications such as cardiovascular disease, major amputation, retinopathy, and renal failure are still the main burden of diabetes mellitus and account substantially for the shortened live of patients [1–3]. Depending on data, diabetic complications are present in about one-third of all patients, with nephropathy (17.8%), polyneuropathy (13.7%), and retinopathy (7.1%) as the most often occurred. Treatment of diabetes and its complications contributes substantially to healthcare costs in Germany [4, 5]. Many factors for the development of these diseases were intensively investigated, and up to date, the cellular mechanisms of hyperglycemic damage are well understood [6].

Surrogate parameters such as the HbA1c are broadly used for managing of therapeutic intervention, but low blood glucose and HbA1c levels do not always reach the aim of preventing diabetic complications [7–9]. In conclusion, there may be more pathogenic factors despite hyperglycemia accountable for the evolvement of damages [10].

Possible pathogenic factors found in other diseases with substantial vascular impairment are agonistic autoantibodies directed (AgAAB) against adrenergic, endothelin and angiotensin receptors.

They have been associated with the outcome of different diseases with vascular complications such as dilated cardiomyopathy [11, 12], hypertension [13–15], dementia [16, 17], preeclampsia [18, 19] and humoral mediated kidney transplant rejection [20, 21].

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AgAAB activates the receptor in a non-physiological manner by surpassing protective mechanisms. Interestingly, GPCR antagonists (so-called receptor blockers) are able to abolish interaction of agAAB with the cognate receptor and may prevent the target tissue from damage [21].

Removal of such antibodies via immunoadsorption resulted in significant improved cardiac function in patients with dilated cardiomyopathy, significant reduction of amputation rates in Buergers disease, and stabilization of cognitive and mental condition in patients with mild-to-moderate dementia [22–24].

In addition, in a small cohort of patients with type 2 diabetes, these antibodies were found (prevalence: 37%), suggesting an increased risk of hypertension and vascular complications for diabetic patients [25].

In a pilot project, we also found these antibodies in a small cohort of 40 patients with longstanding diabetes mellitus type 2. Furthermore, there was an association between agonistic autoantibodies against the beta-2-adrenergic receptor and the number of antihypertensive drugs taken [26].

The objective in this study was to further analyze the prevalence of agAAB against five different GPCR in a larger cohort of patients with diabetes. This study aimed to contribute to the knowledge of the pathogenesis of complications in type 2 diabetes mellitus.

Patients/methods

In a university outpatient department for endocrinology and metabolic diseases, we recruited 200 patients suffering from diabetes mellitus type 2 (DM2). Patients were divided into four different groups depending of the time since diagnosis of diabetes. Group 1 ($n=49$): time since diagnosis ≥ 0 and ≤ 5 years; Group 2 ($n=51$): time since diagnosis >5 and ≤ 10 years; and Group 3 ($n=50$): time since diagnosis >10 years. Furthermore, another Group 4 ($n=50$) with significant cardiovascular complications (myocardial infarction, stroke, hypertension, lower limb amputation, stent, and angioplasty). Patients who were pregnant, suffered from malignant neoplasms, any known autoimmune disease or had current immunosuppressive treatment were excluded. Drug therapy and smoking status were assessed and blood pressure, body weight, height, and HbA1c were measured at the day of recruitment. Renal function was assessed using the last blood and urine check. However, not older than 1 year. Micro- and macrovascular complications were drawn from our electronic patient record, which includes data on out- and inpatient treatments Sera of all patients were tested for agonistic autoantibodies (agAAB) directed against epitopes of alpha1 (A1)-, beta1 (B1)-, and beta2 (B2)- adrenergic, endothelin A (ETA) and angiotensin 2, subtype1 (ATII) receptors using peptide-based ELISA technique, as described in [27, 28]. Laboratory investigations were performed by E.R.D.E-AAB-Diagnostics GmbH, Berlin, Germany.

Clinical data were obtained from electronic patient record EMIL®. Statistical analyses were performed using IBM SPSS 22 statistics. Prevalence is tested by Chi-square test. Comparisons between groups were tested by one-way Anova or *t* test and for correlation the test of Pearson. A p value of <0.05 is considered to be statistically significant. Bonferroni correction was performed where applicable. Multivariate regression analyses were performed in different models for association analyses. HbA1c was DCCT-adjusted.

Investigation was performed as planned. Due to a mistake by our technical personal, one patient was accidentally assigned to the wrong group, causing a difference in the size of Groups 1 and 2. We analyzed all patients in the group that they belonged to by clinical features.

The trial was performed according to the principles of the declaration of Helsinki and meets the criteria of the International Conference on Harmonization Good Clinical Practice (ICH GCP). All investigations were approved by ethics committee of the University of Jena (number of decision: 4916-09/16). All patients gave informed consent to laboratory investigations and data processing.

Results

The overall mean age was 66.9 (±10.4) years, mean BMI 32.9 (±6.8) kg/m^2, mean duration of diabetes 13.2 (±9.9) years, mean systolic blood pressure 141.8 (±17.7) mmHg, mean diastolic blood pressure 82.5 (±12.1) mmHg, and mean HbA1c (DCCT-adjusted) was 6.9 (±0.9) %. 65% ($n=130$) of the patients were of male sex, and 11% were active smokers, 39% stopped smoking. Of all patients, 10.5% did not take antidiabetic drugs, 42% had oral antidiabetic only, 29.5% oral antidiabetic drugs combined with insulin, and only 18% had insulin alone.

Same characteristics for each group as well as the prevalence of arterial hypertension and obesity are depicted in Table 1.

Groups did significantly differ in portion of smokers ($p=0.043$) and in distribution of antidiabetic therapy types ($p=0.001$). Differences in the prevalence of obesity ($p=0.379$) and percentage of males ($p=0.169$) were not statistically significant.

Regarding late complications and concomitant diseases, we found 10% of all patients to have an estimated glomerular filtration rate (eGFR) lower than 45 ml/min, 9.5% already suffered myocardial infarction, and 15.5% were already treated by coronal-artery stenting. In 6.5%, stroke or intracerebral bleeding was documented. 1.5% of all patients were diagnosed any stage of dementia. Diabetic

Table 1 Patient characteristics depending on the study group

	Group 1	Group 2	Group 3	Group 4
Mean RR syst. [mmHg] (SD)	139.2 (±18.8)	143.8 (±19.2)	139.5 (±14.3)	144.7 (±17.7)
Mean RR diast. [mmHg] (SD)	85.4 (±11.3)	87.0 (±11.4)	78.1 (±10.3)	79.6(±13.0)
Mean BMI [kg/m^2] (SD)	33.7 (±7.2)	32.3 (±7.3)	31.8 (±6.3)	33.6 (±6.2)
Mean Age [years] (SD)	59.4 (±11.1)	66.2 (±8.8)	69.9 (±8.9)	71.7 (±8.6)
Mean duration of diabetes [years] (SD)	2.6 (±1.4)	7.7 (±1.4)	21.2 (±7.4)	20.9 (±8.7)
Mean DCCT adj. HbA1c [%] (SD); mmol/mol (SD)	6.5 (±1.0); 47.5 (±5.01)	7.0 (±0.8) 53.0 (±4.5)	7.1 (±0.9) 54.1 (±4.8)	7.3 (±0.8) 56.3 (±4.5)
Male [%] (*n*)	63.3 (31)	54.9 (28)	66.0 (33)	76.0 (38)
Smoking yes [%] (*n*)	22.4 (11)	11.8 (6)	2.0 (1)	8.0 (4)
Smoking stopped [%] (*n*)	30.6 (15)	37.3 (19)	40.0 (20)	48.0 (24)
Smoking never [%] (*n*)	46.9 (23)	51.0 (26)	58.0 (29)	44.0 (22)
Antidiabetic therapy				
None [%] (*n*)	22.4 (11)	13.7 (7)	6.0 (3)	0
OAD [%] (*n*)	69.4 (34)	64.7 (33)	24.0 (12)	10.0 (5)
Insulin [%] (*n*)	0	7.8 (4)	22.0 (11)	42.0 (21)
OAD and Insulin [%] (*n*)	8.2 (4)	13.7 (7)	48.0 (24)	48.0 (24)
Art. hypertension [%] (*n*)	83.7 (41)	80.4 (41)	96.0 (48)	98.0 (49)
Obesity [%] (*n*)	55.1 (27)	56.9 (29)	56.0 (28)	70.0 (35)

Units are given in square brackets, and standard deviation (SD) or absolute numbers are given in round brackets

food syndrome (DFS) as a common complication was known to 8.5%. Any kind of lower extremity amputation was known in 4% of all patients (Table 2). Normal renal function describes an eGFR > 90 ml/min in the absence of Albuminuria > 20 mg albumin/g creatinine. Classification of renal function was performed following the KDIGO 2013 guidelines.

Prevalence of diabetic foot syndrome differs significantly between groups ($p < 0.001$). Renal function decreased with increasing age and duration of diabetes.

91.5% of all patients took at least one antihypertensive drug of any kind. 82% took two or more. The most often prescribed were diuretics (63.5%), followed by beta-blockers (58.5%) and angiotensin-converting enzyme (ACE) blockers

Table 2 Accompanying morbidities depending on the study group

	Group 1	Group 2	Group 3	Group 4
Renal function				
Normal	30.6% (*n* = 15)	17.6% (*n* = 9)	8.0% (*n* = 4)	2.0% (*n* = 1)
CKD1	14.3% (*n* = 7)	9.8% (*n* = 5)	6.0% (*n* = 3)	12.0% (*n* = 6)
CKD2	49.0% (*n* = 24)	51.0% (*n* = 26)	56.0% (*n* = 28)	46.0% (*n* = 23)
CKD3a	6.1% (*n* = 3)	17.6% (*n* = 9)	22.0% (n = 11)	12.0% (n = 6)
CKD3b	0	2.0% (n = 1)	6.0% (*n* = 3)	24.0% (*n* = 12)
CKD4	0	2.0% (*n* = 1)	2.0% (*n* = 1)	2.0% (*n* = 1)
CKD5	0	0	0	2.0% (*n* = 1)
Acc. diseases				
Myocardial infarction	0	0	0	38.0% (*n* = 19)
Stent	0	0	0	62.0% (*n* = 31)
Stroke	0	0	0	26.0% (*n* = 13)
Dementia	0	2.0% (*n* = 1)	4.0% (*n* = 2)	0
Diabetic foot syndrome	2.0% (*n* = 1)	0	6.1% (*n* = 3)	26.0% (*n* = 13)
Amputation	0	0	2% (*n* = 1)*	16% (*n* = 8)

Portion of the group is given; absolute numbers are given in round brackets

CKD chronic kidney disease, stages after KDIGO guidelines 2013, *DFS* diabetic food syndrome

*Traumatic amputation

Table 3 Number of antihypertensive drugs prescribed to patients by drug classes for each patient group

Number of drugs	Group 1	Group 2	Group 3	Group 4
0	14.3 ($n=7$)	15.7 ($n=8$)	4.0 ($n=2$)	0
1	14.3 ($n=7$)	15.7 ($n=8$)	6.0 ($n=3$)	2.0 ($n=1$)
2	26.5 ($n=13$)	17.6 ($n=9$)	22.0 ($n=11$)	18.0 ($n=9$)
3	20.4 ($n=10$)	33.3 ($n=17$)	36.0 ($n=18$)	26.0 ($n=13$)
4	22.4 ($n=11$)	22.4 ($n=5$)	28.0 ($n=14$)	40.0 ($n=20$)
5	2.0 ($n=1$)	2.0 ($n=4$)	4.0 ($n=2$)	12.0 ($n=6$)
6	0	0	0	2.0 ($n=1$)

Proportion given for each group with absolute number in round brackets

SD standard deviation

(45.5%). Statins or fibrates were prescribed to 53.5% of all patients. The number of prescribed drugs per patient is listed in Table 3.

A mean number of prescribed antihypertensive drugs were 2.29 (± 1.4) in Group 1; 2.29 (± 1.47) in Group 2; 2.9 (± 1.13) in Group 3; and 3.5 (± 1.05) in Group 4. Post-hoc analyses revealed significant differences in mean number of prescribed drugs between Groups 1 and 4 ($p<0.001$) and Group 2 and 4 ($p<0.001$). Statistical significant differences between groups were found for statins or fibrates ($p<0.001$), central acting antihypertensive drugs ($p=0.025$), diuretics ($p=0.012$), beta-blockers ($p=0.03$), calcium antagonists ($p=0.021$), and ACE blocker ($p=0.016$).

Prevalence and correlation of antibodies

In 55% of all patients, at least one agonistic autoantibody was detectable. Only one patient harbored antibodies against all tested epitopes.

The most frequently detected was directed against the alpha-1 adrenergic receptor (39% of the cases). Prevalence of antibodies is depicted in Table 4 and in Fig. 1.

Differences in the prevalence of each antibody between the four groups were not statistically significant.

Mean number of positive antibodies per patient was 1.61 (± 2.38) in group 1; 2.1 (± 2.04) in group 2; 1.5 (± 1.8) in group 3; and 1.02 (± 1.53) in group 4.

Statistically significant differences between mean number of positive antibodies were found between Groups 2 and 4 ($p=0.038$).

Correlation analyses were performed between concomitant diseases and either positivity or number of detected

Table 4 Number of patients tested positive for each agonistic autoantibody for the whole collective and for each group

Epitope	Total ($n=200$)	Group 1	Group 2	Group 3	Group 4
α1-AR	39.0% (78)	34.7% (17)	52.9% (27)	36.0% (18)	32.0% (16)
ETA	20.0% (40)	22.4% (11)	27.5% (14)	22.0% (11)	8.0% (4)
AT1 loop1	14.0% (28)	18.4% (9)	13.7% (7)	18.0% (9)	6.0% (3)
AT1 loop2	7.0% (14)	14.3% (7)	5.9% (3)	4.0% (2)	4.0% (2)
β2-AR loop1	34.5% (69)	26.5% (13)	49.0% (25)	38.0% (19)	24.0% (12)
β2-AR loop2	9.0% (18)	14.3% (7)	11.8% (6)	6.0% (3)	4.0% (2)
β1-AR loop1	29.0% (58)	16.5% (13)	41.2% (21)	28.0% (14)	20.0% (10)
β1-AR loop2	4.5% (9)	4.1% (2)	7.8% (4)	0	6.0% (3)

AR adrenergic receptor, *ETA* Endothelin A, *AT* Angiotensin 1

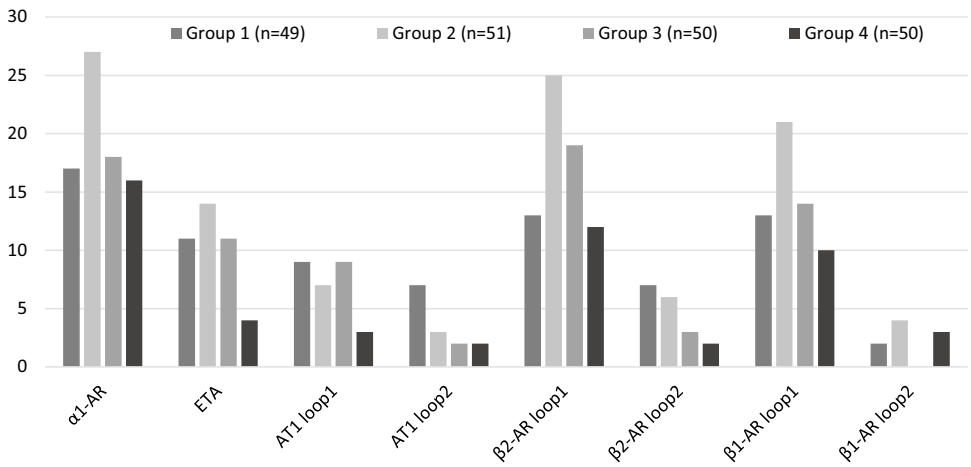

Fig. 1 Number of agonistic autoantibodies detected per epitope in each group. *AR* adrenergic receptor, *ETA* Endothelin A, *AT* Angiotensin 1

agonistic autoantibodies per patient. In addition, the influence of sex and smoking was tested. None of the analyses revealed a statistically significant association.

Correlation analyses further performed for prescribed drugs and either positivity or number of antibodies. Drugs investigated were all anti-hypertensives by classes, statins and fibrates, corticosteroids, and the daily dose of insulin. These analyses did as well not show any association with the presence of agonistic antibodies. Furthermore, no statistically significant association was found between type of antidiabetic therapy (including adapted nutrition therapy) and prevalence of any investigated antibody.

Multivariate regression analysis was performed for the presence of any agonistic antibody detectable against the parameters: ever smoked, hypertension, number of antihypertensive drugs, therapy with statins, any macrovascular event, duration of diabetes, intake of corticosteroids, and GFR. This only identified a statistically significant association between the presence of antibodies and any macrovascular event ($p = 0.028$).

Regression analyses for the number of agonistic antibodies detected per patient against independent variables [ever smoked, any macrovascular event, number of antihypertensive drugs, therapy with statins or fibrates, duration of diabetes, daily dose of insulin and renal function (GFR)] yielded a statistically significant association for the therapy with statins or fibrates ($p = 0.036$) and an inverse associations for the dose of insulin ($p = 0.039$).

We also tested the three most often found agonistic autoantibodies against the before-mentioned independent variables. It only revealed a significant result for the antibody directed against beta2 loop1 and macrovascular complications ($p = 0.021$).

Aggregation of the single epitopes of all receptors (Loop1 and 2) did not show any influence on statistical testing.

Discussion

In this cross-sectional, monocentric study, we were able to investigate the prevalence and possible impact of agonistic autoantibodies against adrenergic receptors in patients with diabetes mellitus type 2. We found several differences of the baseline characteristics of the patients between the groups. All of them are explainable by the inclusion criteria of the groups. For example, the rate of severe accompanying diseases and diabetic complications is associated with higher age, longer duration of diabetes, and the presence of classical-risk factors such as smoking and obesity. HbA1c and renal function are known to have and age-dependent development [29]. Diabetic foot syndrome, as one of the diabetic complications, was mostly present in Group 4, as the causing factor of diabetic polyneuropathy also evolves over time. Amputation as a diabetic complication was only present in Group 4. The patient in Group 3 experienced traumatic amputation years ago. Dementia was only known in three cases, not enabling us to perform reasonable analyses belonging this clinical feature.

A single measured blood-pressure value is very vulnerable to bias by many causes and does not necessarily reflect the severity of the hypertension in already treated patients. Therefore, we choose to register the number and class of antihypertensive drugs prescribe to the patient as a surrogate for severity of hypertension. As expected, the number of antihypertensive drugs increased over groups in accordance with age, duration of diabetes, and diagnosis of hypertension. As arterial hypertension is a classical cardiovascular risk factor, patients in Group 4 who had suffered most complications and also were prescribed the largest amount of antihypertensive drugs. Statins and fibrates as lipid modifying drugs showed the same distribution over the four groups. They are used either as primary or secondary prophylaxis. The rationale to divide the data into four groups was to assess the possible influence of the duration of the diabetes and the presence of diabetic complications on the prevalence of the investigated antibodies. We assumed that the antibodies either evolve over diabetes duration or vanish after they have been present at the beginning. As this was a cross-sectional investigation, we used the different times since diagnosis to shed light on this issue, as we had no follow-up data available. Furthermore, we assumed an association between the antibodies and the presence or evolvement of diabetic complications. To our knowledge, little is known about the prognostic value of these biomarkers. Detectable agonistic antibodies showed a special distribution between groups. Interestingly, most antibodies were found in the group of patients who had the diagnosis of diabetes for 5–10 years, and the less in those who had the most diabetic complications. As this is the only difference that showed significant, we are thinking of reasons for this finding, as correlation analyses with recorded risk factors did also not show any significance.

Based on these results, we want to raise the hypothesis that the prevalence of the investigated antibodies decreases over disease duration. This phenomenon is known in other autoimmune disorders, e.g., for Hashimoto's thyroiditis. To further investigate this hypothesis, prospective studies are needed. Therefore, we are planning a follow-up of the patients in this study. This may also give further information about a possible prognostic value of the investigated antibodies for further diabetic complications. Of special interest are going to be the patients of Group 2. As they were most frequently tested positive for antibodies, it will be interesting if there will be any correlation of the evolvement of diabetic complications and the antibodies detected now.

Regression analyses revealed some further associations of antibodies and clinical features. The presence of macrovascular events and a higher daily dose of Insulin lowers the risk of the detection of agonistic antibodies. This seems concordant with the finding of decreased prevalence in antibodies with a longer duration of diabetes.

An interesting finding is the association of positive AgAAB against the first loop of the beta2 adrenergic receptor and any macrovascular event. This finding stands in line with our preliminary data, where the same antibody correlated with the number of antihypertensive drugs taken [26]. This antibody seems to be the most interesting candidate for further investigations. It is associated with non-ischemic dilatative cardiomyopathy and a potential role in its pathogenesis is discussed. In addition, therapies basing on this concept such as immunoapharesis have been probed and showed positive effects [30]. Maybe, we will find more clues by follow-up of our patients.

Limitations of our work are the limited amount of patients. As the laboratory investigations are cost-intensive, we needed to restrict the number of patients. Due to effort to discriminate between the different stages of diabetic complications, group-size is small. Furthermore, heterogeneity of groups was inevitable, as diabetic complications are known to evolve over time.

Another limitation might be the method used to detect the autoantibodies. Some authors state that an ELISA using the whole receptor antigen and not only short peptide sequences is more sensitive in detecting autoantibodies [31].

Conclusion

In this cross-sectional study, we found a correlation between the prevalence of agonistic autoantibodies against the beta2-receptor and macrovascular complications. These results may suggest a role in pathogenesis, but further evaluation by prospective studies, e.g., by follow-up investigations of our patients will be inevitable to gain more knowledge about these potential pathogenetic factors and their prognostic value.

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Compliance with ethical standards

Conflict of interest Investigations were substantially financed by Fresenius medical care GmbH, Germany. The sponsor had no influence on study design, data processing or manuscript editing. C.W. received travel funding by Novartis oncology. All authors declare not further conflicting interests.

Ethical approval All investigations were approved by ethics-committee of the University of Jena (number of decision: 4916-09/16).

Informed consent All patients gave informed consent to laboratory investigations and data processing.

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