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1, 5-Anhydroglucitol as Marker of Short-Term Hyperglycemic Excursions in Well-Controlled Type 2 Diabetes Mellitus: Associations with the Prevalence of Vascular Complications

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Summary

Background: Intermittent states of hyperglycemia have been identified as risk factor for vascular complications of type 2 diabetes mellitus independent from the mean blood glucose level. 1,5-Anhydroglucitol (1,5-AG) levels decrease when blood glucose is elevated above the renal threshold and has recently been proved as marker of intermittent, e.g. postprandial hyperglycemia. The objective of this cross-sectional study is to identify if 1,5-AG is related to the prevalence of vascular complications in patients with well-controlled type 2 diabetes mellitus.

Methods: 164 patients with type 2 diabetes mellitus and hemoglobin A1c (HbA1c) ≤ 7 % under stable glycemic control were recruited between 2007 and 2010. Sera were analyzed for the 1,5-AG level using an enzymatic test (Glykomark™). Besides other relevant laboratory, biometric and demographic findings, the concomitant therapy and the prevalence of macrovascular (coronary heart disease, peripheral arterial disease, cerebrovascular disease) as well as microvascular (retinopathy, nephropathy) complications were recorded. After differentiation of the patients into cohorts with adequately and inadequately controlled diabetes mellitus according to 1,5-AG levels the prevalences of vascular complications and the used antidiabetic treatments in those groups were compared.

Results: There were no significant differences between patients with normal or reduced 1,5-AG levels regarding demographic and laboratory parameters as well as the kind of therapy. Prevalence of macro- and microvascular complications was 31.7% and 39%, respectively. There were no significant differences in the prevalence of macro- or microvascular complications between the subjects with normal and those with reduced 1,5-AG level. Also the surrogate parameters of cardiovascular complications (NT-proBNP, homocysteine and vitamin D) did also not show any differences between both groups.

Conclusion: In patients with well-controlled type 2 diabetes mellitus, no differences could be found concerning the prevalences of micro- and macrovascular complications between subjects with normal compared to reduced 1,5-AG levels.

Keywords: Type 2 Diabetes Mellitus; Metabolic Control; Intermittent Hyperglycemia; Hemoglobin A1C; 1,5-Anhydroglucitol; Vascular Complications; Insulin Analogues

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Introduction

The importance of an appropriate and stable long-term mean glycemic control, commonly measured by the HbA1c, for the incidence of diabetic complications has been widely recognized [1–4]. The HbA1c reflects the glycemic metabolism of the past 2-3 months and can therefore be recognized as long-term glycemic marker. In contrast, it is only slightly influenced by short-term glycemic excursions, e.g. states of postprandial hyperglycemia. However, short-term excursions also seem to exhibit pathogenetic significance for the development of vascular complications [5–8].

Today the measurement of 1,5-Anhydroglucitol (1,5-AG) provides a reliable opportunity to assess the frequency and extent of intermittent hyperglycemic excursions [9–11]. 1,5-AG is a monosaccharide, which originates to the greatest extent from dietary uptake [12]. Only a little amount is supposed to derive from hepatic synthesis [13]. 1,5-AG is filtrated in the glomerulus and physiologically almost completely reabsorbed in the proximal tubules in competition with glucose [14]. Consequently in presence of hyperglycemia above the renal threshold 1,5-AG is excreted with the urine and the circulating serum levels of 1,5-AG decrease [12]. Therefore 1,5-AG levels reflect intermittent states of hyperglycemia [15].

In the present study we examined the association between 1,5-AG levels and the kind of antidiabetic therapy as well as the prevalence of diabetic complications in a cohort of patients with type 2 diabetes mellitus under adequate glycemic control according to HbA1c.

Methods

164 consecutive patients with type 2 diabetes mellitus under good metabolic control (HbA1c ≤ 7 %) were recruited from the outpatient diabetes clinic of the St. Josefskrankenhaus Heidelberg and the Diabetesinstitut Heidelberg between 2007 and 2011. These patients represent a subgroup of the participants of an observational study on type 2 diabetes previously described in detail [16]. Besides biometric and demographic data (body height and weight, Body Mass Index (BMI), sex, age, and duration of diabetes) and the concomitant therapy the following laboratory parameters were recorded: HbA1c, 1,5-AG, serum lipids (LDL-, HDL- and total cholesterol), triglycerides, serum creatinine, estimated Glomerular Filtration Rate (eGFR) using the formula by Cockcroft-Gault, urinary albumin-creatinine-ratio, and biomarkers (high sensitive (hs) CRP, NT-proBNP, homocysteine, vitamin D). Aliquots of serum and urine probes were stored immediately after withdrawal at -80°C. The kind of insulin therapy was classified as: intensified insulin therapy (i.e. 3 or more insulin injections per day), Basal supported Oral Therapy (BOT, i.e. oral antidiabetic drugs combined with basal insulin), and Supplementary Insulin Therapy (SIT, i.e. oral antidiabetic drugs in combination with mealtime insulin therapy).

Furthermore we evaluated the prevalence of micro- and macrovascular complications based on any history of cardiovascular (myocardial infarction, percutaneous transluminal coronary angioplasty or coronary artery bypass graft), cerebrovascular (ischemic stroke, transient ischemic attack or thrombendarterectomy of the carotid arteries), peripheral vascular (percutaneous transluminal angioplasty, arterial bypass or amputation), renal (eGFR < 60 ml/min or presence of micro- or macroalbuminuria, i.e. urinary albumin-creatinine-ratio > 30 mg/g), and ophthalmological (diabetic retinopathy) diseases. Patients were excluded from the study according to the presence of at least one of the following criteria: malignoma, liver cirrhosis, congestive heart failure, renal insufficiency (eGFR < 30 ml/min), acute infection, asthma, rheumatoid arthritis requiring therapy, history of organ transplantation, congenital cardiac or renal anomalies, pregnancy, treatment with SGLT2-inhibitors.

1,5-AG was analyzed in serum samples by an enzymatic test (Glykomark™). The Glykomark™-test has been recently approved for monitoring the intermediate glycemic control by the FDA in the USA and by means of the CE-certificate in the EU. Clinical trials confirmed the accuracy and

proved that the test's results should not be influenced by hemoglobin, triglycerides, bilirubin, blood glucose, maltose, ascorbic acid, uric acid, urea or creatinine [17, 18]. 1,5-AG is stable in frozen probes. The samples may be even thawed and re-frozen for several times [19]. Samples used in this study were thawed only once for analyses of the 1,5-AG and GA levels in 2013.

The quality of glycemic control according to the 1,5-AG was defined by the following criteria:

- 1,5-AG > 10 µg/ml: good glycemic control

- 1,5-AG 6-10 µg/ml: moderate glycemic control

- 1,5-AG ≤ 5 µg/ml: insufficient glycemic control

The statistical analyses were performed using MedCalc (Version 11.1.1.0, MedCalc Software, Mariakerke, Belgium). The descriptive statistics comprise the calculation of means and standard deviations as well as absolute and relative frequencies. Continuous variables were compared using the Student's t-test. Differences between frequencies were analyzed by the chi-square test. Results were considered statistically significant when $p < 0.05$. The study was approved by the local ethics committee and was conducted according to the Declaration of Helsinki. Written informed consent was obtained from all subjects prior to participation.

Results

Table 1 shows the most important demographic and laboratory findings. The age and BMI are consistent with a typical cohort of patients with type 2 diabetes mellitus. Mean duration of diabetes was 9.2 years. About ¾ of the subjects were treated with oral antidiabetic agents, most frequently with metformin or sulfonylurea (table 2). About one third of the patients applied insulin, most of them performing an intensified therapy (67.4 %). The frequencies of the applied insulins (human insulin or insulin analogues) are also shown in table 2.

Table 1: Main demographic and laboratory findings (mean ± standard deviation).

	Total (n=164)	1, 5-AG ≤ 10 µg/ml (n=53)	1, 5-AG >10 µg/ml (n=111)	p
Age [years]	64.4 ± 8.2	64.3 ± 8.1	64.4 ± 8.3	0.9421
Duration of diabetes [years]	9.2 ± 9.7	9 ± 9	9.4 ± 10.1	0.8064
Body Mass Index [kg/m^2]	30.4 ± 4.7	30.2 ± 4.5	30.5 ± 4.8	0.7031
Hemoglobin A1C [%]	6.3 ± 0.5	6.4 ± 0.4	6.3 ± 0.5	0.2046
1,5-Anhydroglucitol [µg/ml]	12.7 ± 5.2	6.9 ± 2	15.4 ± 3.7	< 0.0001
Total cholesterol [mg/dl] (*)	187.5 ± 40.2 (n=131)	177.4 ± 35 (n=37)	192.4 ± 41.7 (n=94)	0.0552
LDL cholesterol [mg/dl] (*)	114.7 ± 31.5 (n=131)	107.1 ± 28.8 (n=37)	118.4 ± 32.2 (n=94)	0.065
HDL cholesterol [mg/dl] (*)	52.1 ± 16.2 (n=131)	51.4 ± 14.4 (n=37)	52.5 ± 17 (n=94)	0.7289
Triglycerides [mg/dl] (*)	152.7 ± 95.8 (n=131)	142.3 ± 86.4 (n=37)	157.7 ± 99.9 (n=94)	0.4116
Hemoglobin [g/dl]	13.9 ± 1.3	14.1 ± 1.1	13.9 ± 1.4	0.3623
Leukocytes [/nl]	6.7 ± 2	6.7 ± 1.9	6.7 ± 2	1
Estimated glomerular filtration rate [ml/min]	90.1 ± 26.5	90.7 ± 28.2	89.8 ± 25.8	0.8396
Urinary albumin/creatinine-ratio [mg/g]	39.5 ± 116	45.2 ± 172.6	36.7 ± 76.3	0.662
hsCRP [mg/l]	3.56 ± 4.75	3.19 ± 4.3	3.74 ± 4.96	0.4897

NT-proBNP [ng/l]	188.2 ± 381.4	157.5 ± 223.8	202.5 ± 436.4	0.4807
Homocysteine [µmol/l]	14.4 ± 4.4	13.8 ± 3.8	14.8 ± 4.6	0.1714
25-Hydroxy-Cholecalciferol [µg/l]	24.4 ± 11.7	25.3 ± 11.7	24 ± 11.7	0.5067
Blood pressure, systolic [mmHg]	143.5 ± 17.8	146.6 ± 19.8	142 ± 16.6	0.1213
Blood pressure, diastolic [mmHg]	78.2 ± 10.8	79.5 ± 11.3	77.6 ± 10.6	0.2949

(*) 33 patients were excluded from the analysis of serum lipids due to their non-fasting status.

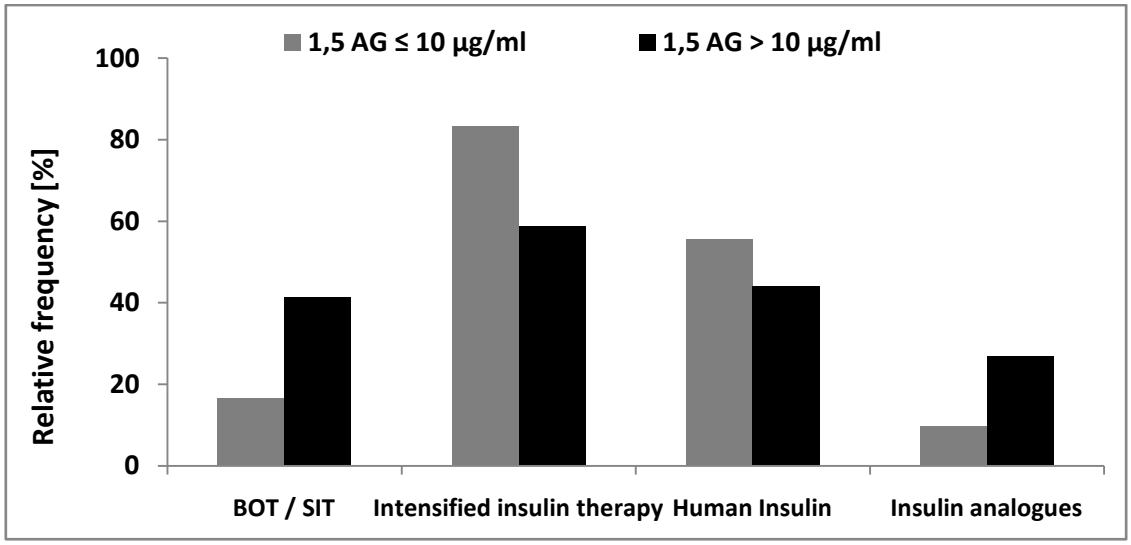
Table 2: Antidiabetic, antihypertensive and other pharmacologic treatments (absolute and relative frequencies).

	Total (n=164)	1,5-AG ≤ 10 µg/ml (n=53)	1,5-AG > 10 µg/ml (n=111)	p
Oral antidiabetic agents	121 (73.8%)	39 (73.6%)	82 (73.9%)	0.8816
Metformin	97 (80.2%)	28 (71.8%)	69 (84.1%)	0.1017
Sulfonylurea	40 (33.1%)	17 (43.6%)	23 (28%)	0.0705
Others	22 (18.2%)	6 (15.3%)	16 (19.5%)	0.6627
Other medication				
Antihypertensive treatment	133 (81.1%)	43 (81.1%)	90 (81.1%)	0.8311
Lipid lowering treatment	77 (47%)	26 (49.1%)	51 (45.9%)	0.8284
Platelet inhibition	61 (37.2%)	19 (35.8%)	42 (37.8%)	0.9401
Anticoagulation	14 (8.5%)	5 (9.4%)	9 (8.1%)	0.9839

The majority of subjects (81.1 %) suffered from arterial hypertension that required pharmaceutical antihypertensive treatment. The most frequently given antihypertensive drugs were Angiotensin-Converting Enzyme (ACE) inhibitors or Angiotensin 2-Receptor Blockers (ARB) in 86 %, diuretics in 65 % and beta-blockers in 60 % of the patients. Almost half of the patients were treated with a lipid lowering medication (47 %). There was no subject with a severe renal insufficiency. The eGFR was > 50 ml/min in all the cases.

All participants had HbA1c values of ≤ 7 %. The mean 1,5-AG level was 12.7 ± 5.5 µg/ml. About one third of the patients (32.3%) had reduced 1,5-AG values ≤ 10 µg/ml indicating an inadequate glycemic control. In about 19% of these patients the 1,5-AG level was even < 5 µg/ml. For further analyses patients were stratified according to the 1,5-AG level of > 10 µg/ml on the one hand and ≤ 10 µg/ml on the other hand. There were no significant differences between the two groups concerning the relevant demographic and laboratory findings (table 1). Also the pharmacologic therapy of arterial hypertension, dyslipidemia and thrombocytic hypercoagulability did not significantly differ. However, the kind of antidiabetic therapy showed slight differences. Subjects with normal 1,5-AG levels were by trend more often treated with metformin (84 %) and less often with sulfonylurea (28 %) than the patients with reduced 1,5-AG (72 % and 44 %, respectively). The differences concerning the insulin therapy and the applied insulins are shown in figure 1. Subjects with normal 1,5-AG levels more often applied a BOT or SIT and less often an intensified insulin therapy than those with reduced 1,5-AG. The use of insulin analogues was more frequent in patients with normal 1,5-AG than in reduced 1,5-AG levels. However these differences were found only by trend but not statistically significant.

Figure 1: Kind of insulin therapy in patients with diabetes mellitus type 2 with 1,5-AG levels ≤ 10 µg/ml versus > 10 µg/ml [relative frequencies in insulin treated patients].



BOT: Basal supported Oral Therapy

SIT: Supplementary Insulin Therapy

The prevalence of micro- and macrovascular complications are given in table 3. About one third of the patients (31.7 %) already had macrovascular complications. Most frequently they suffered from coronary heart disease and peripheral arterial vascular disease. Microvascular complications were found in about 39% of the patients, mostly as an increase of the albumin/creatinine-ratio. We could not find any significant differences in the prevalences of macro- or microvascular complications between the subjects with normal and those with reduced 1,5-AG level. Also the surrogate parameters of cardiovascular complications (NT-proBNP, homocysteine and vitamin D) did not show any differences between the two groups (table 1).

Table 3: Micro- and macrovascular complications in patients with diabetes mellitus type 2 with 1,5-AG levels ≤ 10 µg/ml versus > 10 µg/ml (absolute and relative frequencies).

	Total (n=164)	1.5-AG≤ 10 µg/ml (n=53)	1.5-AG > 10 µg/ml (n=111)	p
Macrovascular complications	52 (31.7%)	16 (30.2%)	36 (32.4%)	0.9173
Coronary heart disease	26 (15.9%)	8 (15.1%)	18 (16.2%)	0.9616
Cerebrovascular disease	19 (11.6%)	8 (15.1%)	11 (9.9%)	0.4762
Peripheral arterial occlusive disease	24 (14.6%)	7 (13.2%)	17 (15.3%)	0.9047
Microvascular complications	64 (39%)	22 (41.5%)	42 (37.8%)	0.777
Diabetic retinopathy	24 (14.6%)	9 (17%)	15 (13.5%)	0.7211
eGFR < 60 ml/min	16 (9.8%)	7 (13.2%)	9 (8.1%)	0.4542
Urinary albumin / g creatinine> 30 mg	37 (22.6%)	10 (18.9%)	27 (24.3%)	0.5659

Discussion

In the present study we analyzed the association between serum levels of 1,5-AG as a marker of short-term glycemic excursions and different kinds of antidiabetic therapies as well as the prevalences of vascular complications in well-controlled type 2 diabetes mellitus. The results show that (a) one third of the diabetic patients with good long-term glycemic control based on HbA1c ≤ 7 % have reduced serum levels of 1,5-AG of ≤ 10 µg/ml and (b) no significant association could be found between the reduced 1,5-AG levels and the prevalence of vascular complications.

1,5-AG is a naturally occurring dietary monosaccharide that is excreted via glomerular filtration and in healthy individuals reabsorbed almost completely via the proximal tubule [14]. In times of hyperglycemia that exceeds the renal threshold and thereby causes glucosuria the glucose in the urine competitively inhibits the reabsorbtion of 1,5-AG [12]. In states of glucosuria the urinary excretion of 1,5-AG is increased and the serum levels are correspondingly reduced [15]. Whereas HbA1c is affected by hypoglycemia as well as hyperglycemia, 1,5-AG only decreases in times of significant glucosuria. Previous studies using Continuous Glucose Monitoring (CGM) systems showed significant correlation between 1,5-AG and parameters of glycemic variability and hyperglycemia [20]. Partly the significant correlation between 1,5-AG and parameters of CGM has only been proved in patients with at least moderately controlled diabetes mellitus (HbA1c ≤ 8.0%). In those patients with HbA1c ≤ 8.0% 1,5-AG is therefore accepted as an indicator of hyperglycemic excursions, which reflects the preceeding 7-14 days [9–11].

Intermittent short-term hyperglycemic excursions are quite common in patients with well-controlled HbA1c. Despite an HbA1c of ≤ 7% about 32% of the patients in our study had a reduced 1,5-AG level of ≤10 µg/ml. An 1,5-AG level < 5 µg/ml was found in 6% of all patients. These findings have not been reported by other studies yet. We found no significant differences between patients with normal and reduced 1,5-AG levels concerning demographic and laboratory parameters as well as concerning the pharmacological therapy of arterial hypertension, dyslipidemia and thrombocytic hypercoagulability. Also there were no significant differences in the antidiabetic therapy between the two groups, although we could find therapeutic differences by trend: Patients with normal 1,5-AG level tend to be treated more often with metformin and less frequently with sulfonylurea or an intensified insulin therapy. This might be seen as a yet better insulin secretion with corresponding positive effects on the postprandial glycemic excursion. To achieve a more effective and stable glycemic control several insulin analogues have yet been approved. In particular the administration of rapid-acting insulin analogues is supposed to reduce the incidence of short-term hyperglycemic excursions [21-23]. In our present study patients with normal 1,5-AG levels were also by trend more often treated with insulin analogues. However these differences were found only by trend but not statistically significant.

Previous studies have already shown that only a part of the vascular complications of diabetes mellitus can be explained by increased HbA1c values. There have to be other factors that are associated with macrovascular diseases independently from HbA1c [24]. In this context the glycemic variability with intermittent hyperglycemia is supposed to have an independent significance for the development of vascular complications [25]. Increased postprandial blood glucose was found to be associated with the incidence of cardiovascular events [26] as well as an increased arterial stiffness [27] in type 2 diabetic patients.

Our present results did not prove any relationship between 1,5-AG levels and the prevalence of micro- and macrovascular complications. Also cardiovascular surrogate parameters, i.e. NT-proBNP, hsCRP, homocysteine and vitamin D did not show any differences between both of the groups as well. Our findings therefore could not confirm the results of other previous studies. Several study groups found a relation between decreased levels of 1,5-AG and the incidence of cardiovascular diseases. [28, 29] Furthermore, Kim et al.

supposed a significant correlation of 1,5-AG with the prevalence of diabetic retinopathy [30].

These varying results could be probably explained by differences in the examined groups of patients and the study design. We only included patients with a well-controlled HbA1c ≤ 7.0%, whereas the other studies were not limited according to the HbA1c [28, 29]. Our results are based on a cross-sectional study with a defined number of patients. This might be seen as a limitation of the present examination. However patients of our study cohort are quite homogeneous, especially concerning age, duration of diabetes, body mass index, and renal function. Confounding factors interfering with the renal excretion of 1,5-AG, e.g. renal function and age-related differing renal glycemic thresholds, could be excluded.

In summary the measurement of 1,5-AG levels for the first time provides a marker for the evaluation of short-term hyperglycemic excursions. One third of our patients with according to HbA1c well-controlled diabetes mellitus type 2 showed reduced 1,5-AG levels. We could not find a relationship between 1,5-AG levels and the prevalence of macro- and microvascular complications. Therefore the relevance of short-term hyperglycemic excursions for the development of vascular complications should be furthermore examined using this parameter.

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Compending interest: The authors declare that they have no compending interests.

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