Is There a HbA1c Threshold for Symptoms of Chronic Hyperglycaemia?

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Abstract

Aims of the study: The minimum therapeutic goals regarding metabolic control for people with diabetes mellitus is “absence of symptoms of hyperglycaemia”. However, it is uncertain, if a level of HbA1c can be defined which guarantees the absence of these symptoms. The aim was to define an HbA1c threshold above which most patients show hyperglycaemic symptoms.

Methods: In a multicenter cross-sectional study 137 patients with type 1 and 285 with type 2 diabetes were asked about their symptoms during periods of hyperglycaemia with a standardized questionnaire. Seventeen symptoms of hyperglycaemia were summarized to the total hyperglycaemia symptom score (THSS; min. 0; max. 68). The answers could be given according to the frequency and intensity in the last 4 to 6.

Results: The HbA1c threshold above which most patients showed hyperglycaemic symptoms was for patients with diabetes type 1 10.05% and with type 2 8.9%. Most confidence was reached on the symptoms of frequent urination” and “tiredness”. The mean THSS was 19.4 (± 9.0) and showed a positive correlation with age ($r=0.167$; $p<0.001$) and HbA1c ($r=0.254$; $p<0.001$).

Conclusions: We identified a HbA1c threshold above which most patients show symptoms of hyperglycaemia. In the treatment of people with diabetes mellitus a safety margin to this threshold should be maintained to preserve well-being and avoid distress. However, since hyperglycaemia symptoms are subject to many influencing factors, an adjustment of the therapy, both intensification and de-intensification, should always be carried out in combination with the requested hyperglycaemia symptoms and HbA1c value.

Introduction

Hyperglycaemia is associated with diabetes-related microvascular and macrovascular complications [1, 2]. These complications are often the result of poor glycaemic control of over a longer period of time. This is the reason why healthy younger adults are counseled to keep tight glycaemic control in order to prevent microvascular and macrovascular complications. According to most guidelines, this therapeutic goal is achieved with a HbA1c of 6.5 to 7.5% [3–5]. However, clinical trials have demonstrated that about 8 years of tight glycaemic control are necessary to yield benefits in terms of vascular endpoints [6].

Most patients with type 2 diabetes mellitus are 65 years and older and many of them are frail and have functional deficits and other chronic conditions, which limit their life expectancy [6–9]. In these elderly patients intensive glucose-lowering therapy may be more harmful than beneficial, because they are more vulnerable to hypoglycaemia [10]. For this reason, the current guidelines recommend a less stringent therapeutic goal for patients, who have, for example, reduced life expectancy or extensive comorbidities [3, 4]. In the National Disease Management Programme for Diabetes mellitus type 2 in Germany two different therapeutic goals regarding metabolic control were defined: “Prevention of microvascular

complications” for patients with substantial life expectancy and “absence of symptoms of hyperglycaemia” for patients with reduced life expectancy.

Also the ADA recommends for older adults to avoid substantial hyperglycaemia for a prolonged period of time producing symptoms of hyperglycaemia [11].

Hyperglycaemia can evoke various symptoms such as increased thirst, poly- and nocturia, fatigue, physical weakness and lack of concentration [12]. Hyperglycaemia-related symptoms can cause distress which is associated with increased negative mood and worse well-being and health related quality of life [13–15]. However, up to now it is uncertain, if a threshold level of HbA1c exists which guarantees the absence of symptoms.

We examined the question which metabolic control in terms of HbA1c values may be required to achieve the treatment goal “absence of symptoms of hyperglycaemia” in patients with diabetes type 1 and 2.

Patients And Methods

In a multicenter cross-sectional study, inpatients and outpatients with diabetes mellitus type 1 and type 2 were asked about their symptoms during periods of hyperglycaemia in the last 6–8 weeks using a standardized questionnaire. Blood glucose measurement was recommended before the patient interview to exclude hypoglycaemia. The questionnaire should not be answered with a blood glucose below 4 mmol/. Hyperglycemia was not defined with specific blood glucose values. Seventeen symptoms of hyperglycaemia (dry mouth, excessive thirst, thirst during the night, frequent urination during night and day, fatigue, lack of energy, low performance, lack of concentration, need for midday nap, increased sleepiness, frequent infections, itching in the genital region, impaired wound healing, nausea, impaired vision, leg cramps during the night) were summarized to form the total hyperglycaemia symptom score (THSS; min 0, max 68). Frequency and intensity of these symptoms in the last 4 to 6 weeks could be scored from never = 0 to always = 4. Inclusion criteria were: diabetes type 1 or type2, at least age of 18 years, positive consent and the exclusion criteria were: Pregnancy, birth, abortion or miscarriage or major operations of all types within the last three months, anemia due to blood loss or haemolysis, diseases of the haematopoietic system, immunosuppression (transplanted, autoimmune diseases), all forms of alcoholism, psychiatric diseases (psychoses, bipolar depression, dementia), neurological diseases (apoplexy with permanent defects, pronounced pareses and dystrophies, Alzheimer's disease, multisystem atrophies, cancer in advanced stages and with reduced general condition, other serious diseases of the heart, liver, lung, kidney (dialysis patients) and intestine, severe other endocrinological diseases of the thyroid gland, the hypothalamus-pituitary anterior lobe axis, the adrenal glands and the presence of diabetes insipidus. 558 patients with diabetes (29% Type 1) could be recruited. Patients with depression (detected by the DS-Depression-Scale (according to Zerssen [16]) and heart failure (NYHA III / IV) were excluded. Finally data of 422 patients (137 type 1 diabetes and 285 type 2 diabetes) could be analyzed.

Diabetes treatment satisfaction was measured by the questionnaire by C. Bradley. HbA1c was adjusted to the level of the DCCT study using the mean normal value of healthy people to the level of the DCC trial [5.05% (32 mmol/mol)]. Laboratory and clinical data were collected from the patients record.

Outcome

The aim was to define an HbA1c threshold above which most patients show hyperglycaemic symptoms and to single out the specific symptoms which most clearly indicate a state of hyperglycaemia.

Statistical Analysis

Statistical analyses of the data were performed using the Statistical Package for the Social Sciences (SPSS), version 26.0 (IBM). Normally distributed values were registered as mean $\pm$ SD and non-normally distributed values as median and range. Comparisons were evaluated with Chi-Square Test and incidences < 6 with the exact test of Fischer. Student's *t*-test and Wilcoxon tests were used to compare the mean. First, the correlation of the symptoms (scale of 0 (never)-4 (always)) with the HbA1c was checked and the significant symptoms were used for further analysis. A score of 0–2 was classified as "not present" and a score of 3–4 was combined as existing symptoms. ROC analysis was used to determine the sensitivity and specificity for each possible HbA1c threshold. The optimal cut-off was determined from the maximum sum of sensitivity and specificity.

Statistical significance was defined as a p value less than 0,05.

Results

Baseline characteristics of included patients are listed in Table 1. The mean HbA1c of patients with type 1 diabetes was 7.7% (61.0 mmol/mol) and ranged from 5.10 to 16.35% (32.2 to 155.2 mmol/mol) and of patients with type 2 diabetes with a mean of 7.8% (61.2 mmol/mol) ranging from 3.95 to 13.95% (19.7 to 129.0 mmol/mol).

Table 1
Patient characteristics (means and SD)

	Type 1 diabetes n = 137	Type 2 diabetes n = 285
Age (years)	44.9 ± 13.5	62.0 ± 10.7
Duration of diabetes (years)	17.5 ± 13.1	12.6 ± 8.9
HbA1c (DCCT adj. in %)	7.7 ± 1.5	7.8 ± 1.5
HbA1c (DCCT adj. in mmol/mol)	61.0 ± 16.7	61.2 ± 16.8
BMI (kg/m ²)	26.0 ± 3.7	31.3 ± 5.5
DTSQ	29.2 ± 5.0	29.9 ± 5.2
Female (%) (n)	47.4 (65)	40.0 (114)
Therapy with CSII (%)	21.2 (29)	0
Therapy with insulin (%)	100 (137)	68.8 (143)
Therapy with oral antihyperglycaemic agents (%)	0	42.1 (120)
Therapy with antihypertensive agents (%)	39.4 (54)	83.2 (237)

The best overall coincidence was obtained with the symptoms “frequent urination” and “tiredness”. All other symptoms received an approval rating of less than 20% (Table 2).

Table 2
Absolute endorsement rates for each of the 17 symptoms in %

Symptom	Type 1 diabetes n = 137	Type 2 diabetes n = 285	All n = 434
Dry mouth	3.6%	10.9%	8.8%
excessive thirst	6.6%	10.2%	10.4%
thirst during the night	5.1%	6.3%	6.0%
frequent urination during night	21.9%	37.2%	32.0%
frequent urination during day	12.4%	22.1%	19.4%
Fatigue	7.3%	14.7%	13.6%
lack of energy	5.8%	9.8%	9.2%
low-performance	8.8%	16.8%	14.5%
lack of concentration	2.2%	3.9%	3.5%
need for midday nap	12.4%	30.9%	24.7%
tiredness	26.3%	29.6%	28.6%
frequent infections	2.9%	5.3%	4.4%
itching in the genital region	3.6%	3.9%	3.9%
impaired of wound healing	8.0%	9.8%	9.2%
Nausea	3.6%	0.4%	1.4%
Visual impairment	5.1%	6.7%	6.5%
leg cramps during the night	0	4.9%	3.7%

The mean total hyperglycaemia symptom score (THSS) was 19.4 ($\pm$ 9.0) and showed a significant positive correlation with age ($r = 0.167$; $p < 0.001$) and HbA1c ($r = 0.254$; $p < 0.001$). A higher satisfaction in DTSQ correlates significantly with a lower THSS ($r = -0.196$; $p < 0.001$). A higher THSS correlated especially with the impression of the patients that their blood glucose was unacceptably high in the last few weeks ($r = 0.222$; $p < 0.001$), but not with the impression that their blood glucose was unacceptably low ($r = -0.008$; $p = 0.869$).

When considering hyperglycaemia symptoms one by one, the HbA1c value showed a significant correlation for the following: “dry mouth”, “excessive thirst”, “thirst during the night”, “urgency”, “fatigue”, “lack of energy”, “low performance”, “lack of concentration”, “itching in the genital region” and “visual impairment” (Table 3). In a second step we merged similar symptoms in one category. The symptoms “dry mouth”, “excessive thirst” and “thirst during the night” were merged into the category “thirst” and the

symptoms “fatigue”, “lack of energy”, “low performance” and “lack of concentration” were combined into the category “performance”. Further analyses were done with the now overall five categories, “thirst”, “performance”, “itching”, “visual impairment” and “urgency”.

Table 3
Correlations of HbA1c and symptoms of hyperglycaemia

Symptom	Coefficient of correlation (r)	p-Value
Dry mouth	0.276	< 0.001
excessive thirst	0.340	< 0.001
thirst during the night	0.322	< 0.001
frequent urination during night	0.082	0.087
frequent urination during day	0.195	< 0.001
Fatigue	0.162	0.001
lack of energy	0.105	0.029
low-performance	0.113	0.018
lack of concentration	0.164	0.001
need for midday nap	0.090	0.062
tiredness	-0.005	0.914
frequent infections	0.068	0.157
itching in the genital region	0.153	0.001
impaired of wound healing	0.026	0.594
Nausea	0.058	0.225
Visual impairment	0.141	0.003
leg cramps during the night	0.078	0.107

Cut-off in patients with type 1 diabetes

The optimal cut-off of the HbA1c-value for occurrence of hyperglycaemia-related symptoms was 10.05% (1.99 fold above normal mean) in patients with diabetes type 1. The sensitivity and specificity for the symptom “thirst” was 25.0% and 95.1% respectively, for the symptom “performance” 14.3 and 94.5%, for the symptom “itching” 22.2% and 93.5%, for the symptom “visual impairment” 28.6% and 94.6% and for the symptom “urgency” is the sensitivity 13% and the specificity 93.5%.

In the analysis of the ROC curves, the area under the ROC curves for “performance” was 0.551 [CI 0.406–0.697], for “thirst” 0.695 [CI 0.544–0.847], “itching” 0.614 [CI 0.385–0.843], “visual impairment” 0.725

[0.481–0.968] and for “urgency” 0.628 [CI 0.484–0.772] (Fig. 1).

Cut-off in patients with type 2 diabetes

The optimal cut-off of the HbA1c-value for the occurrence of hyperglycaemia-related symptoms was 8.9% (1.76 fold above normal mean) in patients with diabetes type 2. The sensitivity and specificity for the symptom “thirst” was 31.3% and 86.7%, respectively, for the symptom “performance” 23.3 and 85.6%, for the symptom “itching” 38.9% and 83.3%, for the symptom “visual impairment” 26.5% and 83.1% and for the symptom “urgency” is the sensitivity 23.6% and the specificity 85.0%.

In the analysis of the ROC curves, the area under the ROC curves for “performance” was 0.652 [CI 0.572–0.732], for “thirst” 0.650 [CI 0.552–0.748], “itching” 0.616 [CI 0.419–0.812], “visual impairment” 0.531 [0.374–0.687] and for “urgency” 0.603 [CI 0.522–0.685] (Fig. 2).

Discussion

In the present study, to our knowledge for the first time, we managed to identify a threshold for hyperglycaemic symptoms. This threshold differs for patients with type 1 and type 2 diabetes. In type 1 diabetes most patients showed hyperglycaemic symptoms above an HbA1c of 10.05% whereas in patients with diabetes type 2 this value was 8.9%, respectively. This means in order to avoid the occurrence of hyperglycemic symptoms, the HbA1c value with a safety-margin should be below these values. The symptom “frequent urination”, which is most frequently mentioned by patients, also showed a significant dependence on the HbA1c value in the correlation analysis. For the symptom “tiredness”, which was also very often endorsed, no significant correlation was found. This suggests that tiredness is less specific than the frequency of urination. In other studies, too, the frequency of urination and fatigue were among the most frequently cited symptoms in addition to thirst [17].

However, the perception of hyperglycaemic symptoms is influenced by various factors. In addition to the HbA1c also burden from comorbid illnesses and depressive symptoms were positively associated with patient-reported hyperglycaemic symptoms [18]. Hyperglycaemic symptoms are mainly caused by the current level of blood glucose [12, 19]. Although a blood glucose test was recommended to avoid answering the questionnaire while having a hypoglycaemia, we unfortunately did not record the current blood glucose, which is a limitation of our study.

In a study of people with diabetes type 1 and 2 depression was significantly associated with the reporting of more diabetes symptoms [20]. For this reason, in our study all patients were screened for depression and serious general diseases or diseases which could produce similar symptoms like the hyperglycaemic symptoms asked for. These patients were excluded accordingly. In daily practice this should be taken into account if patients report impaired well-being. Consequently, depression should be screened for on a regular basis and the unspecific symptoms occurring with high glucose values can also be caused by several other comorbidities. This should also be taken into account before intensifying diabetes therapy.

In our study, patients with type 1 diabetes showed a significantly higher HbA1c threshold than patients with type 2 diabetes. In a study by Warren et al. it could be shown that patients with less hypoglycaemia

awareness also reported hyperglycaemia symptoms at a higher glycaemic level [17]. Hypoglycaemia unawareness is about twofold more often present in patients with type 1 diabetes than in patients with type 2 diabetes [21, 22]. This could be one explanation for the higher HbA1c threshold in type 1 diabetes. Unfortunately, we have no information about the presence of hypoglycaemia unawareness in the patients of this study. Furthermore, due to the more pronounced glucose fluctuations in persons with type 1 diabetes, the hyperglycaemia symptoms in high HbA1c may only be temporary, whereas in people with type 2 diabetes with high HbA1c they are permanent and are more likely to be perceived and communicated as such. Another explanation could be that patients with type 2 diabetes are older and usually have more comorbidities. As already described, comorbidities are positively associated with patient-reported hyperglycaemic symptoms [18]. Although we excluded patients with serious comorbidities from the study, we cannot exclude that this fact contributed to the lower HbA1c threshold in patients with type 2 diabetes. The normal range of the HbA1c-value is different depending on the method. For this reason we have also output the relative HbA1c value.

Warren et al. divided the hyperglycaemic symptoms into four categories: neurological, osmotic, mental agitation and malaise [17]. Some symptoms of the categories neurological and malaise cannot be clearly distinguished from hypoglycaemic symptoms, e.g. poor concentration. Osmotic symptoms, on the other hand, seem to be more specific for hyperglycemia. Also in our analysis these symptoms, especially thirst, showed a high positive correlation to the HbA1c value. The total hyperglycaemia symptom score continued to show a positive correlation with the patients' impression that their blood glucose levels were too high in recent weeks, but not with the impression that the blood glucose levels were too low. This suggests that the vast majority of symptoms are quite specific to hyperglycemia.

Our study has some limitations. The level at which HbA1c patients experience hyperglycaemia symptoms is influenced by various factors. By excluding patients with severe diseases, depression and heart failure, we have tried to limit these, but further influencing factors cannot be excluded. Furthermore, blood glucose values from participants were not systematically collected. By consequence the symptoms of hyperglycaemia could only be correlated with HbA1c values.

Conclusion

We could identify a HbA1c threshold above which most patients show symptoms of hyperglycaemia. The threshold is higher for people with diabetes type 1 than for people with diabetes type 2. The “osmotic” symptoms “thirst” and “frequent urination” showed the strongest correlation to high HbA1c values. In the treatment of people with diabetes mellitus a safety margin to this threshold should be maintained to preserve well-being and avoid distress. Caution is advisable for very old patients because symptoms of high glucose can be confounded with symptoms of depression and comorbid illnesses. Thus the treatment goal “free of symptoms” may be impossible to be achieved by improved blood glucose values.

Declarations

Funding

The study was supported by funds provided by the home institutions of the authors.

Conflicts of interest/Competing interests

The authors declare that they have no conflict of interest.

Availability of data and material

All data available.

Code availability

Not applicable.

Authors' contributions

NM is postdoctoral research fellow at the Jena University Hospital, she analyzed the data and wrote the manuscript.

TL is biostatistician at the Centre for Clinical Studies of the Jena University Hospital.

UAM is Professor for Internal Medicine. He designed the study and contributed to the discussion and reviewed the manuscript

CK is head of the Department for Endocrinology and Metabolic Diseases of the Jena University Hospital. He contributed to the discussion and reviewed the manuscript

Ethics approval

All procedures followed were in accordance with the ethical standards of the committee on human experimentation of the study institutions and German national standards as well as with the Helsinki Declaration of 1975, as revised in 2008.

Consent to participate

All persons gave their informed consent prior to their inclusion in the study

Consent for publication

Not applicable

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Figures

Figure 1

Receiver operating characteristic curves of glycated hemoglobin A1c (HbA1c) for detecting hyperglycaemic symptoms in patients with diabetes type 1

Figure 2

Receiver operating characteristic curves of glycated hemoglobin A1c (HbA1c) for detecting hyperglycaemic symptoms in patients with diabetes type 2