OPEN ACCESS Freely available online

PLOS ONE

HbA_{1c} Variability as an Independent Risk Factor for Diabetic Retinopathy in Type 1 Diabetes: A German/Austrian Multicenter Analysis on 35,891 Patients

Julia M. Hermann[1]*, Hans-Peter Hammes[2], Birgit Rami-Merhar[3], Joachim Rosenbauer[4], Morten Schütt[5], Erhard Siegel[6], Reinhard W. Holl[1] on behalf of the DPV Initiative and the German BMBF Competence Network Diabetes Mellitus

1 Institute of Epidemiology and Medical Biometry, ZIBMT, University of Ulm, Ulm, Germany, **2** 5th Medical Department, Medical Faculty Mannheim, University of Heidelberg, Mannheim, Germany, **3** Department of Pediatrics and Adolescent Medicine, Medical University Vienna, Vienna, Austria, **4** Institute for Biometrics and Epidemiology, German Diabetes Centre, Leibniz Centre at Heinrich-Heine University Düsseldorf, Düsseldorf, Germany, **5** Department of Internal Medicine I, Medical University of Lübeck, Lübeck, Germany, **6** Department of Internal Medicine II, St. Josefs Hospital Heidelberg, Heidelberg, Germany

Abstract

Objective: This study aimed to analyze the effect of HbA_{1c} variability on the occurrence of diabetic retinopathy in type 1 diabetes patients.

Patients and Methods: 35,891 patients with childhood, adolescent or adult onset of type 1 diabetes from a large multicentre survey, the German/Austrian prospective documentation system (DPV), were analysed. Cox proportional hazard models were used to examine whether intra-individual HbA_{1c} variability expressed as variation coefficient is an independent risk factor for the occurrence of diabetic retinopathy.

Results: Kaplan-Meier curves stratified by median HbA_{1c} and variation coefficient revealed that retinopathy-free survival probability is lower when both median HbA_{1c} and HbA_{1c} variability are above the 50^{th} percentile. Cox regression models confirmed this finding: After adjustment for age at diabetes onset, gender and median HbA_{1c}, HbA_{1c} variability was independently associated with the occurrence of diabetic retinopathy. Time-covariate interactions used to model non-proportionality indicated an effect decreasing with duration of diabetes for both median HbA_{1c} and HbA_{1c} variability. Predictive accuracy increased significantly when adding HbA_{1c} variability to the Cox regression model.

Conclusions: In patients with type 1 diabetes, HbA_{1c} variability adds to the risk of diabetic retinopathy independently of average metabolic control.

Citation: Hermann JM, Hammes H-P, Rami-Merhar B, Rosenbauer J, Schütt M, et al. (2014) HbA_{1c} Variability as an Independent Risk Factor for Diabetic Retinopathy in Type 1 Diabetes: A German/Austrian Multicenter Analysis on 35,891 Patients. PLoS ONE 9(3): e91137. doi:10.1371/journal.pone.0091137

Editor: Matthias G. von Herrath, La Jolla Institute for Allergy and Immunology, United States of America

Received December 20, 2013; **Accepted** February 7, 2014; **Published** March 7, 2014

Funding: This study was financially supported by the Kompetenznetz Diabetes mellitus (Competence Network for Diabetes mellitus), which is funded by the Federal Ministry of Education and Research (FKZ 01GI1106), Dr.-Bürger-Büsing-Foundation and European Foundation for the Study of Diabetes (EFSD). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing Interests: The authors have declared that no competing interests exist.

* E-mail: julia.hermann@uni-ulm.de

Introduction

Diabetic retinopathy (DR) is the most frequent microvascular complication in patients with diabetes. It is well established that chronic hyperglycemia is one of the main risk factors for DR [1]. In addition, some recent analyses addressed the effect of HbA_{1c} variability on DR and related outcomes, as patients may show a wide variation in their long-term glycemic control, despite having similar average HbA_{1c} values [2]. Kilpatrick *et al.* [3] stated that longer-term glucose variability expressed as HbA_{1c} fluctuations contributed to the risk of DR in type 1 diabetes, whereas short-term glucose instability was no additional risk factor in the development of microvascular complications [4]. Hietala *et al.* [5] found HbA_{1c} variability to be associated with an increased risk of retinopathy requiring laser treatment in type 1 diabetes. Rodríguez-Segade *et al.* [6] reported that higher HbA_{1c} variability led to an increased risk of progression of nephropathy, independently of updated mean HbA_{1c}. In contrast, Penno *et al.* [7] suggested that long-term fluctuation was no independent correlate of retinopathy in type 2 diabetes. Due to these inconsistent findings for different outcomes, further studies on the relationship between HbA_{1c} variability and DR are needed. Knowledge of whether highly varying HbA_{1c} values increase the risk of DR might help to improve diabetes management.

Patients and Methods

Ethics Statement

Analysis of anonymized routine data within the German/Austrian Diabetes Prospective Documentation Initiative (DPV)

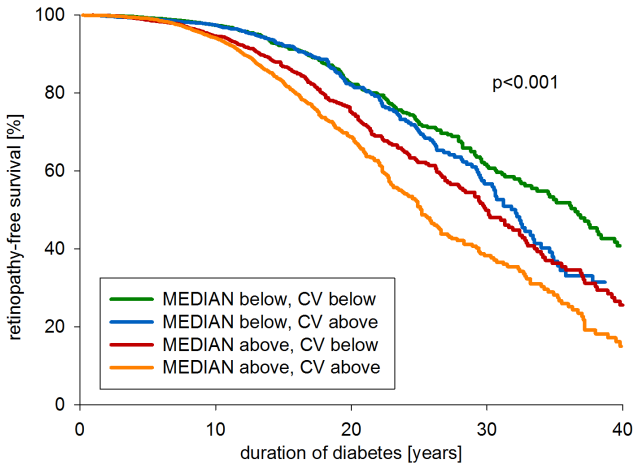

Figure 1. Kaplan Meier curves for retinopathy-free survival according to intrapersonal HbA_{1c}-MEDIAN and HbA_{1c}-CV above/below 50th group percentile. Green line: HbA_{1c}-MEDIAN below, HbA_{1c}-CV below 50th group percentile. Blue line: HbA_{1c}-MEDIAN below, HbA_{1c}-CV above 50th group percentile. Red line: HbA_{1c}-MEDIAN above, HbA_{1c}-CV below 50th group percentile. Orange line: HbA_{1c}-MEDIAN above, HbA_{1c}-CV above 50th group percentile. Patients were assigned to strata based on group-specific 50th percentiles according to duration of diabetes, age and gender. Log-rank test was used for comparisons among strata.
doi:10.1371/journal.pone.0091137.g001

was approved by the Ethics Committee of the Medical Faculty of the University of Ulm.

Patients

The DPV is a nationwide multicenter survey which by March 2013 comprised n = 83,856 patients with type 1 diabetes. Participating centers and data collection methods have been reported previously [8]. A total of 35,891 patients fulfilled the inclusion criteria which were as follows: availability of at least one retinal examination, and at least five HbA_{1c} values prior to the first occurrence of retinopathy or the last retinopathy examination. The latter exclusion criterion leads to more reliable estimates of the HbA_{1c} variability, as only patients with regular center attendance are included [9]. In addition, we repeated the analysis in patients with a minimum of four or six HbA_{1c} values. Assessment of diabetic retinopathy was performed according to the guidelines of the German Diabetes Association [10] and has been described before [11]. In brief, trained ophthalmologists used direct funduscopy in mydriasis to grade DR according to the modified Airlie House Classification/ETDRS standards [12]. The "multiple of the mean" transformation method was used to mathematically standardize HbA_{1c} values to the DCCT reference range (20.7–42.6 mmol/mol, 4.05–6.05%) in order to adjust for between-laboratory differences [13]. Further variables studied were duration of diabetes, gender and age at diagnosis in categories (<5 years, 5–<10 years, 10–<15 years, 15–<20 years and ≥20 years).

Statistical Analysis

Statistical analysis was performed using SAS 9.3 (Statistical Analysis Software, SAS Institute Inc., Cary, NC, USA). Patient characteristics are presented as median with lower and upper quartile (median [Q1–Q3]) for continuous variables and as percentage for categorical variables. Differences between groups were analyzed by Mann-Whitney test. Average HbA_{1c} was calculated for each patient as the median of HbA_{1c} assessments during the individual observation time (HbA_{1c}-MEDIAN). We determined a normalized measure of variability, the coefficient of variation (CV): Intra-individual standard deviation (SD) was divided by mean HbA_{1c} in order to correct for higher SDs due to larger absolute values (CV = SD/MEAN*100). Spearman's rank correlation coefficient (r_s) was computed to assess the strength of the association between median HbA_{1c} and HbA_{1c} variability. There was virtually no correlation between HbA_{1c}-MEDIAN and CV ($r_s = -0.05$, 95% CI −0.06, −0.04), whereas median HbA_{1c} and HbA_{1c}-SD were weakly associated ($r_s = 0.27$, 95% CI 0.25, 0.28). Hence, we used CV as variability measurement in order to avoid collinearity.

Kaplan-Meier curves describe the occurrence of retinopathy in relation to diabetes duration. Log-rank test was used for

Table 1. Relative risk (HR) estimated from multiple Cox regression for the association between HbA_{1c} and development of diabetic retinopathy, adjusted for demographic variables.

	Model 1		Model 2	
Variables	**HR [95% CI]**	**P**	**HR [95% CI]**	**P**
Female gender	0.984 [0.896–1.080]	0.734	0.974 [0.887–1.069]	0.573
Age at onset <5 years	1.0		1.0	
Age at onset 5–<10 years	1.577 [1.359–1.830]	<0.001	1.512 [1.301–1.757]	<0.001
Age at onset 10–<15 years	1.907 [1.606–2.263]	<0.001	1.642 [1.379–1.956]	<0.001
Age at onset 15–<20 years	1.607 [1.249–2.068]	<0.001	1.242 [0.958–1.610]	0.103
Age at onset ≥20 years	2.370 [2.020–2.782]	<0.001	2.238 [1.902–2.634]	<0.001
HbA_{1c}-MEDIAN (mmol/mol)	1.106 [1.102–1.110]	<0.001	1.098 [1.094–1.102]	<0.001
HbA_{1c}-MEDIAN * diabetes duration	0.993 [0.993–0.994]	<0.001	0.994 [0.993–0.994]	<0.001
HbA_{1c}-CV (%)	–		1.110 [1.100–1.121]	<0.001
HbA_{1c}-CV * diabetes duration	–		0.993 [0.992–0.994]	<0.001
c-index [95% CI]	0.831 [0.826–0.837]		0.868 [0.863–0.873]	

Results are presented as hazard ratios and their corresponding 95% confidence intervals. Time scale: duration of diabetes in years.
Example: HR for HbA_{1c}-MEDIAN for ten years of duration of diabetes: $HR = 1.106*0.993^{10} = 1.031$.
doi:10.1371/journal.pone.0091137.t001

comparisons among strata. Patients who did not develop retinopathy during their individual observation time were right-censored. Multiple Cox regression models with duration of diabetes as time-scale were used to simultaneously consider the effect of independent variables. Model 1 included gender, age at diagnosis and median HbA_{1c} as covariates, Model 2 incorporated HbA_{1c}-CV in addition. Proportionality assumption and functional form of covariates were checked by testing time-covariate interactions and by martingale residual plots. Non-proportionality was modeled by time-covariate interactions where necessary. Results are presented as hazard ratios (HR) and their corresponding 95% confidence intervals (CI). $P<0.05$ of a two-sided test was considered statistically significant. To compare the performance of the models, we calculated Gönen and Heller's c-index [14] which is a concordance probability estimate that ranges between 0.5 and 1.0, with 1.0 representing perfect concordance between predicted and observed survival time. Being an extended version of the area under the receiver operating characteristic (ROC) curve that holds for censored data in the context of Cox regression models, it measures how well a model discriminates between different responses. Corresponding confidence intervals indicate whether c-indices differ significantly.

Examination of patients with at least four or at least six HbA_{1c} measurements led to similar results (data not shown).

Results

Median age at the end of the individual observation time was 16.2 [13.1–18.0] years, and median diabetes duration was 6.4 [3.6–10.0] years. 52.3% of patients were male. Patients not included due to the lack of a retinal examination or less than five HbA_{1c} values documented were older (19.8 [13.4–45.4] years, $p<0.0001$) and had shorter duration of diabetes (5.6 [1.3–15.7] years, $p<0.0001$). However, since we investigate the additional effect of glycemic variability on the development of DR, rather than the prevalence of DR, we consider a potential selection bias to be irrelevant. 22.7% of the patients included were younger than 5 years at onset, 34.7% and 31.7% were 5-<10 years and 10-<15 years old, respectively. In 4.8% and 6.1% of the patients, age at onset was 15-<20 years and ≥20 years, respectively. Median number of HbA_{1c} values per patient during one year was 4.3 [3.5–5.3]. HbA_{1c}-MEDIAN of participants was 59 [52–67] mmol/mol (7.5 [6.9–8.3] %), HbA_{1c}-CV was 17.9 [12.7–25.1] %.

HbA_{1c} variability correlated negatively with duration of diabetes ($r_s = -0.34$, 95% CI −0.35, −0.33, $p<0.001$). In order to account for this association, we assigned patients to groups according to duration of diabetes, age and gender and determined respective group-specific 50th percentiles for HbA_{1c} and HbA_{1c}-CV. We then assigned patients to groups with HbA_{1c}-MEDIAN and HbA_{1c}-CV above and below the respective 50th group-specific percentiles and computed Kaplan-Meier curves (Fig. 1). Retinopathy-free survival was lowest (highest) when both median HbA_{1c} and HbA_{1c} variability were in the upper (lower) half ($p<0.001$).

In order to investigate the effect of age at onset, gender and HbA_{1c} simultaneously, we calculated multiple Cox regression models. We included first-order interaction terms between duration of diabetes and HbA_{1c}-MEDIAN or HbA_{1c}-CV to account for non-proportionality of these variables. All potential confounders except female gender were significantly related to retinopathy; age at onset <5 years was protective (Table 1, Model 1). Higher HbA_{1c}-MEDIAN was associated with higher risk for retinopathy, but the effect decreased slightly with time (annual decrease in HR per one mmol/mol HbA_{1c}-MEDIAN increase: 0.993; 95% CI 0.993, 0.994, $p<0.001$). At ten years of duration of diabetes, an increase of one mmol/mol HbA_{1c}-MEDIAN was associated with a 3.1% higher risk of DR. HbA_{1c} variability led to an additional rise in risk (3.5% higher risk of DR per one unit increase of HbA_{1c}-CV at ten years of duration of diabetes) (Model 2). Discriminative ability of the Cox regression model measured by Gönen and Heller's c-index increased significantly from 0.831 (95% CI 0.825, 0.837) to 0.868 (95% CI 0.863, 0.873) after adding HbA_{1c} variability to Model 1.

Discussion

Our study in patients with type 1 diabetes demonstrated that HbA_{1c} variability is an independent risk factor for diabetic retinopathy. In a multiple Cox regression model, HbA_{1c} variability was significantly associated with DR, independent of median HbA_{1c} value. For both median HbA_{1c} and HbA_{1c}-CV, the contribution was lower with longer duration of diabetes. This finding may be explained by genetic susceptibility: Some patients with poor glycemic control do not develop DR even over long time periods [15]. Discriminative ability of the Cox regression model improved significantly compared to a model not containing any fluctuation measurement. Concordance between predicted and observed survival time was good, although we only included gender, age at onset and glycemic control as predictor variables. Adding variables like hypertension, dyslipidemia or ethnicity could improve the overall prediction, but not all of these variables were clearly shown to have an important effect on DR [11,16]. Furthermore, since our investigation focused on the additional impact of variability, we chose a Cox regression model including demographic variables and metabolic control only.

Our database is large and differences in c-index are small, but significant; therefore, the issue of statistical significance versus clinical relevance has to be addressed. Considering the fact that the pathogenesis of DR is complex, a greater improvement in predictive accuracy as a result of adding one variable only is not to be expected. In addition, point estimates expressed by hazard ratios and their associated confidence intervals revealed clear effects of HbA_{1c} variability on the risk of DR.

Kilpatrick (2012) [17] mentioned several possible reasons as to why HbA_{1c} variability might contribute to the risk of DR. He supposed that periods of hyperglycemia are 'remembered' and therefore the effect of HbA_{1c} variability could be caused by the same mechanism underlying the 'metabolic memory' phenomenon. Another explanation comprised the short-term 'early worsening'. There could be insufficient time for long-term benefits in patients with fluctuating glycemic control. The author also suspected that patients with highly varying HbA_{1c} are those with suboptimal diabetes management.

The main strength of our study is the large number of patients and the long observation time. Possible limitations are the varying number of measurements per individual and various time intervals between two examinations. Moreover, data are collected at numerous diabetes centers with different rates of eye examination.

In conclusion, this large routine survey reveals that HbA_{1c} variability adds to the risk of diabetic retinopathy independently of average metabolic control. Our results and the possible explanations mentioned above allow the conclusion that continuous care results in better outcome compared to short interventions triggered by elevated HbA_{1c} values.

Acknowledgments

We thank all DPV centers who contributed data for this analysis:

Aachen - Innere RWTH, Aachen - Uni-Kinderklinik RWTH, Aalen Kinderklinik, Ahlen St. Franziskus Kinderklinik, Aidlingen Praxisge-

meinschaft, Altötting Zentrum Inn-Salzach, Altötting-Burghausen Innere Medizin, Arnsberg-Hüsten Karolinenhosp. Kinderabteilung, Aue Helios Kinderklink, Augsburg Innere, Augsburg Kinderklinik Zentralklinikum, Aurich Kinderklinik, Bad Aibling Internist. Praxis, Bad Driburg/Bad Hermannsborn Innere, Bad Hersfeld Kinderklinik, Bad Kreuznach-Viktoriastift, Bad Kösen Kinder-Rehaklinik, Bad Lauterberg Diabeteszentrum Innere, Bad Mergentheim - Diabetesfachklinik, Bad Mergentheim - Gemeinschaftspraxis DM-dorf Althausen, Bad Oeynhausen Herz-und Diabeteszentrum NRW, Bad Orb Spessart Klinik, Bad Orb Spessart Klinik Reha, Bad Reichenhall Kreisklinik Innere Med., Bad Salzungen Kinderklinik, Bad Waldsee Kinderarztpraxis, Bautzen Oberlausitz KK, Bayreuth Innere Medizin, Berchtesgaden CJD, Berchtesgaden MVZ Innere Med, Berlin DRK-Kliniken, Berlin Endokrinologikum, Berlin Lichtenberg - Kinderklinik, Berlin Oskar Zieten Krankenhaus Innere, Berlin St. Josephskrankenhaus Innere, Berlin Virchow-Kinderklinik, Berlin Vivantes Hellersdorf Innere, Bielefeld Kinderklinik Gilead, Bocholt Kinderklinik, Bochum Universitätskinderklinik St. Josef, Bonn Uni-Kinderklinik, Bottrop Knappschaftskrankenhaus Innere, Braunschweig Kinderarztpraxis, Bremen - Kinderklinik Nord, Bremen - Mitte Innere, Bremen Prof. Hess Kinderklinik, Bremerhaven Kinderklinik, Böblingen Kinderklinik, Celle Klinik für Kinder- und Jugendmedizin, Chemnitz Kinderklinik, Chemnitz-Hartmannsdorf Innere Medizin - DIAKOMED-1, Coesfeld Kinderklinik, Coesfeld/Dülmen Innere Med., Darmstadt Innere Medizin, Darmstadt Kinderklinik Prinz. Margaret, Datteln Vestische Kinderklinik, Deggendorf Kinderarztpraxis, Deggendorf Kinderklinik, Delmenhorst Kinderklinik, Dessau Kinderklinik, Detmold Kinderklinik, Dornbirn Kinderklinik, Dortmund Kinderklinik, Dortmund Knappschaftskrankenhaus Innere, Dortmund Medizinische Kliniken Nord, Dortmund-St. Josefshospital Innere, Dresden Neustadt Kinderklinik, Dresden Uni-Kinderklinik, Duisburg Evang. und Johanniter Krhs, Innere, Duisburg Kinderklinik, Duisburg Malteser St. Anna Innere, Duisburg Malteser St. Johannes, Duisburg-Huckingen, Duisburg-St.Johannes Helios, Düren-Birkesdorf Kinderklinik, Düsseldorf Uni-Kinderklinik, Eberswalde Klinikum Barnim Werner Forßmann - Innere, Erfurt Kinderklinik, Erlangen Uni Innere Medizin, Erlangen Uni-Kinderklinik, Essen Diabetes-Schwerpunktpraxis, Essen Elisabeth Kinderklinik, Essen Uni-Kinderklinik, Esslingen Klinik für Kinder und Jugendliche, Eutin Kinderklinik, Feldkirch Kinderklinik, Forchheim Diabeteszentrum SPP, Frankenthal Kinderarztpraxis, Frankfurt Diabeteszentrum Rhein-Main-Erwachsenendiabetologie (Bürgerhospital), Frankfurt Uni-Kinderklinik, Frankfurt Uni-Klinik Innere, Freiburg St. Josef Kinderklinik, Freiburg Uni Innere, Freiburg Uni-Kinderklinik, Friedrichshafen Kinderklinik, Fulda Innere Medizin, Fulda Kinderklinik, Fürth Kinderklinik, Gaissach Fachklinik der Deutschen Rentenversicherung Bayern Süd, Garmisch-Partenkirchen Kinderklinik, Geislingen Klinik Helfenstein Innere, Gelnhausen Innere, Gelnhausen Kinderklinik, Gelsenkirchen Kinderklinik Marienhospital, Gera Kinderklinik, Gießen Ev. Krankenhaus Mittelhessen, Gießen Uni-Kinderklinik, Graz Universitäts-Kinderklinik, Göppingen Innere Medizin, Göppingen Kinderklinik am Eichert, Görlitz Städtische Kinderklinik, Göttingen Uni-Kinderklinik, Güstrow Innere, Hachenburg Kinderpraxis, Hagen Kinderklinik, Halle Uni-Kinderklinik, Halle-Dölau Städtische Kinderklinik, Hamburg Altonaer Kinderklinik, Hamburg Endokrinologikum, Hamburg Kinderklinik Wilhelmstift, Hamburg-Nord Kinder-MVZ, Hameln Kinderklinik, Hamm Kinderklinik, Hanau Kinderklinik, Hannover Henriettenstift - Innere, Hannover Kinderklinik MHH, Hannover Kinderklinik auf der Bult, Haren Kinderarztpraxis, Heide Kinderklinik, Heidelberg Uni-Kinderklinik, Heidenheim Kinderklinik, Heilbronn Innere Klinik, Heilbronn Kinderklinik, Herdecke Kinderklinik, Herford Innere Med I, Herford Kinderarztpraxis, Herford Klinikum Kinder & Jugendliche, Heringsdorf Inselklinik, Herne Evan. Krankenhaus Innere, Herten St. Elisabeth Innere Medizin, Hildesheim Kinderarztpraxis, Hildesheim Klinikum Kinderklinik, Hinrichsegen-Bruckmühl Diabetikerjugendhaus, Hof Kinderklinik, Homburg Uni-Kinderklinik Saarland, Innsbruck Universitätskinderklinik, Iselsberg - Rehazentrum Ederhof, Iserlohn Innere Medizin, Itzehoe Kinderklinik, Jena Uni-Kinderklinik, Kaiserslautern Kinderarztpraxis, Kaiserslautern-Westpfalzklinikum Kinderklinik, Karlsburg Klinik für Diabetes & Stoffwechsel, Karlsruhe Städtische Kinderklinik, Kassel Klinikum Kinder- und Jugendmedizin, Kassel Städtische Kinderklinik, Kaufbeuren Innere Medizin, Kiel Städtische Kinderklinik, Kiel Universitäts-Kinderklinik, Kirchen DRK Klinikum Westerwald, Kinderklinik, Kirchheim-Nürtingen Innere, Kleve Innere Medizin, Klinikum Hildesheim GmbH, Innere, Koblenz Kemperhof 1. Med. Klinik, Koblenz Kinderklinik Kemperhof, Konstanz Innere Klinik, Konstanz Kinderklinik, Krefeld Innere Klinik, Krefeld Kinderklinik, Krefeld-Uerdingen St. Josef Innere, Kreischa-Zscheckwitz, Klinik Bavaria, Köln Kinderklinik Amsterdamerstrasse, Köln Uni-Kinderklinik, Landshut Kinderklink, Lappersdorf Kinderarztpraxis, Leipzig Uni-Kinderklinik, Leoben LKH Kinderklinik, Leverkusen Kinderklinik, Lienz BKH Pädiatrie, Lilienthal Schwerpunktpraxis, Limburg Innere Medizin, Lindenfels Luisenkrankenhaus Innere, Lingen Kinderklinik St. Bonifatius, Linz Krankenhaus Barmherzige Schwestern Kardiologie Abt. Int. II, Linz Krankenhaus der Barmherzigen Schwestern Kinderklinik, Lippstadt Evangelische Kinderklinik, Ludwigsburg Kinderklinik, Ludwigshafen Kinderklinik St.Anna-Stift, Ludwigshafen diabetol. SPP, Lübeck Uni-Kinderklinik, Lübeck Uni-Klinik Innere Medizin, Lüdenscheid Hilfswerk Kinder & Jugendliche, Lüdenscheid Märkische Kliniken - Kinder & Jugendmedizin, Lünen Klinik am Park, Magdeburg Städtisches Klinikum Innere, Magdeburg Uni-Kinderklinik, Mainz Uni-Kinderklinik, Mannheim Uni-Kinderklinik, Mannheim Uniklinik Innere Medizin, Marburg - UKGM Endokrinologie & Diabetes, Marburg Uni-Kinderklinik, Marpingen-SPP, Mechernich Kinderklinik, Memmingen Kinderklinik, Merzig Kinderklinik, Minden Kinderklinik, Moers - St. Josefskrankenhaus Innere, Moers Kinderklinik, Murnau am Staffelsee - diabetol. SPP, Mutterstadt Kinderarztpraxis, Mödling Kinderklinik, Mönchengladbach Kinderklinik Rheydt Elisabethkrankenhaus, Mühlacker Enzkreiskliniken Innere, Mühldorf Gemeinschaftspraxis, München 3. Orden Kinderklinik, München Diabetes-Zentrum Süd, München Kinderarztpraxis diabet. SPP, München Schwerpunktpraxis.

München von Haunersche Kinderklinik, München-Gauting Kinderarztzentrum, München-Harlaching Kinderklinik, München-Schwabing Kinderklinik, Münster Herz Jesu Innere, Münster St. Franziskus Kinderklinik, Münster Uni-Kinderklinik, Münster pädiat. Schwerpunktpraxis, Nauen Havellandklinik, Neuburg Kinderklinik, Neunkirchen Marienhausklinik Kohlhof Kinderklinik, Neuss Lukaskrankenhaus Kinderklinik, Neuwied Kinderklinik Elisabeth, Neuwied Marienhaus Klinikum St. Elisabeth Innere, Nürnberg Cnopfsche Kinderklinik, Nürnberg Zentrum f Neugeb., Kinder & Jugendl., Oberhausen Innere, Oberhausen Kinderklinik, Oberhausen Kinderpraxis, Oberhausen St.Clemens Hospitale Sterkrade, Offenbach/Main Innere Medizin, Offenbach/Main Kinderklinik, Offenburg Kinderklinik, Oldenburg Kinderklinik, Oldenburg Schwerpunktpraxis, Olpe pädiatrische Gemeinschaftspraxis, Oschersleben MEDIGREIF Bördekrankenhaus, Osnabrück Christliches Kinderhospital, Osterkappeln Innere, Ottobeuren Kreiskrankenhaus, Oy-Mittelberg Hochgebirgsklinik Kinder-Reha, Paderborn St. Vincenz Kinderklinik, Papenburg Marienkrankenhaus Kinderklinik, Passau Kinderarztpraxis, Passau Kinderklinik, Pforzheim Kinderklinik, Pfullendorf Innere Medizin.

Pirmasens Städtisches Krankenhaus Innere, Plauen Vogtlandklinikum, Rastatt Gemeinschaftspraxis, Rastatt Kreiskrankenhaus Innere, Ravensburg Kinderklink St. Nikolaus, Recklinghausen Dialysezentrum Innere, Regensburg Kinderklinik St. Hedwig, Remscheid Kinderklinik, Rendsburg Kinderklinik, Reutlingen Kinderarztpraxis, Reutlingen Kinderklinik, Reutlingen Klinikum Steinenberg Innere, Rheine Mathiasspital Kinderklinik, Rosenheim Innere Medizin, Rosenheim Kinderklinik, Rosenheim Schwerpunktpraxis, Rostock Uni-Kinderklinik, Rostock Universität Innere Medizin, Rotenburg/Wümme Kinderklinik, Rüsselsheim Kinderklinik, Saaldorf-Surheim Diabetespraxis, Saalfeld Thüringenklinik Kinderklinik, Saarbrücken Kinderklinik Winterberg 2, Saarlouis Kinderklinik, Salzburg Kinderklinik, Scheidegg Prinzregent Luitpold, Scheidegg Reha-Kinderklinik Maximilian, Schw. Gmünd Stauferklinik Kinderklinik, Schweinfurt Kinderklinik, Schwerin Innere Medizin, Schwerin Kinderklinik, Schwäbisch Hall Diakonie Kinderklinik, Siegen Kinderklinik, Singen - Hegauklinik Kinderklinik, Sinsheim Innere, Spaichingen Innere, St. Augustin Kinderklinik, St. Pölten Kinderklinik, Stade Kinderklinik, Stolberg Kinderklinik, Stuttgart Olgahospital Kinderklinik, Suhl Kinderklinik, Sylt Rehaklinik, Tettnang Innere Medizin, Traunstein diabetol. Schwerpunktpraxis, Trier Kinderklinik der Borromäerinnen, Trostberg Innere, Tübingen Uni-Kinderklinik, Ulm Endokrinologikum, Ulm Schwerpunktpraxis Bahnhofsplatz, Ulm Uni Innere Medizin, Ulm Uni-Kinderklinik, Vechta Kinderklinik, Viersen Kinderkrankenhaus St. Nikolaus, Villach Kinderklinik, Villingen-Schwenningen Diabetesschule, Villingen-Schwenningen Schwarzwald-Baar-Klinikum Innere, Waiblingen Kinderklinik, Waldshut Kinderpraxis, Waldshut-Tiengen Kinderpraxis Biberbau, Weiden Kinderklinik, Weingarten Kinderarztpraxis, Wernberg-Köblitz SPP, Wetzlar/Braunfels Innere, Wien 3. Med. Hietzing Innere, Wien Preyersches Kinderspital, Wien Rudolfstiftung, Wien SMZ Ost Donauspital,

Wien Uni Innere Med III, Wien Uni-Kinderklinik, Wien Wilhelminenspital 5. Med. Abteilung, Wiesbaden Horst-Schmidt-Kinderkliniken, Wiesbaden Kinderklinik DKD, Wilhelmshaven Reinhard-Nieter-Kinderklinik, Wittenberg Innere Medizin, Wittenberg Kinderklinik, Wolgast Innere Medizin, Worms - Weierhof, Worms Kinderklinik, Wuppertal Kinderklinik.

Author Contributions

Conceived and designed the experiments: RWH. Performed the experiments: HPH BRM JR MS ES. Analyzed the data: JMH RWH. Contributed reagents/materials/analysis tools: HPH BRM JR MS ES. Wrote the paper: JMH. Revision of manuscript: HPH BRM JR MS ES RWH. Final approval of the version to be published: JMH HPH BRM JR MS ES RWH.

References

1. Lachin JM, Genuth S, Nathan DM, Zinman B, Rutledge BN, et al. (2008) Effect of glycemic exposure on the risk of microvascular complications in the diabetes control and complications trial - revisited. Diabetes 57(4): 995–1001.
2. Dawson AJ, Sathyapalan T, Atkin SL, Kilpatrick ES (2013) Biological variation of cardiovascular risk factors in patients with diabetes. Diabet Med 30(10): 1172–1180.
3. Kilpatrick ES, Rigby AS, Atkin SL (2008) A1C variability and the risk of microvascular complications in type 1 diabetes: data from the Diabetes Control and Complications Trial. Diabetes Care 31(11): 2198–2202.
4. Kilpatrick ES, Rigby AS, Atkin SL (2006) The effect of glucose variability on the risk of microvascular complications in type 1 diabetes. Diabetes Care 29(7): 1486–1490.
5. Hietala K, Wadén J, Forsblom C, Harjutsalo V, Kytö J, et al. (2013) HbA_{1c} variability is associated with an increased risk of retinopathy requiring laser treatment in type 1 diabetes. Diabetologia 56(4): 737–745.
6. Rodríguez-Segade S, Rodríguez J, García López JM, Casanueva FF, Camiña F (2012) Intrapersonal HbA_{1c} variability and the risk of progression of nephropathy in patients with Type 2 diabetes. Diabet Med 29(12): 1562–1566.
7. Penno G, Solini A, Bonora E, Fondelli C, Orsi E, et al. (2013) HbA_{1c} variability as an independent correlate of nephropathy, but not retinopathy, in patients with type 2 diabetes: The Renal Insufficiency And Cardiovascular Events (RIACE) Italian Multicenter Study. Diabetes Care 36(8): 2301–2310.
8. Schwab KO, Doerfer J, Hecker W, Grulich-Henn J, Wiemann D, et al. (2006) Spectrum and prevalence of atherogenic risk factors in 27,358 children, adolescents, and young adults with type 1 diabetes: cross-sectional data from the German diabetes documentation and quality management system (DPV). Diabetes Care 29(2): 218–225.
9. Luk AO, Ma RC, Lau ES, Yang X, Lau WW, et al. (2013) Risk association of HbA_{1c} variability with chronic kidney disease and cardiovascular disease in type 2 diabetes: prospective analysis of the Hong Kong Diabetes Registry. Diabetes Metab Res Rev 29(5): 384–390.
10. Hammes HP, Lemmen KD, Bertram B (2012) Diabetische Retinopathie und Makulopathie [Diabetic retinopathy and maculopathy]. Diabetologie (Suppl 2): 103–107.
11. Hammes HP, Kerner W, Hofer S, Kordonouri O, Raile K, et al. (2011) Diabetic retinopathy in type 1 diabetes-a contemporary analysis of 8,784 patients. Diabetologia 54(8): 1977–1984.
12. Early Treatment Diabetic Retinopathy Study Research Group (1991) Grading diabetic retinopathy from stereoscopic color fundus photographs - an extension of the modified Airlie House classification. ETDRS report number 10. Ophtalmology (Suppl 5): 786–806.
13. Gerstl EM, Rabl W, Rosenbauer J, Gröbe H, Hofer SE, et al. (2008) Metabolic control as reflected by HbA1c in children, adolescents and young adults with type-1 diabetes mellitus: combined longitudinal analysis including 27,035 patients from 207 centers in Germany and Austria during the last decade. Eur J Pediatr 167(4): 447–453.
14. Gönen M, Heller G (2005) Concordance probability and discriminatory power in proportional hazards regression. Biometrika 92(4): 965–970.
15. Liew G, Klein R, Wong TY (2009) The role of genetics in susceptibility to diabetic retinopathy. Int Ophthalmol Clin 49(2): 35–52.
16. Mostafa SA, Davies MJ, Webb DR, Srinivasan BT, Gray LJ, et al. (2012) Independent effect of ethnicity on glycemia in South Asians and white Europeans. Diabetes Care 35(8): 1746–1748.
17. Kilpatrick ES (2012) The rise and fall of HbA_{1c} as a risk marker for diabetes complications. Diabetologia 55(8): 2089–2091.