Patients with Type 2 Diabetes Mellitus have Varying Relationships between Mean Hba1c and Hba1c Variability in Terms of Issues Related to Their Diabetes

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Abstract

Objectives: To investigate the distinct effects of variation in HbA1c and mean HbA1c on diabetes-related complications in type 2 diabetes patients.

Methods: In a Diabetes Shared Care Program, 1869 type 2 diabetes patients were followed up for an average of 9.5 years. Mean HbA1c (HbA1c-mean) and standard deviation of HbA1c (HbA1c-SD) were determined during the initial 5 years. Nephropathy (urine albumin-to-creatinine ratio [UACR] greater than 300 mg/g and doubling of serum creatinine), any and advanced retinopathy, and all-cause and cardiovascular disease mortality were among the clinical outcomes.

Results: UACR > 300 mg/g (Hazard ratio [HR] 1.308 [95% confidence interval [CI], 1.194–1.433]), any retinopathy (HR 1.274 [1.171–1.385]), and advanced retinopathy (HR 1.237 [1.014–1.509]) were all independently associated with HbA1c-mean. UACR > 300 mg/g, doubling of serum creatinine (HR 2.133 [1.470–3.095]), all-cause mortality (HR 1.880 [1.561–2.266]), and CVD mortality (HR 1.431 [1.069–1.915]) were all independently associated with HbA1c-SD. HbA1c-mean was more correlated with any retinopathy than HbA1c-SD, whereas HbA1c-SD was more correlated with all-cause and CVD mortality and doubling of serum creatinine.

Conclusion: Majority of diabetes-related complications in type 2 diabetes patients were predicted by HbA1c-mean and HbA1c-SD. In any case, HbA1c-mean was more powerful at anticipating retinopathy, while HbA1c-SD was more successful at foreseeing disintegration of renal capability and expanded mortality.

Keywords: HbA1c variability; Mean HbA1c; Diabetes complications

Introduction

Total proof shows that long haul glycemic control is the principal risk factor for the improvement of miniature and full scale vascular complexities in diabetic patients. Since glycated hemoglobin (HbA1c) levels are a reflection of average glycemia over approximately three months, current guidelines typically use HbA1c to evaluate glycemic control [1]. However, hypoglycemia and glycemic variability are not measured by HbA1c. Glycemic changeability connects with vacillations in blood glucose levels. The potential dangers related with glycemic changeability appear to be connected with conceivable vascular harm because of abundance glucose vacillations, as well as an expanded gamble of hypoglycemia and its ramifications. Within-day and between-day glycemic variability, or short-term glycemic variability, may eventually result in elevated HbA1c levels [2]. HbA1c changeability connects with changes in glycemic command over longer periods, which brings about HbA1c changes between visits. As a result, long-term glycemic variability is typically assessed using HbA1c variability.

Variability in HbA1c has been found to be positively correlated with mortality as well as micro- and macro-vascular complications. HbA1c variability and diabetes-related complications and mortality in diabetes mellitus patients were examined in a recent meta-analysis. It showed that, regardless of HbA1c levels, HbA1c variability was positively correlated with diabetes-related complications and mortality, suggesting that HbA1c variability might be used in clinical assessment in the future. Some diabetes-related complications were also linked to increased visit-to-visit glycemic variability, according to more recent observational studies [3].

Combined proof proposes that both hyperglycemia and expanded glycemic fluctuation assume significant parts in diabetes-related difficulties. Nonetheless, there are not many examinations that analyze the impacts of hyperglycemia and glycemic changeability on these difficulties. In patients with type 2 diabetes, we hypothesize that HbA1c variability and mean HbA1c may have distinct effects on the occurrence of diabetes-related complications. As a result, we conducted this study to investigate the various effects of mean HbA1c and HbA1c variability on complications related to diabetes in type 2 diabetes patients [4].

Research Design and Methods

Study population and baseline examination

This was a forthcoming report intended to assess the connection between glycemic control and diabetes-related complexities in patients with type 2 diabetes. There were 4450 subjects with type 2 diabetes who were somewhere around 20 years of age and who gave composed informed assent and in this way partaken in the Diabetes Shared Care Program. We eliminated patients with a UACR > 300 mg/g; a serum creatinine of more than 1.50 mg/dL; those who were followed for less than five years and had a diagnosis or history of retinopathy, myocardial infarction, stroke, cardiovascular diseases, or cancer at baseline. Last but not least, we selected 1869 patients for additional analysis. The benchmark information were gathered from January 2004 to December 2015. Between January 2004 and December 2019, the subjects were regularly monitored at the Taipei Veterans General Hospital. The Taiwanese Taipei Veterans General Hospital's institutional review board approved the study.

Our diabetes case managers obtained demographic information, diabetes duration, prescribed medication, and smoking status. The height, weight, and blood pressure of the patients were measured. For the purpose of determining the levels of fasting blood glucose, HbA1c, creatinine, cholesterol, and triglyceride, venipuncture was performed, and fasting serum samples were collected. Using a prediction formula from the four-variable Modification of Diet and Renal Disease study equation, the estimated glomerular filtration rate (eGFR) was determined. The urine albumin-to-creatinine ratio (UACR) was used to calculate urinary albumin excretion from spot urine samples that were prepared in the early morning. Variety photos of the retinas, including macula-and circle focused sees, were taken at a point of 45° with a fundus camera after pharmacological mydriasis. The fundus photos were assessed via prepared doctors.

Assessment of glycemic control

In terms of serial HbA1c measurements, glycemic control was documented.

From January 2004 to September 30, 2018, HbA1c was measured with the TOSOH Automated Glycohemoglobin Analyzer HLC 723 G7/G8 (Tosoh, Japan) using high-performance liquid chromatography. At mean A1C levels between 4.4% and 8.2%, the inter-assay and between-batch coefficient of variance was less than 2.0%. HbA1c was measured by electrophoresis using the Sebia CAPILLARYS 3 TERA (Sebia, France) from October 1, 2018, to September 30, 2021. The between measure with between-group coefficient of change was under 2.0% at mean A1C levels somewhere in the range of 5.5% and 10.1%. In the first five years after patients participated in the Diabetes Shared Care Program, mean HbA1c and HbA1c variability were calculated. Over the course of five years, these subjects received an average of 19 HbA1c measurements, with the highest reading being 42 and the lowest reading being 10. For the first five years, median HbA1c values from each year were taken to avoid the impact of taking multiple measurements in a short amount of time. These values were then used to calculate mean HbA1c (HbA1c-mean).

Assessment of HbA1c variability

Both the standard deviation (SD) and the coefficient of variation (CV) of HbA1c were utilized as indicators of HbA1c variability in previous studies. In our review, we observed that there was areas of strength for a between HbA1c-mean and standard deviation of HbA1c (HbA1c-SD) (Supplemental Figure 1, $\gamma = 0.503$, $p < 0.001$), which implied that a high HbA1c-mean was normally connected with a high HbA1c-SD. If we select the CV of HbA1c for analysis, high mean HbA1c values may conceal some patients with high HbA1c variability. As a result, we decided to measure HbA1c variability with the SD of HbA1c rather than the CV of HbA1c. We used the highest and lowest HbA1c values in each year, twice a year, for a total of ten times over five years to calculate the HbA1c-SD using the same number of measurements.

Assessment of outcomes

Nephropathy (UACR greater than 300 mg/g and doubling of serum creatinine) and retinopathy (any retinopathy and advanced retinopathy) were the clinical outcomes of interest, as was mortality (all-cause mortality and CVD mortality). Using a fundus camera, a 45-degree central view of the macula and disc was taken to assess retinopathy. The severity of the retinopathy was divided into the following four categories by us: Proliferative retinopathy, mild-to-moderate non-proliferative retinopathy, and no apparent retinopathy are all possible. Ophthalmologists were referred to patients with abnormal findings for additional evaluation. Proliferative retinopathy or having undergone vitrectomy or post-laser photocoagulation was considered to be advanced retinopathy. The Department of Health, Executive Yuan, ROC (Taiwan) provided information regarding the date and cause of death, which was then calculated up until December 31, 2019 [5].

Results

Characteristics of the study population

A flow diagram of the patient selection process and the number of patients who met each study outcome during the follow-up period are depicted. The recruited patient population consisted of 50.4% men, with an average baseline age of 63.2 12.7 years. The initial HbA1c was 8.06 1.77%, and the average body mass index was 26.10 3.98 kg/m2. The middle subsequent span was 9.5 years (IQR 7.4-12.0). Our data were analyzed, and the mean and standard deviation of HbA1c were found to be 7.69 1.18% and 0.728 0.528 percent, respectively [6].

Supplemental display the baseline demographics according to HbA1c-mean and HbA1c-SD quartiles, respectively. Patients in the fourth quartile of HbA1c-mean and HbA1c-SD had higher HbA1c-mean and HbA1c-SD, diabetes duration, body weight, BMI, systolic blood pressure, fasting blood glucose, levels of triglycerides, UACR, and total cholesterol and LDL cholesterol, as well as decreased age. However, eGFR was lower and serum creatinine was higher in patients in the fourth quartile of HbA1c-SD. Additionally, male patients outnumbered female patients in the fourth quartile of HbA1c-SD, whereas female patients outnumbered male patients in the fourth quartile of HbA1c-mean [7].

Effect of mean HbA1c and variability of HbA1c on diabetes outcomes

Both HbA1c-mean and HbA1c-SD were related with an essentially expanded hazard of fostering the circumstances recorded as our six review endpoints. We utilized either HbA1c-SD or HbA1c-mean to change the investigation (Model 2). After we changed HbA1c-SD, HbA1c-mean was still fundamentally connected with our six review endpoints. HbA1c-SD remained significantly associated with a UACR greater than 300 mg/g, doubling of serum creatinine, all-cause mortality, and CVD mortality after we adjusted HbA1c-mean, but it was not significantly associated with any or advanced retinopathy. HbA1c-mean was still significantly associated with any retinopathy and advanced retinopathy in the fully adjusted model. However, HbA1c-SD was still significantly linked to all-cause and CVD mortality, a UACR greater than 300 mg/g, and a doubling of serum creatinine [8].

Comparison differential prognostic importance according to Glycemic levels

We examined the HRs of HbA1c-SD on diabetes-related complications in patients with low and high mean HbA1c in order to investigate the effects of mean HbA1c on HbA1c variability and diabetes-related complications. Higher HbA1c-SD was significantly associated with UACR > 300 mg/g, doubling of serum creatinine, all-cause mortality, and CVD mortality in patients with a mean HbA1c below the median. However, HbA1c-SD was only significantly associated with a UACR greater than 300 mg/g and a doubling of serum creatinine in patients with mean HbA1c values above the median [9].

We compared the HRs of an HbA1c-SD above the median and an HbA1c-mean below the median, as well as an HbA1c-SD below the median and an HbA1c-mean above the median, to better understand the difference in prognostic significance based on glycemic levels. The groups with an HbA1c-mean below the median and an HbA1c-SD above the median had significantly higher HRs for all-cause mortality and the doubling of serum creatinine. The HRs of the other complications caused by diabetes that was looked at did not significantly differ between the two groups [10].

Comparison of the different effects of HbA1c-mean and HbA1c-SD on patient outcomes

We plotted ROC curves and calculated AUC values to compare the predictive power of HbA1c-mean and HbA1c-SD on our study outcomes in order to further investigate the various effects of mean HbA1c and HbA1c variability on diabetes-related complications. HbA1c-mean was superior to HbA1c-SD at foreseeing any retinopathy, while HbA1c-SD was better at anticipating multiplying of serum creatinine, all-cause mortality and CVD mortality [11].

Discussion

This is the first prospective study to our knowledge to examine the various effects of mean HbA1c and HbA1c variability on diabetes-related complications in type 2 diabetes patients. Our crude model (Model 1) revealed that patients with elevated HbA1c-mean and HbA1c-SD had a significantly increased risk of developing diabetes-related complications, which were listed as our six study endpoints, after being monitored for a median of 9.5 years [12]. Increased HbA1c-SD was associated with a significantly increased risk of a UACR > 300 mg/g, doubling of serum creatinine, all-cause mortality, and CVD mortality, whereas increased HbA1c-mean was associated with a significantly increased risk of a UACR > 300 mg/g. Further examination was led with ROC bends, which showed that the HbA1c-mean was more powerful than the HbA1c-SD at anticipating any retinopathy, though the HbA1c-SD was more viable at foreseeing the multiplying of serum creatinine, all-cause mortality and CVD mortality [13].

Late proof recommends that diabetes-related confusions are anticipated by HbA1c levels as well as by HbA1c inconstancy between visits, free of normal HbA1c and other gamble factors present. Gorst and co. conducted a meta-analysis and systematic review to investigate the relationship between diabetes patients' outcomes and HbA1c variability. In patients with type 2 diabetes, higher HbA1c variability was linked to an increased risk of

renal disease, cardiovascular disease, and death [14]. In patients with type 2 diabetes, the retinopathy did not appear to be associated with HbA1c variability, as our study also revealed. All the more as of late, new proof has additionally upheld glycemic fluctuation as an autonomous gamble factor for nephropathy, all-cause mortality, and cardiovascular sickness mortality. The majority of studies have not mentioned the correlation between HbA1c variability and retinopathy, and some studies gave contradictory findings for retinopathy, despite the fact that cumulative evidence has suggested a role for HbA1c variability in diabetes-related complications [15].

Conclusion

In conclusion, our research demonstrated that a significantly increased risk of developing a UACR greater than 300 mg/g, which indicates deteriorating kidney function, was associated with an increased mean HbA1c and HbA1c variability. The risk of retinopathy was significantly increased with an increase in mean HbA1c, and the risk of doubling serum creatinine (indicating deterioration of renal function), all-cause mortality, and CVD mortality was significantly increased with an increase in HbA1c variability.

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None

Conflict of Interest

None

References

1. Powers AC, Stafford JM, Rickels MR. Diabetes Mellitus: Complications. Jameson JL, Fauci AS, Kasper DL, Hauser SL, Longo DL, Loscalzo J (Eds.) Harrison's Principles of Internal Medicine (20th ed.), McGraw-Hill, New York. 2019: 2875-2883.
2. American Diabetes Association. 6. Glycemic Targets: Standards of Medical Care in Diabetes-2021. Diabetes Care. 2021; 44: 73-84.
3. Ceriello A, Monnier L, Owens D. Glycaemic variability in diabetes: clinical and therapeutic implications. Lancet Diabetes Endocrinol. 2019; 7 (3): 221-230
4. Home P. Contributions of basal and post-prandial hyperglycaemia to micro- and macrovascular complications in people with type 2 diabetes. Curr Med Res Opin. 2005; 21 (7): 989-998.
5. Kilpatrick ES, Rigby AS, Atkin SL. A1c variability and the risk of microvascular complications in type 1 diabetes: data from the Diabetes Control and Complications Trial. Diabetes Care. 2008; 31: 2198-2202.
6. Cavalot F. Do data in the literature indicate that glycaemic variability is a clinical problem? Glycaemic variability and vascular complications of diabetes. Diabetes Obes Metab. 2013; 15: 3-8.
7. Gorst C, Kwok CS, Aslam S, Buchan I, Kontopantelis E, Myint PK, et al. Long-term Glycemic Variability and Risk of Adverse Outcomes: A Systematic Review and Meta-analysis. Diabetes Care. 2015; 38(12): 2354-2369.
8. Sugawara A, Kawai K, Motohashi S. HbA(1c) variability and the development of microalbuminuria in type 2 diabetes: Tsukuba Kawai Diabetes Registry 2. Diabetologia. 2012; 55: 2128-2131.
9. Luk AO, Ma RC, Lau ES. Risk association of HbA1c variability with chronic kidney disease and cardiovascular disease in type 2 diabetes: prospective analysis of the Hong Kong Diabetes Registry. Diabetes Metab Res Rev. 2013; 29: 384-390.
10. Penno G, Solini A, Bonora E. Renal Insufficiency and Cardiovascular Events Study Group. HbA1c 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. 2013; 36: 2301-2310.
11. Chiu WC, Lai YR, Cheng BC, Huang CC, Chen JF, Lu CH. HbA1C Variability Is Strongly Associated with Development of Macroalbuminuria in Normal or Microalbuminuria in Patients with Type 2 Diabetes Mellitus: A Six-Year Follow-Up Study. Biomed Res Int. 2020; 25: 7462158.
12. Lee S, Liu T, Zhou J, Zhang Q, Wong WT, Tse G. Predictions of diabetes complications and mortality using HbA1c variability: a 10-year observational cohort study. Acta Diabetol. 2021; 58 (2): 171-180.
13. Levey AS, Coresh J, Greene T. Using standardized serum creatinine values in the modification of diet in renal disease study equation for estimating glomerular filtration rate. Ann Intern Med. 2006; 145: 247-254.
14. Monnier L, Mas E, Ginet C. Activation of oxidative stress by acute glucose fluctuations compared with sustained chronic hyperglycemia in patients with type 2 diabetes. JAMA. 2006; 295 (14): 1681-1687.
15. Wei F, Sun X, Zhao Y, Zhang H, Diao Y, Liu Z. Excessive visit-to-visit glycemic variability independently deteriorates the progression of endothelial and renal dysfunction in patients with type 2 diabetes mellitus. BMC Nephrol. 2016; 17 (1): 67.

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