Glycated hemoglobin variability, mean HbA1c and heart failure in patients with type 2 diabetes

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Abstract

Background: Heart failure (HF) is a common presentation in patients with type 2 diabetes mellitus (T2DM). Previous studies revealed that HbA1c level is significantly associated with HF. However, little is known about the association between HbA1c variability and HF. We aimed to evaluate the association of HbA1c variability and mean HbA1c with HF in patients with T2DM.

Methods: Using Diabetes Share Care Program data, patients with T2DM had mean HbA1c (HbA1c-Mean), HbA1c variability (tertiles of HbA1c-SD and HbA1c-adjSD) within 12-24 months during 2001-2008 were included. The cutoffs of HbA1c-Mean were set at <7%, 7-7.9%, and $\geq 8\%$. Hazard ratios (HRs) for HF during 2008-2018 were estimated using Cox proportional hazards models.

Results: A total of 3824 patients were included, of whom 315 patients developed HF during the 11.72 years observation period. The associated risk of HF increased with tertiles of HbA1c variability and cutoffs of HbA1c-Mean. In mutually adjusted models, HbA1c-Mean showed a consistent dose-response association with HF, while the association of HbA1c variability with HF disappeared. Among patients with HbA1c-Mean < 7%, the associated risk of HF in patients with HbA1c variability in tertile 3 was comparable to patients with HbA1c-Mean $\geq 8\%$.

Conclusions: Mean HbA1c was an independent predictor of HF and not explained by HbA1c variability. In addition to absolute HbA1c level, targeting on stability of HbA1c in patients with well glycemic control was also important for the development of HF in patients with T2DM.

Background

Heart failure (HF) is one of the most common initial manifestations of cardiovascular disease in patients with type 2 diabetes mellitus (T2DM) [1]. A previous study showed that the mortality rate of patients with diabetes and HF is 4- to 6-fold increase than patients with diabetes who do not develop HF [2]. A recent study also reported that the development of HF is associated with the highest 5-year risk of death compared with the development of other cardiovascular diseases in patients newly diagnosed T2DM [3]. An epidemiological study revealed that the incidence of HF is approximately 2 times higher in patients with diabetes than patients without diabetes [4]. Clinically, hypertension and coronary heart disease are well known causes of HF. These two risk factors are common comorbidities in patients with T2DM [5] which may partly explain the higher incidence of HF in patients with diabetes. However, previous studies showed that diabetes itself is an independent risk factor for the development of HF irrespective of blood pressure and coronary heart disease [6,7] which implies that there is a residual risk(s) for the development of HF in patients with T2DM. Several studies revealed that glycated hemoglobin (HbA1c) level is positively associated with HF in patients with T2DM [8-12]. In addition, a cohort study reported that an 1% reduction in mean HbA1c is associated with a 16% risk reduction in HF [13]. Recently, many studies showed that HbA1c variability is positively associated with macrovascular complications [14-16] and all-cause mortality [17] in patients with T2DM. However, little is known about the association of HbA1c

variability with HF. In this study, we aimed to examine the associated risk of HbA1c variability and mean HbA1c with HF in patients with T2DM.

Methods

2.1 Data source and design

In 2001, the Taiwan National Health Insurance Bureau established a Diabetes Shared Care Program to promote diabetes care. In this program, certified diabetes educators used a standardized electronic questionnaire to record basic data, personal habits, current and past diseases, and medications. Patients with a clinical diagnosis of diabetes were enrolled to the program at the outpatient clinic of China Medical University hospital, Taichung, Taiwan. In this study, we used data of patients enrolled between January 2001 and April 2008 for study analyses. The exclusion criteria included patients with a history of HF before enrollment, development of HF within 1 year after enrollment (for avoiding reverse causality), aged >80 years, age of diabetes onset <30 years, type 1 DM, cardiac dysrhythmia, congenital heart disease, valvular heart disease, estimated glomerular filtration rate (eGFR) <30 mL/min/1.73m², and HbA1c measurements fewer than 3 times within 12-24 months. We linked each patient's personal identification number to the annual inpatient and outpatient claim database of the Taiwan National Health Insurance, provided by the Taiwan Health and Welfare Data Science Center, to verify the diagnoses of primary outcome (HF) and cardiovascular risk factors (hypertension, coronary heart disease, valvular heart disease, congenital heart disease, cardiac dysrhythmia, and stroke). Each patient was followed from the identified date to the development of HF, death, or December 31, 2018. The International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) and ICD-10-CM codes used in this study were presented in supplementary Table S1. This study was approved by the Ethical Review Board of China Medical University Hospital in Taiwan (CMUH107-REC2-163).

2.2 Statistical analyses

The mean and standard deviation (SD) of continuous variables and number and percentage for categorical variables were used to describe the distributions of the patients. The Student's t test and the chi-square test (or the Fisher's exact test) were used to compare continuous and categorical variables between patients with HF and patients without HF, respectively. HbA1c variability was presented with SD (HbA1c-SD). Because the number of HbA1c measurements could influence the SD [18], the inter-individual difference in the numbers of HbA1c measurements was adjusted according to the formula: $SD/\sqrt{[n/(n-1)]}$ (HbA1c-adjSD) (18). For comparison, individuals' HbA1c-SD and HbA1c-adjSD were divided by tertiles; for mean HbA1c (HbA1c-Mean), the cutoffs were set at <7%, 7-7.9%, and ≥8%. A Cox proportional hazards model was used to estimate the hazard ratios (HRs) and 95% confidence intervals. Multiple confounders in the adjusted model included sex, age, diabetes duration, body mass index, systolic blood pressure, total cholesterol, triglyceride, High-density lipoprotein cholesterol, Low-density lipoprotein cholesterol, eGFR, coronary heart disease, hypertension, stroke, the use of sulfonylureas, metformin, thiazolidinediones, insulin, statin, antiplatelet agents, warfarin, angiotensin converting enzyme

inhibitors, angiotensin II receptor blockers, beta-blockers, calcium channel blockers, diuretics, and alpha-blockers. In Table 2, model 1 was adjusted for multiple confounders; model 2 was a mutually (HbA1c-SD or HbA1c-adjSD vs HbA1c-Mean) adjusted model, adjusted for the same confounders as model 1 plus HbA1c-Mean in HbA1c-SD and HbA1c-adjSD; in HbA1c-Mean, multiple confounders plus either HbA1c-SD or HbA1c-adjSD (shown with hashtag). Data management and analysis were performed using SAS 9.4 software (SAS Institute, Cary, NC, USA). The significance level was set at a P-value <0.05 for two-sided testing.

Results

As shown in Figure 1, a total of 8636 patients were enrolled in the program. We excluded 285 patients with a history of HF before enrollment, 44 patients who developed HF within 12 months after enrollment, 195 patients with age at enrollment of >80 years, 516 patients with age at diabetes onset of <30 years, 170 patients with type 1 DM, 246 patients with cardiac dysrhythmia, 4 patients with congenital heart disease, 55 patients with valvular heart disease, 173 patients with eGFR <30 mL/min/1.73m², and 3124 patients who underwent HbA1c measurement fewer than three times. In total, 3824 patients were identified for analyses in this study; among these, 315 patients who developed HF during the 11.72 years observation period.

As shown in Table 1, the patients who developed HF had older ages, diabetes for longer, higher systolic blood pressure and higher mean HbA1c, lower eGFR, more cardiovascular diseases, been administered more sulfonylureas, thiazolidinediones, insulin, statin and cardiovascular medications, and higher HbA1c variability and more proportion of patients with HbA1c ≥8% at baseline than patients who did not develop HF.

Table 2 reveals that the unadjusted risk of HF increased with tertiles of HbA1c-SD, HbA1c-adjSD, and higher HbA1c-Mean (mean HbA1c ≥8% vs <7%, HR 1.85 [1.39-2.46], P <0.001). As shown in model 1, the associations of HbA1c-SD, HbA1c-adjSD, and HbA1c-Mean remained when adjustment for multiple confounders. In model 2, the associated risk of HbA1c-SD and HbA1c-adjSD with HF disappeared after further adjustment for HbA1c-Mean. However, the associated risk of HbA1c-Mean with HF remained even further adjustment for either HbA1c-SD (HbA1c-Mean ≥8% vs <7%, HR 1.56 [1.09-2.22], P = 0.015), or HbA1c-adjSD (mean HbA1c ≥8% vs <7%, HR 1.57 [1.10-2.23], P = 0.013).

Supplementary Table S2 shows all HRs by categories of tertiles of HbA1c-SD or HbA1c-adjSD and cutoffs of HbA1c-Mean. As shown in Figure 1A, the unadjusted HR reveals that the risk of HF was lowest in patients with HbA1c-adjSD in tertile 1 and HbA1c-Mean <7%; highest in those patients with HbA1c-adjSD in tertile 1 and HbA1c-Mean ≥8%, following by HbA1c-adjSD in tertile 3 and HbA1c-Mean ≥8%, then by HbA1c-adjSD in tertile 3 and HbA1c-Mean <7%. When adjustment for multiple confounders (Figure 1B), the HF risk of patients with HbA1c-Mean <7% and HbA1c-adjSD in tertile 3 was comparable with those patients with HbA1c-Mean ≥8% and HbA1c-adjSD in either tertile 1 or tertile 3.

Discussion

This study shows that raised mean HbA1c level was associated with a higher risk to develop HF. The effect of HbA1c variability on HF was crucial in patients with mean HbA1c <7%. The associated risk of HF in patients with mean HbA1c <7% and a greater HbA1c variability was comparable to patients with HbA1c $\geq 8\%$ irrespective of HbA1c variability.

Many previous studies revealed that HbA1c level is positively associated with HF in patients with T2DM [8-12]. However, these studies did not take HbA1c variability into consideration for the adjustment. So far, there were a few studies to evaluate the association of HbA1c variability with HF. A longitudinal study with small patient numbers (201 subjects) and limited HF events (18 events) showed a positive association between HbA1c variability and new-onset HF [19]. Another study focused on the prediction of incident HF by mean HbA1c, additionally reported that less HbA1c variability has a less incidence of HF [20]. Again, this study did not adjust for mean HbA1c in the analyses of the association between HbA1c variability and HF. In our study, the adjusted model showed that both HbA1c variability and mean HbA1c level independently predict HF. In mutually adjusted models, however, only mean HbA1c revealed a consistent dose-response association, while the association of HbA1c variability with HF disappeared, which indicated that the association of HbA1c variability was largely explained by mean HbA1c. Nevertheless, HbA1c variability is still important among patients with well glycemic control. The risk of HF in well glycemic control patients with greater HbA1c variability was comparable to patients with poor glycemic control. Our study supported that further targeting on HbA1c stability after well glycemic control is crucial to reduce the risk of HF.

The underlying mechanism(s) to explain why the effect of absolute HbA1c level on HF was greater than HbA1c variability remains unclear. An excess production of reactive oxygen species has been reported to be an important pathophysiology to develop HF [21]. A previous study showed that acute (24 hours) glucose fluctuations activate more oxidative stress than chronic hyperglycemia (by using one baseline HbA1c level) [22]. Another study also revealed that acute (24 hours) glucose oscillations produce more oxidative stress than 24 hours mean blood glucose level at 180 mg/dL [23]. However, these two studies were unable to explain our results because the glucose exposure period was rather short in comparison with our study. The possible mechanism(s) needs further investigation in the future.

Study Strengths and Limitations

The strength of this study included a large sample size with long-term follow-up of real-world data. Nevertheless, our study had some limitations. First, the patients in this study were from a tertiary referral outpatient clinic. They are usually more complicated. Therefore, our findings may not be generalizable to all patients with diabetes. Second, most of our patients were on sulfonylureas and used metformin and statins less; such medication regimens are different from current managements. This difference should be considered before generalizing our results to patients with current medication patterns. Finally, as the inherent limitation of a database, we cannot categorize HF into HF with preserved ejection fraction and

HF with reduced ejection fraction; echocardiography and laboratory data are also lack to confirm the diagnosis.

Conclusions

Our study shows that higher mean HbA1c was independently associated with increased risk of HF regardless of HbA1c variability. In patients with well glycemic control, less HbA1c variability was pivotal for the development of HF.

Declarations

Acknowledgments

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Author contributions

YTL, WLH, and CCC designed the study. YTL, WLH, HPW, and CCC analyzed and interpreted the data. MPC and CCC drafted the manuscript, which was critically revised by CCC; CCC approved the manuscript and is the guarantor of this work, and takes responsibility for the integrity of the data and the accuracy of the data analyses. All authors read and approved the final manuscript.

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Availability of data and materials

This study use the database of the Taiwan National Health Insurance (<https://dep.mohw.gov.tw/DOS/lp-2501-113.html>) which are available following application for Taiwanese researchers.

Ethics approval and consent to participate

The Ethical Review Board of China Medical University Hospital in Taiwan (CMUH107-REC2-163) approved the study before commencement.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Abbreviations

eGFR: Estimated glomerular filtration rate; HbA1c: Glycated hemoglobin; HF: Heart failure; HRs: Hazard ratios; ICD-9-CM: International Classification of Diseases, Ninth Revision, Clinical Modification; SD: Standard deviation; T2DM: Type 2 diabetes mellitus.

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Tables

Table 1 Baseline characteristics of the study patients

	non-HF	HF	
Variables	(n=3,509)	(n=315)	p-value
Man	1,785 (50.9%)	134 (42.5%)	0.005
Age, years	57.3 (10.7)	63.9 (9.4)	<0.001
Diabetes duration, years	6.1 (6.5)	10.1 (7.3)	<0.001
Body mass index, kg/m ²	25.4 (3.8)	25.8 (4.2)	0.083
Systolic blood pressure, mmHg	134.6 (17.4)	140.6 (18.0)	<0.001
Fasting plasma glucose, mg/dL	162.7 (58.9)	170.6 (66.7)	0.043
Mean HbA1c	7.7 (1.3)	8.2 (1.6)	<0.001
Total Cholesterol	195.5 (43.2)	201.5 (45.1)	0.018
Triglyceride	160.3 (194.0)	177.2 (120.1)	0.025
HDL-cholesterol, mg/dL	41.3 (11.5)	39.7 (9.5)	0.004
LDL-cholesterol, mg/dL	120.0 (35.6)	121.7 (37.1)	0.422
Creatinine, mg/dL	0.9 (0.3)	1.0 (0.3)	<0.001
eGFR, mL/min/1.73m ²			<0.001
30-59	451 (12.9%)	105 (33.3%)	
≥60	3,058 (87.1%)	210 (66.7%)	
mean	87.3 (24.6)	72.7 (24.7)	<0.001
Exercise	1,676 (59.1%)	142 (58.9%)	0.952
Smoking	636 (18.1%)	41 (13.0%)	0.023
Alcohol-drinking	417 (11.9%)	24 (7.6%)	0.024
Coronary heart disease	361 (10.3%)	70 (22.2%)	<0.001
Hypertension	1,636 (46.6%)	219 (69.5%)	<0.001
Stroke	409 (11.7%)	73 (23.2%)	<0.001
Sulfonylureas	2,805 (79.9%)	267 (84.8%)	0.039
Metformin	1,255 (35.8%)	108 (34.3%)	0.599
Thiazolidinediones	727 (20.7%)	90 (28.6%)	0.001
Insulin	727 (20.7%)	90 (28.6%)	0.001
Statin	739 (21.1%)	91 (28.9%)	0.001

	non-HF	HF	
Variables	(n=3,509)	(n=315)	p-value
Antiplatelet agents	317 (9.0%)	65 (20.6%)	<0.001
Warfarin	14 (0.4%)	6 (1.9%)	0.004
Angiotensin converting enzyme inhibitors	1,107 (31.5%)	151 (47.9%)	<0.001
Angiotensin II receptor blockers	640 (18.2%)	106 (33.7%)	<0.001
Beta-blockers	951 (27.1%)	129 (41.0%)	<0.001
Calcium channel blockers	1,256 (35.8%)	179 (56.8%)	<0.001
Other anti-hypertension drugs	156 (4.4%)	37 (11.7%)	<0.001
Diuretics	626 (17.8%)	108 (34.3%)	<0.001
Alfa-blockers	496 (14.1%)	78 (24.8%)	<0.001
HbA1c-SD			0.011
tertile1	1,215 (34.6%)	84 (26.7%)	
tertile2	1,138 (32.4%)	122 (38.7%)	
tertile3	1,156 (32.9%)	109 (34.6%)	
HbA1c-adjSD			0.037
tertile1	1,181 (33.7%)	84 (26.7%)	
tertile2	1,174 (33.5%)	120 (38.1%)	
tertile3	1,154 (32.9%)	111 (35.2%)	
HbA1c-Mean			<0.001
<7%	1,098 (31.3%)	70 (22.2%)	
7-7.9%	1,216 (34.7%)	97 (30.8%)	
≥8%	1,195 (34.1%)	148 (47.0%)	

HF, heart failure; SD, standard deviation; eGFR, estimated glomerular filtration rate; HDL, High-density lipoprotein; LDL: Low-density lipoprotein.

Table 2 Hazard ratios of heart failure by measures of HbA1c variability and mean HbA1c

Adjusted						
Unadjusted			Model 1		Model 2	
Variable	HR [95%CI]	P	HR [95%CI]	P	HR [95%CI]	P
HbA1c-SD						
tertile 1	1.00 [ref.]		1.00 [ref.]		1.00 [ref.]	
tertile 2	1.53 [1.16-2.02]	0.002	1.39 [1.04-1.85]	0.024	1.29 [0.96-1.73]	0.095
tertile 3	1.38 [1.04-1.83]	0.026	1.42 [1.04-1.92]	0.025	1.17 [0.84-1.64]	0.350
HbA1c-adjSD						
tertile 1	1.00 [ref.]		1.00 [ref.]		1.00 [ref.]	
tertile 2	1.43 [1.08-1.89]	0.012	1.29 [0.97-1.72]	0.086	1.19 [0.89-1.60]	0.239
tertile 3	1.37 [1.03-1.82]	0.029	1.39 [1.03-1.88]	0.032	1.16 [0.83-1.61]	0.386
HbA1c-Mean						
<7%	1.00 [ref.]		1.00 [ref.]		1.00 [ref.]	
7-7.9%	1.22 [0.90-1.66]	0.204	1.20 [0.88-1.65]	0.259	1.15 [0.83-1.58]	0.411
≥8%	1.85 [1.39-2.46]	<0.001	1.66 [1.20-2.29]	0.002	1.56 [1.09-2.22]	0.015
					#1.00 [ref.]	
					#1.16 [0.84-1.59]	0.376
					#1.57 [1.10-2.23]	0.013

HR, hazard ratio

Model 1: adjusted for multiple confounders (as shown in method)

Model 2: adjusted for the same confounders as model 1 plus HbA1c-Mean in HbA1c-SD and HbA1c-adjSD; in HbA1c-Mean, multiple confounders plus either HbA1c-SD or HbA1c-adjSD (shown with #)

Figures

Figure 1

The hazard ratios (HRs) of heart failure (HF) by categories of HbA1c-adjSD and HbA1c-Mean. (A) The unadjusted HRs reveals that the risk of HF was lowest in patients with HbA1c-adjSD in tertile 1 and HbA1c-Mean <7%; highest in those patients with HbA1c-adjSD in tertile 1 and HbA1c-Mean $\geq 8\%$, follow by HbA1c-adjSD in tertile 3 and HbA1c-Mean $\geq 8\%$, then by HbA1c-adjSD in tertile 3 and HbA1c-Mean <7%. (B) When adjustment for multiple confounders, the HF risk of patients with HbA1c-Mean <7% and HbA1c-adjSD in tertile 3 was comparable with those patients with HbA1c-Mean $\geq 8\%$ and HbA1c-adjSD in either tertile 1 or tertile 3. Abbreviation: T, tertile

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