Relationship between hemoglobin glycation index and extent of coronary heart disease in individuals with type 2 diabetes mellitus: A cross-sectional study (#19225)

First revision

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Daniela Foti / 5 Sep 2017

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Please read in full before you begin

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When ready **submit your review online**. The review form is divided into 5 sections. Please consider these when composing your review:

1. **BASIC REPORTING**
2. **EXPERIMENTAL DESIGN**
3. **VALIDITY OF THE FINDINGS**
4. General comments
5. Confidential notes to the editor

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- Clear, unambiguous, professional English language used throughout.
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- Methods described with sufficient detail & information to replicate.

VALIDITY OF THE FINDINGS

- Impact and novelty not assessed. Negative/inconclusive results accepted. *Meaningful* replication encouraged where rationale & benefit to literature is clearly stated.
- Data is robust, statistically sound, & controlled.
- Conclusions are well stated, linked to original research question & limited to supporting results.
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Relationship between hemoglobin glycation index and extent of coronary heart disease in individuals with type 2 diabetes mellitus: A cross-sectional study

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Background. Individuals with type 2 diabetes (T2D) are at an increased risk of coronary heart disease (CHD). Diabetic complications have recently been associated with a measure of glucose metabolism known as the hemoglobin glycation index (HGI). Currently there is insufficient information regarding a potential link between HGI and cardiovascular disease. This study aimed to investigate the relationship between HGI and extent of CHD in individuals with T2D. **Methods.** This cross-sectional study screened individuals visiting the endocrinology clinic between June 2012 and May 2016 for eligibility. Enrollment criteria included individuals above 21 years of age with T2D diagnosed in the preceding ten years. Candidates with hemoglobin disorders, pregnancy, and existing coronary artery disease were excluded. Fasting plasma glucose (FPG) and glycated hemoglobin A1c (HbA1c) were sampled three months prior to angiography. The regression equation of predicted HbA1c = 0.008 x FPG + 6.28 described the linear relationship between these variables. HGI was calculated as the difference between the measured HbA1c and predicted HbA1c. Participants were classified into two groups according to the presence of supranormal HGI ≥ 0 or subnormal HGI < 0. **Results.** Among 423 participants, people with supranormal HGI harbored an increased prevalence of multiple vessel disease relative to those with subnormal HGI (Odds ratio (OR): 3.9, 95% confidence interval (CI): 2.64 – 5.98, $P < 0.001$). Moreover, individuals with supranormal HGI more frequently demonstrated lesions involving the left anterior descending artery (OR: 3.0, 95% CI: 1.97 – 4.66, $P < 0.001$). The intergroup difference in mean HbA1c was statistically nonsignificant (7.5 ± 1.0 % versus 7.4 ± 1.1 %, $P = 0.80$). **Discussion.** This study demonstrated that HGI correlated with the extent of CHD in individuals with T2D. People with supranormal HGI harbored a higher prevalence of extensive cardiovascular disease compared to those with subnormal HGI. The relationship between HGI and extent of CHD enables cardiovascular risk stratification

in at risk individuals. Overall, HGI provides useful information concerning cardiovascular risk in clinical practice.

Author Cover Page

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Abstract

Background. Individuals with type 2 diabetes (T2D) are at an increased risk of coronary heart disease (CHD). Diabetic complications have recently been associated with a measure of glucose metabolism known as the hemoglobin glycation index (HGI). Currently there is insufficient information regarding a potential link between HGI and cardiovascular disease. This study aimed to investigate the relationship between HGI and extent of CHD in individuals with T2D.

Methods. This cross-sectional study screened individuals visiting the endocrinology clinic between June 2012 and May 2016 for eligibility. Enrollment criteria included individuals above 21 years of age with T2D diagnosed in the preceding ten years. Candidates with hemoglobin disorders, pregnancy, and existing coronary artery disease were excluded. Fasting plasma glucose (FPG) and glycated hemoglobin A1c (HbA1c) were sampled three months prior to angiography. The regression equation of predicted HbA1c = 0.008 x FPG + 6.28 described the linear relationship between these variables. HGI was calculated as the difference between the measured HbA1c and predicted HbA1c. Participants were classified into two groups according to the presence of supranormal ~~HGI~~ HGI ≥ 0 or subnormal HGI < 0.

Results. Among 423 participants, people with supranormal HGI harbored an increased prevalence of multiple vessel disease relative to those with subnormal HGI (Odds ratio (OR): 3.9, 95% confidence interval (CI): 2.64 – 5.98, $P < 0.001$). Moreover, individuals with supranormal HGI more frequently demonstrated lesions involving the left anterior descending artery (OR: 3.0, 95% CI: 1.97 – 4.66, $P < 0.001$). The intergroup difference in mean HbA1c was statistically nonsignificant (7.5 ± 1.0 % versus 7.4 ± 1.1 %, $P = 0.80$).

Discussion. This study demonstrated that HGI correlated with the extent of CHD in individuals

with T2D. People with supranormal HGI harbored a higher prevalence of extensive cardiovascular disease compared to those with subnormal HGI. The relationship between HGI and extent of CHD enables cardiovascular risk stratification in at risk individuals. Overall, HGI provides useful information concerning cardiovascular risk in clinical practice.

Relationship between hemoglobin glycation index and extent of coronary heart disease in individuals with type 2 diabetes mellitus: A cross-sectional study

1 Introduction

Type 2 diabetes mellitus (T2D) is a developing epidemic that affects a substantial proportion of the adult population (*Chen, Magliano & Zimmet, 2011*). Changes in dietary habit, urbanization, and sedentary lifestyle contribute to an increasing incidence of the disease (*Yang et al., 2010*). Hyperglycemia exerts detrimental effects on blood vessels, as evidenced by a predisposition to develop retinopathy, nephropathy, and coronary heart disease (CHD) (*Mohammedi et al., 2017*). These vascular complications profoundly influence the quality of life in affected individuals.

Specifically, individuals with T2D are at risk of developing cardiovascular disease (*Shah et al., 2015*), which accounts for nearly sixty percent of diabetes related mortality (*Kalofoutis et al., 2007*). Although glycemic control as represented by glycated hemoglobin A1c (HbA1c) influences vascular disease, this association is not particularly robust (*Laakso, 2010*). Investigators have proposed that elements of hyperglycemia not captured by HbA1c measurement may modify cardiovascular risk (*Fox, 2010*).

The hemoglobin glycation index (HGI) is an indicator of glucose metabolism linked to diabetic complications (*Soros et al., 2010*). HGI correlated with a composite index of cardiac, cerebral, and peripheral vascular events in a recent study involving individuals with T2D (*Nayak, 2013*). Specifically, this glycation index may correlate with cardiovascular disease risk. This study

97 investigated the relationship between HGI and extent of coronary vascular disease in people with
98 T2D.
99
100 2 Materials and Methods
101
102 2.1 Study population
103
104 This cross-sectional study screened patients visiting the endocrinology clinic at Changhua
105 Christian Hospital, Changhua City, Taiwan, between June 2012 and May 2016 for eligibility.
106 Enrollment criteria included individuals exceeding 21 years of age, with T2D diagnosed in the
107 preceding ten years, who received hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase
108 inhibitors since diabetes onset and underwent coronary angiography (CAG) during the study
109 period. Exclusion criteria involved people who had undertaken CAG prior to the study, those
110 with existing CHD, or who lacked concomitant HbA1c and fasting plasma glucose (FPG)
111 measurements. Candidates with hemoglobin disorders, pregnancy, and congenital coronary
112 artery abnormalities were also ineligible. Decision to perform coronary artery survey was made
113 by cardiologists based on high risk findings on non-invasive testing or high pre-test probability
114 of coronary artery disease. All participants provided written informed consent for CAG. The
115 study was approved by the Institutional Review Board of Changhua Christian Hospital (CCH
116 IRB number: 161111).
117
118 2.2 Calculation of HGI
119
120 Concomitant HbA1c and FPG measurements from all participants were graphed to establish the

121 linear relationship between these variables, as shown in Figure 1, from which the regression
122 equation of predicted HbA1c = 0.008 x FPG + 6.28 was derived. Individual FPG in milligrams
123 per deciliter was substituted into this linear regression equation to derive the predicted HbA1c.
124 HGI was calculated as the difference between the measured HbA1c and predicted HbA1c
125 (*Hempe et al., 2015*). Supranormal HGI was defined as levels above or equivalent to zero,
126 whereas subnormal HGI designated values below zero.
127
128 2.3 Classification of CHD
129
130 The extent of vascular disease involving the left anterior descending, left circumflex, and right
131 coronary arteries was documented by CAG. Significant stenosis was defined as more than fifty
132 percent narrowing of the diseased vascular segment compared to a proximal or distal normal
133 segment (*Leopold & Faxon, 2015*). Single vessel disease was defined as one or more stenotic
134 lesions in one of the major coronary arteries, whereas multiple vessel disease involved lesions in
135 two or more of the coronary arteries (*Tazaki et al., 2013*). Arteriosclerosis described the
136 observation that none of the stenotic lesions resulted in more than fifty percent narrowing of the
137 major coronary arteries.
138
139 2.4 Statistical analysis
140
141 Baseline characteristics including age, gender, lipid profile, mean HbA1c, and cigarette smoking
142 were compared between the HGI subgroups. Intergroup comparisons were made using Student's
143 *t* test for continuous variables and Pearson's χ^2 test for categorical variables. For the HGI
144 subgroups, the prevalence of multiple vessel disease as opposed to single vessel disease or

145 arteriosclerosis was compared using Pearson's χ^2 test. Tests of statistical significance were based
146 on a two-tailed $P < 0.05$. Statistical analysis was performed using Statistical Package for the
147 Social Sciences (version 22.0, SPSS, Chicago, IL).
148
149 3 Results
150
151 Initially 480 individuals with T2D were screened for eligibility. Twenty patients were excluded
152 due to lack of HMG-CoA reductase inhibitor prescription, 32 individuals had received CAG
153 prior to the study and were ineligible, and five candidates were excluded due to absence of
154 concomitantly measured HbA1c and FPG. Figure 2 illustrates the enrollment process of this
155 study.
156
157 The study enrolled 423 individuals who were classified according to the presence of either
158 supranormal (HGI ≥ 0) or subnormal HGI (HGI < 0). Baseline characteristics including age,
159 gender, and kidney function were similar between groups, as summarized in Table 1. Levels of
160 low-density lipoprotein cholesterol, presence of cigarette smoking, and degree of systolic blood
161 pressure were also comparable. The intergroup difference in mean HbA1c was nonsignificant
162 (7.5 ± 1.0 % versus 7.4 ± 1.1 %, $P = 0.80$), and both HGI groups harbored similar degree of
163 proteinuria (0.25 ± 0.95 grams per day versus 0.19 ± 0.57 grams per day, $P = 0.467$).
164
165 As shown in Table 2, individuals with supranormal HGI harbored a higher prevalence of
166 multiple vessel disease relative to those with subnormal HGI (Odds ratio (OR): 3.9, 95%
167 confidence interval (CI): 2.64 - 5.98, $P < 0.001$). This observation suggests that people with
168 higher HGI are at an increased risk of extensive CHD. Moreover, the supranormal HGI group

more frequently demonstrated lesions involving the left anterior descending artery (OR: 3.0, 95% CI: 1.97 - 4.66, $P < 0.001$), which supplies a sizable proportion of the myocardium and may contribute to the degree of myocardial ischemia.

As illustrated in Table 3, the length of hospitalization was similar between groups. Intriguingly, people with supranormal HGI demonstrated a trend towards requiring multiple stent deployment relative to those with subnormal HGI (23.0% versus 16.7%, $P = 0.067$). Therefore, the supranormal HGI subgroup not only harbored an increased prevalence of extensive CHD, but the healthcare cost of stent deployment may also be higher in this population.

4 Discussion

Cardiovascular disease affects a considerable proportion of people with T2D and detracts from their survival (*Naito& Kasai, 2015; White et al., 2016*). However, HbA1c measurements delineated only a fraction of cardiovascular disease risk (*Rawshani et al., 2017*). This study demonstrated that HGI consistently correlated with the extent of CHD in T2D. As observed by previous investigators, people with elevated HGI harbor an accelerated rate of protein glycation with subsequent endothelial injury (*Nayak et al., 2011*). Supranormal HGI may also reflect an excess of advanced glycosylation end products that arise from chronic hyperglycemia (*Singh et al., 2014*).

Researchers have postulated that specific patterns of glucose variation, as measured by HGI, constitute a distinctive risk factor for diabetic complications. Whereas HbA1c measures protein

glycosylation within the red blood cell, diabetic complications may arise from protein glycation in both the extracellular and intracellular space. HGI was suggested as an indicator of the rate of extracellular protein glycation (*Leslie & Cohen, 2009*). Another potential explanation for a supranormal HGI may be postprandial hyperglycemia, which raises the measured HbA1c above that predicted from FPG (*Rizza, 2010; Riddle & Gerstein, 2015*). Indeed, several studies have implicated hyperglycemia after meals in the development of cardiovascular disease (*Cavalot et al., 2011; Node & Inoue, 2009; Ceriello, 2009*). These findings were corroborated by the observation in this study that different HGI subgroups, potentially reflecting the degree of postprandial hyperglycemia, consistently correlated with the extent of CHD.

Whereas researchers previously identified an association between HGI and a composite index of cardiac, cerebral, and peripheral vascular events (*Nayak et al., 2013; Hempe et al., 2015*), this study provides novel information by focusing on the link between HGI and coronary vascular disease. An implication of this study is that cardiovascular risk assessment may be refined by HGI, particularly in individuals with similar baseline HbA1c. Furthermore, people with supranormal HGI who experience angina pectoris are at risk of CHD and should receive comprehensive examination. Considering the aforementioned link between postprandial hyperglycemia, HGI, and cardiovascular disease risk (*Riddle & Gerstein, 2015; Raz et al., 2011*), controlling postprandial hyperglycemia in individuals with supranormal HGI may be an appropriate therapeutic approach to attenuate CHD.

This study benefits from an objective assessment of macrovascular disease by CAG. Conventional risk factors for CHD were similar between the HGI subgroups. Furthermore, potential confounding effects of lipid-lowering therapy were reduced by enrolling recipients of

HMG-CoA reductase inhibitors since diabetes outset (*Jellinger et al., 2012*). Data regarding cardiovascular risk factors such as dyslipidemia, blood pressure, and cigarette smoking were available for the entire study population.

Several limitations may arise from the study design. Degree of insulin resistance and mode of antidiabetic treatment may influence CHD but were not uniformly available (*Syed Ikmal et al., 2013; Marso et al., 2016*). Although participants received comprehensive diabetes education by certified educators, adherence to lifestyle intervention could not be ascertained. Body weight may influence cardiovascular risk, but investigators previously demonstrated that high-risk coronary anatomy was paradoxically less frequent in obese patients (*Rubinshtein et al., 2006*). The relationship between body weight and CHD remains uncertain and was not assessed in this study. Participants were diagnosed with T2D in the preceding ten years according to their medical records, but precise disease duration could not be confirmed due to the latent nature of T2D. Finally, any complication associated with HGI may be difficult to dissect from the influence of HbA1c (*Sacks, Nathan & Lachin, 2011*).

5 Conclusions

HGI consistently correlated with the extent of CHD in individuals with T2D. People with supranormal HGI harbored a higher prevalence of multiple vessel disease compared to those with subnormal HGI, which may further complicate their management. In clinical practice, HGI provides useful information regarding cardiovascular disease risk in T2D.

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Table 1(on next page)

Demographic characteristics of the hemoglobin glycation index groups

Data are expressed as mean with standard deviation for continuous variables and number (%) for categorical variables. Hemoglobin glycation index is defined as the difference between an individual's observed HbA1c and the HbA1c predicted from fasting plasma glucose. HbA1c, glycated hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglycerides; SCr, serum creatinine; HGI, hemoglobin glycation index.

1 Demographic characteristics of the hemoglobin glycation index groups

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	HGI < 0 (n = 180)	HGI ≥ 0 (n = 243)	P value
HbA1c (%)	7.5 ± 1.0	7.4 ± 1.1	0.80
Age (years)	67 ± 11	67 ± 10	0.56
Gender			
Female	84 (46.7%)	98 (40.3%)	0.19
Male	96 (53.3%)	145 (59.7%)	
HDL-C (mg/dL)	42 ± 12	39 ± 14	0.06
LDL-C (mg/dL)	88 ± 30	91 ± 34	0.38
TG (mg/dL)	159 ± 126	155 ± 109	0.76
SCr (mg/dL)	1.5 ± 1.7	1.6 ± 1.7	0.52
Cigarette smoking			
Yes	138 (76.7%)	189 (77.8%)	0.79
No	42 (23.3%)	54 (22.2%)	
Systolic blood pressure (mm Hg)	136 ± 24	135 ± 19	0.65
Proteinuria (g/day)	0.25 ± 0.95	0.19 ± 0.57	0.47

Table 2(on next page)

Extent of coronary heart disease in hemoglobin glycation index groups

Data are expressed as number (%) for categorical variables. Hemoglobin glycation index is defined as the difference between an individual's observed HbA1c and the HbA1c predicted from fasting plasma glucose. HGI, hemoglobin glycation index; LAD, left anterior descending artery; CI, confidence interval.

Extent of coronary heart disease in hemoglobin glycation index groups

	HGI < 0 (n = 180)	HGI ≥ 0 (n = 243)	Odds ratio	95% CI	P value
Arteriosclerosis or single vessel disease	111 (61.7%)	70 (28.8%)	3.9	2.64 – 5.98	< 0.001
Multiple vessel disease	69 (38.3%)	173 (71.2%)			
LAD disease					
No	78 (43.3%)	49 (20.2%)	3.0	1.97 – 4.66	< 0.001
Yes	102 (56.7%)	194 (79.8%)			

Table 3(on next page)

Clinical outcome of the hemoglobin glycation index groups

Data are expressed as mean with standard deviation for continuous variables and number (%) for categorical variables. Hemoglobin glycation index is defined as the difference between an individual's observed HbA1c and the HbA1c predicted from fasting plasma glucose. HGI, hemoglobin glycation index.

1 Clinical outcome of the hemoglobin glycation index groups

2

3

	HGI < 0 (n = 180)	HGI ≥ 0 (n = 243)	P value
Length of stay (days)	2.8 ± 2.3	3.0 ± 2.5	0.41
Number of stent			
None or single	150 (83.3%)	187 (77.0%)	0.067
Multiple	30 (16.7%)	56 (23.0%)	

Figure 1

Relationship between hemoglobin A1c and fasting plasma glucose

Linear regression for the calculation of predicted hemoglobin A1c from measured hemoglobin A1c and fasting plasma glucose.

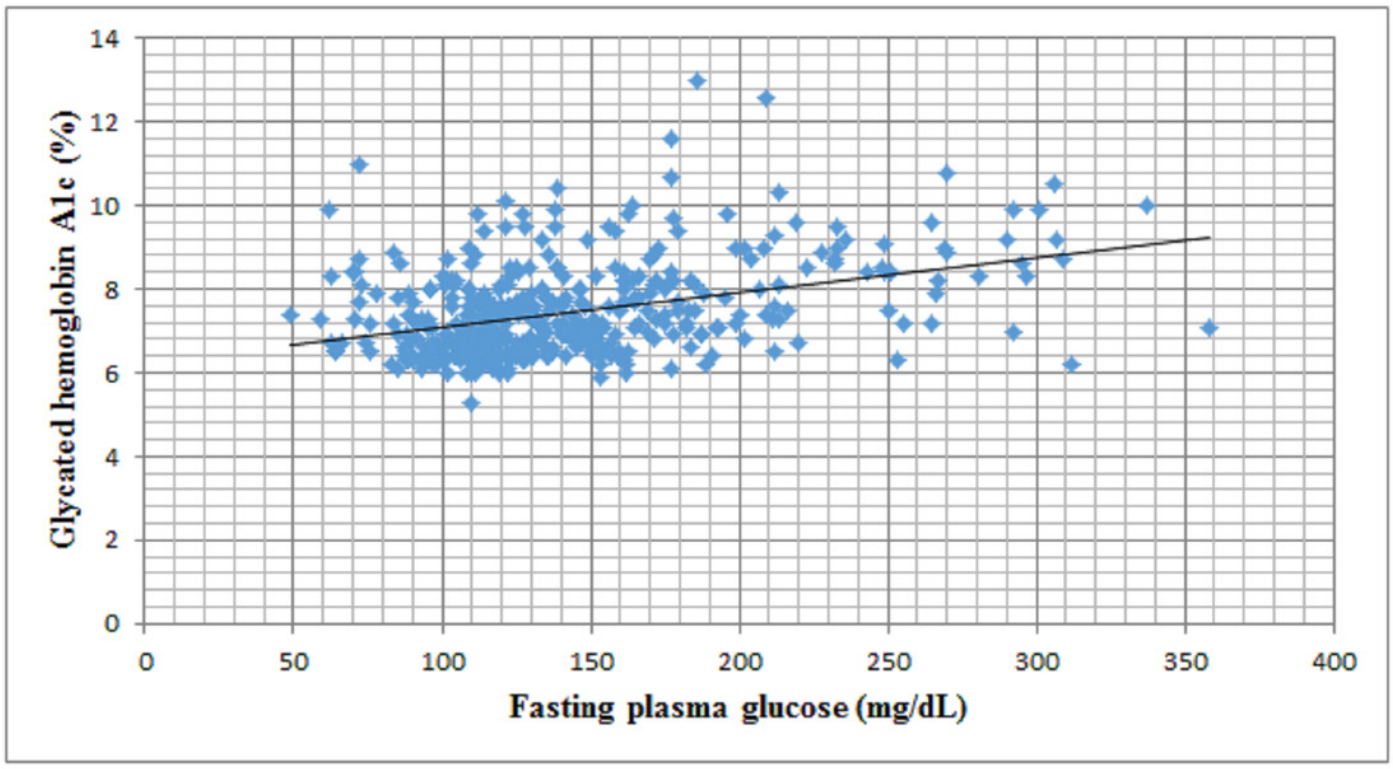

Figure 2

Enrollment protocol of the study

Enrollment protocol of the study with number and reason for candidate exclusion.