

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

1

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Daniela Foti / 6 Aug 2017

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Organize by importance of the issues, and number your points

1. Your most important issue
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Line 56: Note that experimental data on sprawling animals needs to be updated. Line 66: Please consider exchanging "modern" with "cursorial".

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I thank you for providing the raw data, however your supplemental files need more descriptive metadata identifiers to be useful to future readers. Although your results are compelling, the data analysis should be improved in the following ways: AA, BB, CC

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I commend the authors for their extensive data set, compiled over many years of detailed fieldwork. In addition, the manuscript is clearly written in professional, unambiguous language. If there is a weakness, it is in the statistical analysis (as I have noted above) which should be improved upon before Acceptance.

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 diabetes. **Methods.** This cross-sectional study screened individuals visiting the endocrinology clinic between June 2012 and May 2016 for eligibility. Enrollment criteria included individuals exceeding 21 years of age, with T2D diagnosed in the preceding ten years, who underwent coronary angiography during the study period. Candidates with hemoglobin disorders, pregnancy, and congenital coronary artery abnormalities were excluded. Decision to perform angiography was made by cardiologists according to established clinical criteria. HGI was derived from fasting plasma glucose and glycated hemoglobin A1c (HbA1c) three months prior to angiography. Participants were classified according to the presence of supranormal ($HGI \geq 0$) or subnormal HGI ($HGI < 0$). **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 diabetes. 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 diabetes.

Methods. This cross-sectional study screened individuals visiting the endocrinology clinic between June 2012 and May 2016 for eligibility. Enrollment criteria included individuals exceeding 21 years of age, with T2D diagnosed in the preceding ten years, who underwent coronary angiography during the study period. Candidates with hemoglobin disorders, pregnancy, and congenital coronary artery abnormalities were excluded. Decision to perform angiography was made by cardiologists according to established clinical criteria. HGI was derived from fasting plasma glucose and glycated hemoglobin A1c (HbA1c) three months prior to angiography. Participants were classified according to the presence of supranormal ($HGI \geq 0$) or subnormal HGI ($HGI < 0$).

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 diabetes. 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

Diabetes mellitus 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 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) (*Fowler, 2008*). These vascular complications profoundly influence the quality of life in affected individuals.

Specifically, individuals with type 2 diabetes (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 (*Laakso, 2001*).

The hemoglobin glycation index (HGI) is an indicator of glucose metabolism linked to diabetic complications (*Cohen, 2003*). 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

investigated the relationship between HGI and extent of coronary vascular disease in people with T2D.

2 Materials and Methods

2.1 Study population

This cross-sectional study screened patients visiting the endocrinology clinic between June 2012 and May 2016 for eligibility. Enrollment criteria included individuals exceeding 21 years of age, with T2D diagnosed in the preceding ten years, who received hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors since diabetes onset and underwent coronary angiography (CAG) during the study period. Exclusion criteria involved people who had undertaken CAG prior to the study, or who lacked concomitant HbA1c and fasting plasma glucose (FPG) measurements. Candidates with hemoglobin disorders, pregnancy, and congenital coronary artery abnormalities were also ineligible. Decision to perform coronary artery survey was made by cardiologists according to established clinical criteria. All participants provided written informed consent for CAG. The study was approved by the Institutional Review Board of Changhua Christian Hospital (CCH IRB number: 161111).

2.2 Calculation of HGI

HGI of participants were calculated from concomitant HbA1c and FPG measurements taken three months prior to CAG. For the study population, the regression equation of predicted $HbA1c = 0.008 \times FPG + 6.28$ established the linear relationship between these variables. An

individual's FPG in milligrams per deciliter was substituted into the regression equation to derive the predicted HbA1c. HGI was calculated as the difference between the observed HbA1c and predicted HbA1c (*Hempe et al., 2015*). Supranormal HGI was defined as levels exceeding or equivalent to zero, whereas subnormal HGI designated values below zero.

2.3 Classification of CHD

The extent of vascular disease involving the left anterior descending, left circumflex, and right coronary arteries was documented by CAG. Significant stenosis was defined as more than fifty percent narrowing of the diseased vascular segment compared to a proximal or distal normal segment (*Leopold & Faxon, 2015*). Single vessel disease was defined as one or more stenotic lesions in one of the major coronary arteries, whereas multiple vessel disease involved lesions in two or more of the coronary arteries (*DiSciascio et al., 1988*). Arteriosclerosis described the observation that none of the stenotic lesions resulted in more than fifty percent narrowing of the major coronary arteries.

2.4 Statistical analysis

Baseline characteristics including age, gender, lipid profile, mean HbA1c, and cigarette smoking were compared between the HGI subgroups. Intergroup comparisons were made using Student's *t* test for continuous variables and Pearson's χ^2 test for categorical variables. For the HGI subgroups, the prevalence of multiple vessel disease as opposed to single vessel disease or arteriosclerosis was compared using Pearson's χ^2 test. Tests of statistical significance were based on a two-tailed $P < 0.05$. Statistical analysis was performed using Statistical Package for the

Social Sciences (version 22.0, SPSS, Chicago, IL).

3 Results

Initially 480 individuals with T2D were screened for eligibility. Twenty patients were excluded due to lack of HMG-CoA reductase inhibitor prescription, 32 individuals had received CAG prior to the study and were ineligible, and five candidates were excluded due to absence of concomitantly measured HbA1c and FPG.

The study enrolled 423 individuals who were classified according to the presence of either supranormal ($HGI \geq 0$) or subnormal HGI ($HGI < 0$). Baseline characteristics including age, gender, and kidney function were similar between groups, as summarized in Table 1. Levels of low-density lipoprotein cholesterol, presence of cigarette smoking, and degree of systolic blood pressure were also comparable. The intergroup difference in mean HbA1c was nonsignificant (7.5 ± 1.0 % versus 7.4 ± 1.1 %, $P = 0.80$), and both HGI groups harbored similar degree of proteinuria (0.25 ± 0.95 grams per day versus 0.19 ± 0.57 grams per day, $P = 0.467$). Overall, conventional risk factors for CHD were similar between the HGI subgroups.

As shown in Table 2, individuals with supranormal HGI harbored a higher prevalence of multiple vessel disease relative to those with subnormal HGI (Odds ratio (OR): 3.9, 95% confidence interval (CI): 2.64 - 5.98, $P < 0.001$). This observation suggests that people with 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 (*Juutilainen et al., 2005; Stamler et al., 1993*). However, HbA1c measurements delineated only a fraction of cardiovascular disease risk (*Juutilainen et al., 2008*). This study demonstrated that HGI consistently correlated with the extent of CHD in [diabetes](#). 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 also reflects an excess of advanced glycosylation end products that arise from intracellular hyperglycemia (*Brownlee, Cerami & Vlassara, 1988; Leslie & Cohen, 2009*).

Furthermore, researchers proposed that a supranormal HGI, as characterized by an observed HbA1c higher than HbA1c predicted from FPG, may arise from postprandial hyperglycemia (*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*). The Framingham Offspring Study also established postprandial hyperglycemia as a robust

risk factor for cardiovascular events (*Meigs et al., 2002*). 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. Although complications associated with HGI may be difficult to dissect from the influence of HbA1c (*Sacks, Nathan & Lachin, 2011*), HGI may provide additional information in terms of cardiovascular disease risk.

The relationship between HGI and extent of CHD facilitates risk stratification in people with diabetes. A high index of suspicion for coronary artery disease should be entertained for symptomatic individuals with supranormal HGI. Considering the aforementioned link between postprandial hyperglycemia, HGI, and cardiovascular disease risk (*Riddle & Gerstein, 2015; Chiasson et al., 2003; Raz et al., 2011*), controlling postprandial hyperglycemia in individuals with supranormal HGI may be an appropriate therapeutic approach.

This study benefits from an objective assessment of macrovascular disease by CAG. 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. Insulin resistance and mode of antidiabetic

treatment may influence CHD but were not uniformly available (*Abbasi et al., 2002; 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 therefore not assessed in this study. Participants were diagnosed with diabetes in the preceding ten years according to their medical records, but precise disease duration could not be ascertained due to the latent nature of T2D.

5 Conclusions

HGI consistently correlated with the extent of CHD in individuals with diabetes. 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 (<i>n</i> = 180)	HGI ≥ 0 (<i>n</i> = 243)	<i>P</i> 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 (<i>n</i> = 180)	HGI ≥ 0 (<i>n</i> = 243)	Odds ratio	95% CI	<i>P</i> 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%)			

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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

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	HGI < 0 (<i>n</i> = 180)	HGI ≥ 0 (<i>n</i> = 243)	<i>P</i> 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%)	