Glycosylated Hemoglobin A1c (HbA1c) in Non-diabetic Patients: An Independent Predictor of Coronary Artery Disease and its Severity

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Disclosures

• None
Sanjay Gandhi Post Graduate Institute, Lucknow, India
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Background

- **Glycosylated hemoglobin (HbA1c)** -
  - Indicator of average glycemia over the last 2-3 months
  - Its estimation have been used as an indicator of glycaemic control in diabetics

- **High levels of HbA1c in diabetics** -
  Associated with higher adverse cardiovascular outcomes
• Even in nondiabetic individuals, high HbA1c levels have been correlated with:
  
  - Higher CVD & mortality (ARIC study\textsuperscript{1}, EPIC-NORFLOK study\textsuperscript{2})
  - Higher carotid IMT\textsuperscript{3}
  - Increased carotid plaque prevalence (Tromso study\textsuperscript{4})

• HbA1c levels have not been correlated with angiographically proven CAD

1. Selvin et al, NEJM 2010
3. Huang et al, J Clin Endocrinol Metab 2011
Objectives of Study

To evaluate the association between HbA1c in non-diabetics with the-

- Presence of angiographically proven CAD
- Disease severity & complexity
Methods
An observational, single centre, cross-sectional study

**Inclusion Criteria:**
Consecutive patients undergoing diagnostic Coronary Angiography between January – December 2011

**Exclusion criteria:**
- Known diabetics (on / off medications)
- Newly detected diabetics (ADA diagnostic criteria)
- Use of anti-diabetic medications
History & Clinical Examination

- Detailed clinical history: CAD risk factor evaluation
- Detailed clinical examination including BP measurement
- Anthropometric measurements- Height, body weight
  BMI was calculated
Laboratory Evaluation

• Haemogram
• Biochemical examination:
  - Serum creatinine
  - Random blood sugar
  - Fasting blood sugar
  - Fasting lipid profile
  - HbA1c levels
• The e-GFR (Glomerular Filtration Rate) was calculated from MDRD study equation
Laboratory Evaluation

HbA1c measurement

Bio-Rad D-10 dual program (Bio-Rad Co., Hercules, CA) using ion-exchange high-performance liquid chromatography
All patients underwent coronary angiography.

Significant CAD was defined as >50% diameter stenosis in any vessel >1.5mm.

Disease severity and complexity was analyzed by SYNTAX score calculation.
Study Population

Total number of patients screened
n=1897

Total number of nondiabetics
n=1141

Total excluded 756
a) Known diabetics 692
b) Newly detected diabetics 62
c) Hb A variant 02

No CAD
n=236 (20.7%)

CAD
N=905 (79.3%)
Glycosylated Haemoglobin

Total number of patients = 1141

- HbA1c <5.5% 227 (23%)
- HbA1c 5.5-5.8% 368 (20%)
- HbA1c 5.8-6.1% 285 (32%)
- HbA1c >6.1% 261 (25%)

Mean HbA1c level 5.8±4.8% (range 4.2-6.4%)
Statistical Analysis

Data were analyzed using SPSS 16 statistical software (SPSS Inc., Chicago, Illinois, USA)

• Student t-test: continuous variables
• Chi-square test: categorical variables
• ANOVA (Analysis of variance): compare the means among the four inter-quartiles
• p-trend:
  For continuous variable- Linear regression analysis
  For categorical variables- Cochrane Armitage trend test
• Logistic regression analysis was done to determine the predictors of CAD
• A p value <0.05 was considered statistically significant
Results
HbA1c and CAD Risk Factors

- **Age >60 years**
  - p-trend = 0.256

- **Male Gender**
  - p-trend < 0.001

- **BMI >23 kg/m²**
  - p-trend < 0.001

- **Hypertension**
  - p-trend = 0.187

- **Smoking**
  - p-trend < 0.001
HbA1c and Blood Sugar Levels

**Fasting blood sugar >100mg%**

- IQ 1: 29.1%
- IQ 2: 26.6%
- IQ 3: 18.1%
- IQ 4: 10%

**p-trend=<0.001**
HbA1c and Lipid Profile

- Total Cholesterol: p-trend = 0.084
- Triglycerides: p-trend = 0.772
- Low density Lipoprotein: p-trend = 0.356
- High density Lipoprotein: p-trend = 0.886
- Very low density lipoprotein: p-trend = 0.001
## HbA1c and RFT

<table>
<thead>
<tr>
<th></th>
<th>HbA1C &lt;5.5 (n=261)</th>
<th>HbA1C 5.5-&lt;5.8 (n=227)</th>
<th>HbA1C 5.8-6.1 (n=368)</th>
<th>HbA1C &gt;6.1 (n=285)</th>
<th>p-trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum Creatinine (mg%)</td>
<td>1.3±1.1</td>
<td>1.1±0.37</td>
<td>1.3±0.9</td>
<td>1.2±0.4</td>
<td>0.353</td>
</tr>
<tr>
<td>e-GFR (ml/minute)</td>
<td>67.3+20.8</td>
<td>69.5+17.5</td>
<td>64.6+17</td>
<td>65.5+19.4</td>
<td>0.039</td>
</tr>
<tr>
<td>e-GFR &lt;60ml/min/1.73m²</td>
<td>83(31.8%)</td>
<td>55(24.2%)</td>
<td>132(35.9%)</td>
<td>108(37.9%)</td>
<td>0.019</td>
</tr>
</tbody>
</table>
HbA1c and Angiographic CAD

- IQ 1: HbA1c <5.5 (n=261) - 62.8%
- IQ 2: HbA1c 5.5-<5.8 (n=227) - 75.3%
- IQ 3: HbA1c 5.8-6.1 (n=368) - 85.3%
- IQ 4: HbA1c >6.1 (n=285) - 89.8%

p=<0.001

n=1141

P<0.001

IQ 1: HbA1c <5.5 (n=227)
IQ 2: HbA1c 5.5-<5.8 (n=227)
IQ 3: HbA1c 5.8-6.1 (n=368)
IQ 4: HbA1c >6.1 (n=285)
p-trend for Angiographic CAD

![Graph showing the relationship between HbA1c Inter-Quartiles and CAD Proportions with a p-trend of <0.001.](image)
Odds Ratios of CAD According to HbA1c Quartiles

<table>
<thead>
<tr>
<th>HbA1c quartiles</th>
<th>Model 1 (Unadjusted)</th>
<th>Model 2 (Adjusted for age and gender)</th>
<th>Model 3 (Adjusted for BMI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>p-value</td>
<td>OR (95% CI)</td>
</tr>
<tr>
<td>&lt;5.5</td>
<td>1 (Reference)</td>
<td>-</td>
<td>1 (Reference)</td>
</tr>
<tr>
<td>5.5-&lt;5.8</td>
<td>1.8 (1.2-2.6)</td>
<td>0.003</td>
<td>1.73 (1.1-2.6)</td>
</tr>
<tr>
<td>5.8-6.1</td>
<td>3.4 (2.3-5.0)</td>
<td>&lt;0.001</td>
<td>3.28 (2.2-4.8)</td>
</tr>
<tr>
<td>&gt;6.1</td>
<td>5.2 (3.3-8.2)</td>
<td>&lt;0.001</td>
<td>4.94 (3.1-7.9)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>HbA1c quartiles</th>
<th>Model 4 (Adjusted for smoking, hypertension and dyslipidemia)</th>
<th>Model 5 (Adjusted for fasting blood sugar &gt;100 mg%)</th>
<th>Model 6 (Adjusted with all covariates)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>p-value</td>
<td>OR (95% CI)</td>
</tr>
<tr>
<td>&lt;5.5</td>
<td>1 (Reference)</td>
<td>-</td>
<td>1 (Reference)</td>
</tr>
<tr>
<td>5.5-&lt;5.8</td>
<td>1.76 (1.1-2.6)</td>
<td>0.007</td>
<td>1.87 (1.2-2.7)</td>
</tr>
<tr>
<td>5.8-6.1</td>
<td>3.68 (2.4-5.4)</td>
<td>&lt;0.001</td>
<td>3.69 (2.4-5.4)</td>
</tr>
<tr>
<td>&gt;6.1</td>
<td>5.25 (3.2-8.4)</td>
<td>&lt;0.001</td>
<td>5.67 (3.5-9.0)</td>
</tr>
</tbody>
</table>
Risk of CAD

IQ 1
HbA1c < 5.5

IQ 2
HbA1c 5.5 - < 5.8

IQ 3
HbA1c 5.8 - 6.1

IQ 4
HbA1c > 6.1

Reference - 1

p = 0.007
p = < 0.001
p = < 0.001
## Predictors of CAD

<table>
<thead>
<tr>
<th>Variables</th>
<th>No CAD (n=236)</th>
<th>CAD (n=905)</th>
<th>Odds Ratio (95% CI)</th>
<th>p-value</th>
<th>Odds Ratio (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt; 60 years</td>
<td>64 (27.1)</td>
<td>396 (43.8)</td>
<td>2.09 (1.5-2.8)</td>
<td>&lt;0.001</td>
<td>1.89 (1.3-2.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male Gender</td>
<td>156 (66.1)</td>
<td>788 (87.1)</td>
<td>3.45 (2.4-4.8)</td>
<td>&lt;0.001</td>
<td>2.75 (1.8-3.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Smoking</td>
<td>22 (9.3)</td>
<td>261 (28.8)</td>
<td>3.49 (2.4-6.2)</td>
<td>&lt;0.001</td>
<td>3.19 (1.9-5.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypertension</td>
<td>117 (49.6)</td>
<td>489 (54.0)</td>
<td>1.19 (0.9-1.5)</td>
<td>0.222</td>
<td>1.26 (0.9-1.7)</td>
<td>0.167</td>
</tr>
<tr>
<td>BMI &gt; 23 kg/m²</td>
<td>162 (68.6)</td>
<td>734 (81.1)</td>
<td>1.96 (1.4-2.7)</td>
<td>&lt;0.001</td>
<td>2.28 (1.5-3.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>eGFR &lt; 60 ml/min/1.73 m²</td>
<td>87 (36.9)</td>
<td>291 (32.2)</td>
<td>1.23 (0.9-1.6)</td>
<td>0.171</td>
<td>1.40 (0.9-2.0)</td>
<td>0.065</td>
</tr>
<tr>
<td>Fasting Blood Sugar &gt; 100 mg%</td>
<td>53 (22.5)</td>
<td>195 (21.5)</td>
<td>0.95 (0.6-1.3)</td>
<td>0.763</td>
<td>0.85 (0.6-1.1)</td>
<td>0.431</td>
</tr>
<tr>
<td>LDL &gt; 100 mg%</td>
<td>38 (15.7)</td>
<td>210 (23.3)</td>
<td>1.69 (1.1-2.4)</td>
<td>0.003</td>
<td>1.61 (1.1-2.7)</td>
<td>0.013</td>
</tr>
<tr>
<td>HDL &lt; 40 mg% in males, &lt; 50 mg% in females</td>
<td>38 (15.8)</td>
<td>159 (17.7)</td>
<td>1.15 (0.7-1.7)</td>
<td>0.459</td>
<td>0.86 (0.5-1.3)</td>
<td>0.521</td>
</tr>
<tr>
<td>TG &gt; 150 mg%</td>
<td>71 (30.1)</td>
<td>263 (29.1)</td>
<td>0.95 (0.7-1.3)</td>
<td>0.781</td>
<td>0.84 (0.6-1.4)</td>
<td>0.674</td>
</tr>
<tr>
<td>HbA1c 5.5-&lt;5.8</td>
<td>56 (23.7)</td>
<td>171 (18.9)</td>
<td>1.80 (1.2-2.6)</td>
<td>0.003</td>
<td>1.74 (1.1-2.6)</td>
<td>0.011</td>
</tr>
<tr>
<td>HbA1c 5.8-6.1</td>
<td>54 (22.9)</td>
<td>314 (34.7)</td>
<td>3.43 (2.3-5.0)</td>
<td>&lt;0.001</td>
<td>3.48 (2.3-5.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HbA1c &gt; 6.1</td>
<td>29 (12.3)</td>
<td>256 (28.3)</td>
<td>5.2 (3.3-8.2)</td>
<td>&lt;0.001</td>
<td>4.34 (2.6-7.0)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
HbA1c as a predictor of angiographic complexity & severity of CAD
HbA1c and Severity & Complexity of CAD

Mean SYNTAX Score

Mean Number of Vessels

Diseased

IQ 4

IQ 3

IQ 2

IQ 1

IQ 4

IQ 3

IQ 2

IQ 1

p-trend <=0.001

p-trend <=0.001

p-trend <=0.001

IQ 1

IQ 2

IQ 3

IQ 4

p-trend <=0.001

p-trend <=0.001

p-trend <=0.001

CAD

TVD/ Left main coronary disease

SYNTAX Score>22

0

10

20

30

40

50

60

70

80

90

100

0

10

20

1.9±1.0

1.5±1.1

1.3±1.0

1.1±1.2

19.0±15.5

15.4±15.2

12.9±12.7

9.9±12.2

#esc2012 www.escardio.org
With increasing HbA1c levels, severity & complexity of CAD increases.
## HbA1c and Angiographic Severity of CAD
(After excluding patients with normal coronaries)

<table>
<thead>
<tr>
<th></th>
<th>IQ 1 HbA1C &lt;5.5 (n=164)</th>
<th>IQ 2 HbA1C 5.5-&lt;5.8 (n=171)</th>
<th>IQ 3 HbA1C 5.8-6.1 (n=314)</th>
<th>IQ 4 HbA1C &gt;6.1 (n=256)</th>
<th>p-trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Syntax Score</td>
<td>15.9±11.9</td>
<td>17.2±11.8</td>
<td>18.1±14.9</td>
<td>21.1±14.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Syntax &gt;22</td>
<td>39 (23.8%)</td>
<td>46 (26.9%)</td>
<td>99 (31.5%)</td>
<td>102 (39.8%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TVD/LM Disease</td>
<td>35 (21.3%)</td>
<td>41 (24.0%)</td>
<td>84 (26.8%)</td>
<td>97 (37.9%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Number of Vessels</td>
<td>1.77±0.77</td>
<td>1.74±0.82</td>
<td>1.82±0.82</td>
<td>2.09±0.81</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
</tbody>
</table>
## HbA1c and SYNTAX Score

<table>
<thead>
<tr>
<th>SYNTAX Categories</th>
<th>IQ 1 vs. IQ 2 (n= 261 vs. 227)</th>
<th>IQ 1 vs. IQ 3 (n = 261 vs. 368)</th>
<th>IQ 1 vs. IQ 4 (n = 227 vs. 285)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (C.I.)</td>
<td>OR (C.I.)</td>
<td>OR (C.I.)</td>
</tr>
<tr>
<td>SYNTAX &lt;22</td>
<td>0.81 (0.7-1.0)</td>
<td>1.21 (1.0-1.4)</td>
<td>0.82 (0.7-1.0)</td>
</tr>
<tr>
<td></td>
<td>1.0</td>
<td>0.034</td>
<td>0.053</td>
</tr>
<tr>
<td>SYNTAX 22-32</td>
<td>0.86 (0.4-1.5)</td>
<td>1.81 (1.0-3.0)</td>
<td>2.18 (1.3-3.6)</td>
</tr>
<tr>
<td></td>
<td>0.64</td>
<td>0.024</td>
<td>0.002</td>
</tr>
<tr>
<td>SYNTAX &gt;32</td>
<td>1.58 (0.8-2.9)</td>
<td>3.47 (2.0- 5.9)</td>
<td>3.16 (1.8-5.4)</td>
</tr>
<tr>
<td></td>
<td>0.135</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
Conclusions

• In the non-diabetic patients, higher HbA1c levels are significantly associated with CAD

• This association is graded, continuous and is independent of conventional major cardiovascular risk factors

• Elevated HbA1c is also strongly correlated with disease severity and higher SYNTAX score

• HbA1c is a surrogate marker for chronic dysglycemia and could be utilized as an independent predictor of CAD and its severity even in non-diabetic subjects
Clinical Implications

• Pre-diabetics and individuals with milder abnormalities in glucose control should be identified and advised for aggressive coronary risk factor modification and management

• Therapeutic strategy to specifically lower the HbA1c levels in nondiabetics still remain uncertain, randomized controlled clinical trials need to be done in this direction
Thank you