TITLE: Diabetes Screening for Asymptomatic Adults: A Review of the Diagnostic Accuracy, Cost Effectiveness, and Guidelines

DATE: 10 December 2013

RESEARCH QUESTIONS

1. What is the diagnostic accuracy of hemoglobin A1c compared with oral glucose tolerance testing or fasting blood glucose for diabetes screening?

2. What is the cost-effectiveness of diabetes screening with hemoglobin A1c, oral glucose tolerance testing or fasting blood glucose for diabetes screening?

3. What are the evidence based guidelines for screening asymptomatic patients for diabetes?

KEY MESSAGE

One health technology assessment, 23 non-randomized studies and three evidence-based guidelines were identified concerning the accuracy or appropriate use of hemoglobin A1c for diabetes screening.

METHODS

A limited literature search was conducted on key resources including PubMed, The Cochrane Library (2013, Issue 10), University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. To address research question one, methodological filters were applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses, randomized controlled trials and non-randomized studies. To address research question two, methodological filters were applied to limit retrieval to economic studies. To address research question three, methodological filters were applied to limit retrieval to guidelines. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2009 and November 26, 2013. Internet links were provided, where available.
The summary of findings was prepared from the abstracts of the relevant information. Please note that data contained in abstracts may not always be an accurate reflection of the data contained within the full article.

RESULTS

Rapid Response reports are organized so that the higher quality evidence is presented first. Therefore, health technology assessment reports, systematic reviews, and meta-analyses are presented first. These are followed by randomized controlled trials, non-randomized studies, economic evaluations, and evidence-based guidelines.

One health technology assessment and 23 non-randomized studies were identified regarding the accuracy of hemoglobin A1c (HbA1c) compared to fasting plasma glucose or oral glucose tolerance testing for diabetes screening in asymptomatic adults. Three evidence-based guidelines were found regarding for screening asymptomatic adults for diabetes. No systematic reviews, meta-analyses, randomized controlled trials, or economic evaluations were identified.

Additional references of potential interest are provided in the appendix.

OVERALL SUMMARY OF FINDINGS

Diagnostic Accuracy of Screening for Diabetes with Hemoglobin A1c

One health technology assessment and 23 non-randomized studies examined the diagnostic accuracy of hemoglobin A1c (HbA1c) compared to fasting plasma glucose or the oral glucose tolerance test for diabetes screening or diagnosis. The majority found that HbA1c testing has a high specificity but a lower sensitivity. The health technology assessment concluded that absolute values of HbA1c may be more useful as part of an overall diabetes risk assessment than for dichotomous diagnosis due to this lack of sensitivity. While some non-randomized studies used the American Diabetes Association and World Health Organization-recommended HbA1c screening cutoff of ≥6.5%, others determined the optimal cutoff threshold to be lower and that the threshold or accuracy may vary by age or ethnicity. Further details are included in Table 1.

Cost-Effectiveness of Screening for Diabetes with Hemoglobin A1c

The health technology assessment identified two studies that examined the relative costs of HbA1c versus other blood tests. One study, from 2004, reported HbA1c followed by an oral glucose tolerance test to have a high detection rate, costing £16-26 per detected case of diabetes. The other study found that for the healthcare system as a whole, a 50 g glucose challenge test was the best strategy compared to HbA1c, fasting plasma glucose, or oral glucose tolerance testing.

Evidence-Based Guidelines on Screening Asymptotic Adults for Diabetes

American Diabetes Association

The 2013 Standards of Medical Care in Diabetes recommends that testing for type 2 diabetes or pre-diabetes in asymptotic people should be considered for any overweight or obese adult who has one or more additional risk factors for diabetes. For adults without risk factors, testing should begin at age 45. Hemoglobin A1c, fasting plasma glucose, and 75 g two hour oral
glucose tolerance testing are all considered appropriate and should be repeated if results are normal every 3 to 5 years.

**Canadian Task Force on Preventative Health Care**

The 2012 recommendations on screening for type 2 diabetes in adults do not recommend routine screening for adults who are considered at low to moderate risk on a validated risk calculator. For adults at high risk, the recommendation is to screen with HbA1c every 3 to 5 years, with annual screening for those deemed to be at very high risk.

**National Institute for Health and Care Excellence**

The 2012 guidance on preventing type 2 diabetes recommends that most adults over 40 should assessed using a validated diabetes risk assessment and if at high risk be given a fasting plasma glucose or HbA1c test. Adults in higher risk ethnic groups or who have conditions which increase the risk of diabetes should be assessed starting at age 25.

<table>
<thead>
<tr>
<th>First Author, Year</th>
<th>Comparator</th>
<th>Patients</th>
<th>HbA1c Threshold</th>
<th>Accuracy</th>
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<tbody>
<tr>
<td>Alqahtani 2013²</td>
<td>FPG, OGTT</td>
<td>Saudi patients who attended an internal medicine outpatient clinic and had FPG, OGTT and HbA1c measurements; patients with diagnosed DM or on DM meds excluded. (n=1,814)</td>
<td>Not Reported</td>
<td>Sensitivity: 69.6%</td>
</tr>
<tr>
<td>Bhowmik 2013³</td>
<td>OGTT</td>
<td>Bangladeshi individuals ≥ 20 years of age with no history of DM randomly selected from population. (n=2,293)</td>
<td>6.0%</td>
<td>Sensitivity: 86.2% Specificity: 93.3%</td>
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<tr>
<td>Du 2013⁴</td>
<td>FPG</td>
<td>Chinese individuals with at least one risk factor for DM but without known DM, selection method not reported. (n=1,610)</td>
<td>6.5%</td>
<td>HbA1c resulted in the same classification as FPG for 90.1% of participants. Kappa = 0.75 (95% CI 0.72-0.78)</td>
</tr>
<tr>
<td>Lee 2013⁵</td>
<td>OGTT</td>
<td>Korean adults, stratified by age, recruited from university hospitals without a history of DM. (n=4,616)</td>
<td>Overall optimal threshold : 6.1% Optimal threshold age 18-39: 5.9% age 40-64: 6.2% age ≥65: 6.4%</td>
<td>Sensitivity 63.8% Specificity 88.1%</td>
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</table>
Table 1: Included Non-Randomized Studies Examining the Diagnostic Accuracy of HbA1c

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>Mostafa 2013⁶</td>
<td>OGTT</td>
<td>Adults aged 40 to 75 years from the LEADER cohort (UK) who underwent HbA1c and OGTT testing. (n=8,696)</td>
<td>6.5%</td>
<td>Two threshold rule: if ≥ 6.8% [rule in] DM if ≤ 5.8 [rule out] DM if between 5.9% - 6.7%, conduct second test * See reference 6 for clarification</td>
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<tr>
<td></td>
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<td></td>
<td></td>
<td>Sensitivity White Europeans: 62.1% South Asians: 78.9%</td>
</tr>
<tr>
<td>Adamska 2012⁷</td>
<td>OGTT</td>
<td>Adults aged 18 to 79 (mean: 40.1) taking an OGTT, selection method not reported. (n=441)</td>
<td>6.5%</td>
<td>Sensitivity: 45.9% Specificity: 97.5%</td>
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<tr>
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<td></td>
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<td></td>
<td>Optimal threshold 5.9% Sensitivity: 86.6% Specificity: 73%</td>
</tr>
<tr>
<td>Hutchinson 2012⁸</td>
<td>OGTT</td>
<td>All subjects from the Tromso study with HbA1c 5.8% to 6.9% and a random sample of subjects with HbA1c 5.3% to 5.7% invited to complete an OGTT. (n=3,476)</td>
<td>6.5%</td>
<td>Sensitivity:34.7% Specificity: 97.1%</td>
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<td></td>
<td>Optimal threshold: 6.2% Sensitivity: 69.8% Specificity: 81.8%</td>
</tr>
<tr>
<td>Kim 2012⁹</td>
<td>FPG, OGTT</td>
<td>Korean rural population. Selection method not reported. (n=10,111)</td>
<td>Optimal threshold: 5.95%</td>
<td>Sensitivity: 77% Specificity: 89.4%</td>
</tr>
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<tr>
<td>Marini 2012</td>
<td>FPG, OGTT</td>
<td>Italian Caucasians without known DM who completed an OGTT and HbA1c test. Selection method not reported. (n=1,019)</td>
<td>6.5%</td>
<td>HbA1c and FPG: Kappa = 0.522 85.5% classified without DM by both 5.8% classified with DM by both HbA1c and OGTT: Kappa = 0.427 81.8% classified without DM by both 6.0% classified with DM by both.</td>
</tr>
<tr>
<td>Yang 2012</td>
<td>FPG</td>
<td>Chinese patients with at least three high risk factors for DM. Selection method not reported. (n=424)</td>
<td>Optimal threshold: 6.2%</td>
<td>Sensitivity: 66% Specificity: 91%</td>
</tr>
<tr>
<td>Yu 2012</td>
<td>OGTT</td>
<td>Chinese patients (27% female) with FPG ≥ 5.6mmol/L, selection method not reported. (n=497)</td>
<td>6.5%</td>
<td>Sensitivity: 62.7% Specificity: 93.5%</td>
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<td>Optimal threshold: 6.3%</td>
<td>Sensitivity: 79.6% Specificity: 82.2%</td>
</tr>
<tr>
<td>Choi 2011</td>
<td>OGTT</td>
<td>Participants from the Ansung-Ansan (Korean) cohort study. Selection method not reported. (n=9,466)</td>
<td>Optimal threshold for immediate DM diagnosis: 5.9%</td>
<td>Sensitivity: 68% Specificity: 91%</td>
</tr>
<tr>
<td>Cosson 2011</td>
<td>OGTT</td>
<td>Overweight or obese adults (80% European, 83% female) without known DM fulfilling ADA 2010 dysglycaemia screening criteria (n=1157)</td>
<td>6.5%</td>
<td>Sensitivity: 44.7% Specificity 92.7%</td>
</tr>
<tr>
<td>Dong 2011</td>
<td>OGTT</td>
<td>Adults from Jinan area of Shandong, China without known DM who had HbA1c and OGTT tests on the same day. (n=701)</td>
<td>6.5%</td>
<td>Sensitivity 48.2% Specificity: 97.8%</td>
</tr>
<tr>
<td>Hajat 2011</td>
<td>OGTT</td>
<td>Abu Dhabi nationals, selection method not reported. (n not reported)</td>
<td>Optimal threshold: 6.4%</td>
<td>Sensitivity: 72.0% Specificity: 84.3%</td>
</tr>
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<tr>
<td>Peter 201117</td>
<td>OGTT</td>
<td>Caucasians at risk for DM but without known DM. Selection method not reported. (n=2,036)</td>
<td>6.5%</td>
<td>Sensitivity: 46.8% Specificity: 98.7% 47% of patients had same classification by HbA1c and OGTT.</td>
</tr>
<tr>
<td>Pinelli 201118</td>
<td>FPG, OGTT</td>
<td>Population-based representative, randomly selected sample of adults Arabs without known diabetes. (n=482)</td>
<td>6.5% (reported as ADA criteria)</td>
<td>Sensitivity: 19% Specificity: 100% Optimal threshold: 6.2% Missed 73% of those classified as having DM by other tests. Kappa=0.2835</td>
</tr>
<tr>
<td>Tay 201119</td>
<td>OGTT</td>
<td>Singaporean patients, stratified by age, and without previous history of DM who underwent HbA1c and OGTT at the same time, selection method not reported. (n=90)</td>
<td>Optimal threshold: 6.2%</td>
<td>Accuracy details not reported, though sensitivity and specificity of HbA1c may decrease as age increases.</td>
</tr>
<tr>
<td>Zemlin 201120</td>
<td>FPG, OGTT</td>
<td>Participants (76% female) from a community-based South African study, selection method not reported. (n=946)</td>
<td>Optimal threshold against both comparators: 6.1%</td>
<td>FPG as standard Sensitivity: 80% Specificity: 77% OGTT as standard Sensitivity: 75% Specificity:75%</td>
</tr>
<tr>
<td>Hu 201021</td>
<td>OGTT</td>
<td>High risk subjects, selection method not reported. (n=2298)</td>
<td>Optimal threshold: 6.1%</td>
<td>Sensitivity: 81.0% Specificity:81.0%</td>
</tr>
<tr>
<td>Kumar 201022</td>
<td>OGTT</td>
<td>Adults aged 20 years or older, randomly selected from Chandigarh in north India. (n=1972)</td>
<td>Optimal threshold: 6.1%</td>
<td>Sensitivity: 81% Specificity: 81% 6.5% Sensitivity: 65% Specificity: 88% 7.0% Sensitivity: 42% Specificity: 92%</td>
</tr>
<tr>
<td>Olson 201023</td>
<td>OGTT</td>
<td>Non-Hispanic white or black adults without known DM included in the SIGT, NHANES III or NHANES 2005-2006 studies (USA) who had measured OGTT and HbA1c. (n=4,706)</td>
<td>6.5%</td>
<td>Sensitivity: 30% ROC curve area: 0.79-0.83 Racial differences: more false positives in blacks and false negatives in whites.</td>
</tr>
</tbody>
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Table 1: Included Non-Randomized Studies Examining the Diagnostic Accuracy of HbA1c

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| Zhou 2010²⁴        | OGTT       | Adults aged 35-74 years participating in a population-based diabetes survey in Qingdao, China. Selection method not reported (n=2,332) | Optimal threshold 5.6% | Men                
|                    |            |                                                       |                 | Sensitivity: 64.4%          |
|                    |            |                                                       |                 | Specificity: 61.6%          |
|                    |            |                                                       |                 | Women              
|                    |            |                                                       |                 | Sensitivity: 62.3%          |
|                    |            |                                                       |                 | Specificity: 63.3%          |

ADA = American Diabetes Association; CI = confidence interval; DM = diabetes mellitus; FPG = fasting plasma glucose; Hb = hemoglobin; NHANES = National Health and Nutrition Examination Survey; OGTT = oral glucose tolerance test; ROC = receiver operating characteristic; SIGT = Screening for Impaired Glucose Tolerance study; a assumed from pre-diabetes range of 5.7%-6.4%.

REFERENCES SUMMARIZED

Health Technology Assessments

   See Chapter 2: Glycated haemoglobin, page 16; Chapter 2: Reservations about the use of glycated haemoglobin, page 18; and Chapter 6: Review of cost effectiveness studies: Which test of blood glucose should be used? Page 49.

Systematic Reviews and Meta-analyses
No literature identified.

Randomized Controlled Trials
No literature identified.

Non-Randomized Studies

   PubMed: PM24130943


Economic Evaluations
No literature identified.

Guidelines and Recommendations


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APPENDIX – FURTHER INFORMATION:

Studies Comparing Number of Patients Diagnosed with DM using HbA1c versus Comparators


Studies on HbA1c for Predicting Diabetes


Studies on HbA1c Accuracy for Screening for Diabetes in Patients with Other Conditions

PubMed: PM21775751

Clinical Practice Guidelines

See Recommendations 2, 3, and 4 and Figure 1: Screening and diagnosis algorithm for type 2 diabetes.

47. Mannarino M, Tonelli M, Allan GM. Screening and diagnosis of type 2 diabetes with HbA1c. Can Fam Phys [Internet]. 2013 Jan [cited 2013 Dec 6];59(1):42. Available from: http://www.cfp.ca/content/59/1/42.full

Studies on Ethnic Differences in HbA1c Correlation to FPG/OGTT

PubMed: PM20739381

PubMed: PM20547905