THE ADVISIBILITY OF USING A1c AS A SCREENING METHOD FOR EARLY DETECTION OF TYPE 2 DIABETES MELLITUS

By

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A non-thesis submitted in partial fulfillment of the requirements for the degree of

MASTER OF NURSING

WASHINGTON STATE UNIVERSITY - YAKIMA
College of Nursing
December 2010
To the Faculty of Washington State University:

The members of the Committee appointed to examine the non-thesis of JODY B. GRAY find it satisfactory and recommend that it be accepted.

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ACKNOWLEDGEMENTS

I would like to express my gratitude and appreciation to everyone who supported me during the process of attaining my Master’s degree in nursing.

First I would like to thank Laura Hahn for her encouragement and constant reminders that it was never too late to return to college. Thanks to my many classmates, coworkers, friends, WSU faculty and staff for their support and encouragement.

I would also like to thank the members of my project committee, faculty, and support personnel who answered all of my questions and pointed me in the right direction when I felt lost. Cindy, your encouragement and advisement was instrumental in writing this paper and without your expert knowledge I would have been lost, thank you so much. To Sandy and Josh, thanks for the insight and advise, you were both great to work with and made this process seem like a dream.

Lastly, I would like to thank my family for their unending support and encouragement. To my husband Greg, thanks for the encouragement, picking up the slack around the house and taking care of Ashley when I felt like I was buried in paper work. I think we’re even now in the chores department, let’s hire a maid! To Ashley my sweet precious daughter thanks for the hugs, kisses, and being such a great kid. You are the light of my life, and yes this is what it’s like to go to college when you’re old.
THE ADVISIBILITY OF USING HEMOGLOBIN A1c AS A SCREENING METHOD FOR EARLY DETECTION OF TYPE 2 DIABETES MELLITUS

Abstract

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December 2010

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Submitting to The Nurse Practitioner

Type 2 diabetes in the United States is on the rise. Millions of individuals are asymptomatic yet have undiagnosed diabetes. With daunting numbers of individuals who are obese, inactive, and have other risk factors that contribute to the development of diabetes, it is imperative for practitioners to screen individuals at point of care (POC) in an attempt to diagnose type 2 diabetes as early as possible to assure early management of glycemic control to prevent future complications. Current standards of care recommend using the plasma A1c as one possible test for diagnosing and screening for diabetes in patients with known risk factors, and those over 45 years of age. There is good evidence that the A1c is a reliable test for diagnosing diabetes, and the POC test is as accurate as the laboratory A1c. Studies indicate that individuals may have elevated blood sugars for years before an actual diagnosis of diabetes is known. Research also suggests that this hyperglycemic period can be as long as 7-12 years before symptoms occur, though the exact number of years is unknown. Once symptoms of diabetes have occurred, there are indications that retinopathy, nephropathy, and neuropathy are already underway. Further, studies have shown that lifestyle interventions of weight loss,
exercise, diet, and oral anti-diabetic medications can delay or prevent a diagnosis of diabetes.\textsuperscript{5}

Using the Chronic Care Model as a guiding framework, this paper reviews available literature to determine the advisability of using POC A1c to screen for type 2 diabetes.\textsuperscript{5,10}
# TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACKNOWLEDGEMENTS</td>
<td>iii</td>
</tr>
<tr>
<td>ABSTRACT</td>
<td>iv</td>
</tr>
<tr>
<td>LIST OF TABLES</td>
<td>vii</td>
</tr>
<tr>
<td>LIST OF FIGURES</td>
<td>viii</td>
</tr>
<tr>
<td>INTRODUCTION</td>
<td>1</td>
</tr>
<tr>
<td>THEORETICAL FRAMEWORK</td>
<td>2</td>
</tr>
<tr>
<td>LITERATURE REVIEW</td>
<td>3</td>
</tr>
<tr>
<td>DISCUSSION</td>
<td>7</td>
</tr>
<tr>
<td>REFERENCES</td>
<td>11</td>
</tr>
</tbody>
</table>
List of Tables

Table 1:  Modifiable and non-modifiable risk factors .......................... 13
Table 2:  American Diabetes Association criteria for diagnosing type 2 diabetes.......... 14
List of Figures

Figure 1: Conceptual Framework of Chronic Care Model..............................15
Introduction

The number of new cases of diabetes for those between the ages of 18-79 was 1.6 million in 2008, and it is apparent the United States (U.S.) is facing an epidemic.\textsuperscript{1} According to the Centers for Disease Control (CDC), more than 24 million people have diabetes, this number increased by over 3 million people between 2006 and 2007.\textsuperscript{2} Complications from diabetes range from developing retinopathy, neuropathy, nephropathy, amputations, cardiovascular disease, and stroke. It is estimated that the costs of diabetes care and the associated loss of work, and disability is $174 billion annually.\textsuperscript{3} Diabetes as a cause of death is underreported in the U.S., but never-the-less remains the seventh leading cause of death.\textsuperscript{3}

There are an estimated 5.7 million people with undiagnosed diabetes in the U.S. that would benefit from early interventions if elevations of plasma hemoglobin A1c (A1c) were detected early in the disease process.\textsuperscript{3} The A1c is a blood test that reflects overall glycemic control over the preceding 1 to 3 months.\textsuperscript{4} The prevalence of undiagnosed type 2 diabetes (T2DM) has serious implications to individuals if the disease is allowed to progress or develop because of non-detection, not to mention the astronomic cost of the disease. The American Diabetes Association (ADA) now recommends the use of the plasma A1c to diagnose T2DM as it is a reliable and standardized test, yet there is no recommendation for using the finger stick A1c as a screening tool at point of care (POC) for diagnosing T2DM. In fact, its use in this manner is discouraged.\textsuperscript{5}

As the number of individuals in the U.S. with modifiable risk factors (Table 1) increase, practitioners are increasingly aware of the benefits of detecting T2DM early.\textsuperscript{6} Plasma A1c levels are currently used in diagnosing T2DM and it is the test of choice, in conjunction with self monitoring of blood glucose, for the chronic management of T2DM in the clinical setting.\textsuperscript{6,7}
There are four methods recommended by the ADA for diagnosing T2DM, and these tests are also recommended for screening. These methods are based on a plasma sample (or blood, or serum) and include fasting plasma glucose (FPG), 2 hour oral glucose tolerance test (OGTT) after a 75 gram glucose load, random plasma glucose (RPG), and the plasma A1c which was added to the ADA standard of care in 2010. The current position of the ADA is that the finger stick (capillary) A1c is not accurate enough to use at POC for the diagnosis of T2DM. The American Association of Clinical Endocrinology (AACE) and the American College of Endocrinology (ACE), and the ADA endorse the use of plasma A1c performed at a laboratory using the National Glycohemoglobin Standardization Program (NGSP) certified method and following the Diabetes Control and Complications Trial (DCCT) standards for diagnosing T2DM. The ACCE/ACE does not recommended using the A1c as the primary means of testing for T2DM. The use of finger stick A1c testing at POC is recommended as a means of chronic glycemic management for those diagnosed with diabetes, with these results providing evidence for necessary treatment changes to meet glycemic goals. It has been suggested that screening populations at risk for T2DM using POC A1c tests may be of benefit, and that these opportunistic screenings may already be occurring.

The Chronic Care Model (CCM) provides a framework for evaluating the research related to opportunistic A1c screening for T2DM. The CCM suggests that chronic care can be improved when patients are informed and activated (Figure 1). From a practical perspective, the cost and convenience of performing the test must outweigh the benefit of the screening. The cost of a plasma A1c is about three times the cost of a plasma FPG, which is no more than $20 in a laboratory. In contrast to a plasma A1c, the relative cost of a finger stick POC A1c is less than $20. Though the relative costs may be expensive, the convenience of doing
an A1c which requires no fasting and can be done at the time of service, with results available within minutes must be factored into the cost-benefit equation. FPG testing requires the patient to be fasting for at least 8 hours, and it is not always possible for the patient to be fasting at the time of the office appointment. The purpose of this paper is to evaluate existing evidence on using A1c as a POC screening method for T2DM.

Literature Review

Methods

A literature search was conducted using the Cumulative Index to Nursing and Allied Health Literature, Google, the Center for Disease Control, and PubMed; key words used in the search in various combinations included hemoglobin A1c, screening, diabetes, pre-diabetes, fasting blood sugar, 2 hour glucose tolerance test, early detection, point of care, prevention, and community. The search was limited to studies involving adult subjects and journal articles in English. The date range for the search was 1990 to 2010. Articles identified (N=1072) were further screened by title, then by abstract in order to exclude irrelevant articles, such as those focusing on type 1 diabetes, treatment, monitoring, pregnancy, adolescence, inpatients, and complications. Four articles that met the inclusion criteria focusing on using the A1c as a screening method for T2DM in the community setting were identified.

Ginde, Cagliero, Nathan, and Camargo, examined a nationally representative sample from the National Health and Nutrition Examination Survey to validate the A1c as a screening test for undiagnosed T2DM while using risk stratification measures. This study used a large probability sample of participants (N=6,723) who were ≥ 18 years of age. There were a total of
622 participants excluded from the study due to a previous diagnosis of diabetes. The data set included a physical examination, laboratory testing of FPG, triglycerides, high density lipoproteins, and A1c. The FPG levels were classified according to the standard diagnostic criteria of the ADA. The A1c levels were measured by the same laboratory using “Primus CLC 330 and Primus CLC 385 that utilizes a high performance liquid chromatography method that is standardized to a reference method for the Diabetes Control and Complications Trial”. This particular method has a “precision coefficient of variation <3%, and is not effected by hemoglobin variants S, C, D or elevated fetal hemoglobin (HbF)”.

A risk score system was developed using a point system for predicting increased risk of T2DM that included the following: “age 45-64 (2.5 points), age ≥65 (4 points), male sex (1.5 points), black race (1 point), hypertension (1 point), elevated waist circumference (1.5 points), elevated triglycerides (1 point), and low high density lipoprotein level (1 point)”. Resulting scores where then placed into three categories of risk, low (0-4.5 points), moderate (5-6.5 points), and high (≥7 points). It was noted that there was an increasing prevalence of undiagnosed diabetes in the risk groups with 0.44% in the low risk group, 4.1% in the moderate, and 11.1% in the high risk group category, respectively. The authors determined that those who fell into the high risk category were 25 times more likely to have undiagnosed diabetes. An A1c threshold range of ≥ 6.1% was used in predicting undiagnosed T2DM for the sample. In the moderate risk group (n=100), 45 participants had an A1c ≥ 6.1%. In the high risk group, (n=177), 91 participants had an A1c ≥ 6.1%. The study findings indicate that risk stratification methods to determine patients’ relative risk for developing T2DM based on clinical factors could be beneficial to practitioners in determining whether to do A1c testing. Clearly defined risk factors and risk score points would need to be predetermined.
Rohlfing and colleagues examined a large population based sample (N=6,559) from The Third National Health and Nutrition Examination Survey conducted from 1988 to 1994, to determine the usefulness of A1c as a screening tool for detecting T2DM. Participants were ≥20 years of age. The investigators compared the data of participants who had a FPG ≥ 126 mg/dl with A1c results. The study included 265 participants with an elevated FPG, and of these 197 (74.3%) had an A1c reading that was > 6.1% suggesting that the A1c is a reliable screening measure for detecting undiagnosed T2DM. There were a total of 72 participants with an A1c ≤ 6.1%, and of these 21 (29.2%) had FPG values close to normal (126 mg/dl). Also in this group 24 participants (33.3%) had a 2 hour plasma glucose value of <200 mg/dl which further demonstrated the sensitivity of the A1c. The study identified differences among ethnic groups for A1c sensitivity and specificity, with a higher prevalence of diabetes among the non-Hispanic black and Mexican-American populations. The study results further suggested that A1c values >6.1% are less sensitive, yet the specificity increases with these values. The study authors noted that FPG is an inconvenient test for participants. This study is 10 years old and was completed at a time when the ADA was making new recommendations for diagnosing diabetes with a FPG of 126 mg/dl (Table 2), which at the time was recommended over the OGTT. Since the time of this study, the ADA has adopted standards changes that include the use of A1c as a diagnostic tool. The sensitivity and specificity of plasma A1c results ≥ 6.1%, however, indicate that A1c may be an effective screening, as well as diagnostic, tool.

Ginde et al, conducted a study using the A1c as a screening method for undiagnosed diabetes in the Emergency Department (ED) at Massachusetts General Hospital. The study enrolled 355 ED patients that met the criteria for enrollment and who had agreed to participate. A comparison of POC A1c and random glucose levels were collected at the bedside using finger
stick capillary blood samples, and approved hand held POC A1c testing equipment. Additionally, plasma samples for comparison of A1c were obtained at the same time. A1c samples were also performed in a subset of 32 participants with known diabetes, these samples were used to expand the range of potential A1c values for the study. The POC devices used in testing were the Bayer Contour blood glucose meter for random glucose levels, and the Bayer A1CNow+ device for finger stick analyses of A1c which is certified by the National Glycohemoglobin Standardization Program (NGSP). For additional accuracy, the A1c was also measured by high performance liquid chromatography in the hospital’s laboratory. The correlation between POC A1c and the laboratory reference was high (r= 0.96), with slightly higher POC values with a mean difference of +0.33% (95% CI = 0.27% to 0.39%). Categories of POC A1c were defined as normal (≤5%), borderline (5.5-6.0%), and abnormal (≥6.1%). The A1c measure was used to determine further need for follow up with an oral glucose tolerance test (OGTT). Participants returned 1-6 weeks following the ED visit if abnormal or borderline A1c results were obtained. Of the 76 participants that had an abnormal POC A1c, 29 (38.2%) returned for the OGTT test, and results indicated that 11 had T2DM, 10 had prediabetes, and 8 were normal. Only 19 participants with a borderline A1c (5.5-6.0%) returned for the OGTT, and 1 was diagnosed with T2DM and 9 were diagnosed with prediabetes. The findings of this study indicate that 14% of the participants seeking treatment in the ED had undiagnosed T2DM. The study also shows that opportunistic screening can be effective in identifying undiagnosed T2DM or prediabetes. Referrals to primary care providers, lifestyle changes and education at the POC may delay or circumvent future complications. Unfortunately, a substantial number of study participants who had higher than normal A1c levels did not follow up or return for further testing. The implications of failing to
follow-up with the healthcare system include financial burden and neglect of treatable conditions requiring increased demand at a later stage in the illness.

Kramer, Araneta, and Barrett-Conner conducted a large (n=2,107) community based study using OGTT and A1c. The ADA criteria of A1c ≥ 6.5% and OGTT ≥ 200 mg/dL were utilized as the baseline set point for diagnosing T2DM. The mean age for the participants in this study was 69.4 ± 11.1 years. Participants with known anemia were excluded from the study. A1c was measured using high performance liquid chromatography. In addition, ophthalmologic evaluations were performed on all participants using nonmydriatic retinal photography. When using the A1c set point of 6.5% the agreement between A1c and OGTT results were low, as 85% of the participants with an A1c ≥6.5% were classified as non-diabetic by the OGTT ADA criteria. The set point of 6.15% had a higher sensitivity and specificity, but missed one-third of those with T2DM and misclassified one-third without T2DM. Similar findings were identified when comparing the FPG and the OGTT. Thus, this study did not find good evidence for recommending A1c as a POC screening method. The participants in this study, as compared to the other three studies reviewed, were on average much older, suggesting that that age may be an important criterion when evaluating effective screening methods for T2DM.

Discussion

The use of A1c as a screening tool remains controversial despite evidence that some practitioners currently use the test to screen for T2DM. The prevalence of T2DM continues to increase by the millions annually in the U.S. These cases are possibly being detected due to opportunistic screening, current technologies and new standards allowing A1c to be used as a diagnostic tool. Experts at this time do not recommend using the finger stick A1c as a POC
screening tool. Increasing numbers of studies suggest that the A1c is a good screening tool. Though there is no current method that is considered superior for screening or testing for T2DM, the current ADA guidelines recommend using any of the currently recommended tests (FPG, A1c, OGTT, or random PG), though the method used should ideally be the method that is repeated to confirm the diagnosis. The cost of these tests can be expensive, and they are not always as convenient as using POC A1c or the plasma A1c, both of which are being used increasingly in clinical settings. The Chronic Care Model (CCM) provides an evidence-based framework for health care delivery that supports system designs to improve provider knowledge and patient and provider interactions. When appropriately implemented, health care delivery guided by the CCM (Figure 1) engages patients in their own care leading to better health care outcomes with the potential to delay future complications. For patients at high risk for T2DM, screening and early detection is fundamental to care delivery guided by the CCM. A1c screening provides information needed by practitioners so they can be prepared and proactive, and initiate productive interactions with patients which can then lead to informed, activated, empowered patients who can make decisions about lifestyle changes. Current ADA recommendations for T2DM screening in asymptomatic individuals includes those with known risk factors (see Table 1) and those who are age 45 or greater only, regardless of risk. There are no other criterion recommended for screening asymptomatic individuals. In fact, mass screenings of asymptomatic individuals has not been effective, and definitive and rigorous trials to provide such evidence are unlikely to occur.
specific in most instances, though some researchers suggest that missed or under-diagnosing can occur with several methods of testing.\textsuperscript{16} Risk stratification tools increased the likelihood of predicting those who would be determined to have T2DM. Therefore, this type of tool may help the practitioner in deciding to perform an A1c test on their patients.\textsuperscript{15} Findings also indicate that certain ethnic groups and older patients have a higher prevalence of elevated A1c.\textsuperscript{16,18} One study was able to demonstrate that using a plasma A1c compared to a finger stick A1c showed very little difference in the values, those being slightly higher with finger stick method by +0.33\%.\textsuperscript{17} This study also demonstrates the value of finger stick POC testing and the ability of the practitioner to interact with the patient regarding lifestyle changes which is supported by the CCM to prevent future complications of chronic disease.\textsuperscript{11,12,17}

In conclusion, opportunistic screening for undiagnosed T2DM is not recommended as a standard of care unless the individual has risk factors that would indicate screening.\textsuperscript{5} Those 45 years of age or older should be screened every 3 years for T2DM if asymptomatic.\textsuperscript{5} The A1c and other testing methods previously mentioned are acceptable for these individuals when done in the laboratory setting.\textsuperscript{5} Several studies have been done indicating that the A1c is a reliable test for screening for undiagnosed T2DM and its current use for diagnosing T2DM is an acceptable standard, but it may not be as reliable when used in the elderly, or in certain ethnic groups.\textsuperscript{5,10} The ADA, ACCE, and ACE do not recommend using the POC A1c for diagnosing or screening for T2DM.\textsuperscript{5,10} Despite these standards, opportunistic screening using the A1c is being done by some practitioners in clinical settings.\textsuperscript{5,10} The burden of opportunistic screening lies with practitioners who must make clinical decisions to screen individuals based on access to care, history, risk, and reported symptoms. A clinical decision to use POC A1c may be appropriate in
some instances when care access or other issues that may impede their ability to follow-up with the recommended screening procedures.

Standardization of screening methods would provide clear guidelines to practitioners for screening individuals using A1c. The specificity and sensitivity of the A1c in some studies was questionable at certain set points. These variances in the A1c could compromise the care and treatment of patients, possibly delaying care and diagnosis in some instances, making its reliability and use questionable. Further research is needed in this area, as the set points may need to be lowered in order to capture those with T2DM and those with abnormal A1c levels. Further research is needed with POC A1c methods to examine their role in the clinical setting as a screening tool for T2DM, as some POC machines have been shown to be reliable and accurate.17 Thus, despite the generally positive research findings related to POC A1c screening, the current evidence does not clearly substantiate that it provides clinical information that is sensitive and specific enough for practitioners to consistently make informed and proactive patient care decisions. Therefore, POC A1c screening cannot be recommended to be routinely used for diagnostic purposes in clinical practice at this time.

Practitioners should generally use the plasma A1c for diagnosing T2DM, and repeat the plasma A1c test to verify the diagnosis. With rare exceptions, POC A1c levels should only be used in the clinical setting to manage those with diabetes to guide treatment regimen and therapy changes. Opportunistic screening in those with known risk factors can lead to an early diagnosis of T2DM with the appropriate method of testing. POC A1c testing may be appropriate in select cases when risk factors are present and the practitioner is concerned that the follow-up required by the patient for other diagnostic methods is unlikely to occur. Early detection of T2DM allows the practitioner to be proactive in chronic disease management as outlined in the Chronic Care
Model, which utilizes resources within the health care system and community.\textsuperscript{13} Once a diagnosis of T2DM is known, the practitioner is able to inform and activate patients through productive interactions, thus engaging the patient in self-management strategies that positively impact clinical outcomes in chronic diseases like T2DM.\textsuperscript{13}
REFERENCES


http://www.quickmedical.com/metrika/index.html


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<th>Modifiable Risks</th>
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</thead>
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<tr>
<td>Overweight or obese (BMI ≥25 kg/m²)</td>
<td>Diabetes diagnosis in a first degree relative</td>
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<tr>
<td>Physical inactivity</td>
<td>High risk ethnic groups</td>
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<tr>
<td>Hypertension or known heart disease</td>
<td>≥45 years of age</td>
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<tr>
<td>Low HDL or elevated Triglyceride Levels</td>
<td>Women with a history of polycystic ovary syndrome</td>
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</tbody>
</table>
### Table 2

Criteria for the diagnosis of diabetes

<table>
<thead>
<tr>
<th>Test</th>
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</tr>
</thead>
<tbody>
<tr>
<td>A1c ≥6.5% *</td>
<td>A NGSP certified laboratory test standardized to the DCCT assay</td>
</tr>
<tr>
<td>FPG ≥126 mg/dl (7.0 mmol/l)*</td>
<td>Fasting- no caloric intake for at least 8 hours</td>
</tr>
<tr>
<td>Two hour glucose ≥200 mg/dl (11.1 mmol/l) during OGTT*</td>
<td>WHO defined test using 75 g of anhydrous glucose dissolved in water</td>
</tr>
<tr>
<td>Random plasma glucose ≥200 mg/dl (11.1 mmol/l)</td>
<td>Symptoms of hyperglycemia or hyperglycemia crisis</td>
</tr>
<tr>
<td></td>
<td>*Repeat test if absence of unequivocal hyperglycemia</td>
</tr>
</tbody>
</table>
Figure 1: Chronic Care Model, which establishes the theoretical framework for this research used with permission.