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Diabetes epidemic in the Asia Pacific region: has hemoglobin A1C finally earned its place as a diagnostic tool?

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PEER REVIEW

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Comments

This is a well-researched and presented paper that will be especially helpful to clinicians and public health administrators tasked with implementing and managing regimes to treat the growing number of diabetic patients along with problems associated with their comorbidities.
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ABSTRACT

Two-third of the world's population lives in the Asia Pacific region where prevalence of diabetes has reached epidemic proportion. With China and India being the most populous nations on the globe, it is believed that over 150 million diabetes reside in the region with more than 95% being of type 2 diabetes mellitus (T2DM). Furthermore, other Pacific islands in the region have high rates of T2DM including Tonga, Fiji, French Polynesia, and Nauru. The latter has the highest prevalence of T2DM per population in the world. Over the past two decades, in Australia and New Zealand, the prevalence of T2DM has more than doubled, mainly amongst the Aboriginal and Torres Strait Islander and Maori peoples respectively. With the increasing prevalence of diabetes in the Asia Pacific region coupled with the limited number of resources, use of a reliable and effective mode of diagnosis for T2DM is warranted. Yet to date, only New Zealand has adopted the American Diabetes Association recommendation of using hemoglobin A1C in the diagnosis of the disease. The aim of this review is to discuss the clinical usefulness of hemoglobin A1C and highlight its diagnostic role in the Asia Pacific region where T2DM is increasingly encountered.

KEYWORDS
Hemoglobin A1C, Diagnostic tool, Asia Pacific region

1. Introduction

Diabetes mellitus (DM) is a concerning health problem for the Asia Pacific region where late diagnosis and poor monitoring is associated with increased risk of microvascular and macrovascular disease, disability and mortality often prematurely[1-3]. Recently, the Australian diabetes, obesity and lifestyle study indicated that in a national sample of those aged greater than 25 years old, there was an overall DM prevalence of 7.5%, with an estimated 50% of these cases being previously undiagnosed[4]. The importance of early and accurate diagnosis has been proven to significantly reduce the risk of unwanted complications as demonstrated by the United Kingdom prospective diabetes study[5]. Prior to 2010, blood glucose analysis has been the exclusive and gold standard method to diagnose T2DM. However, recently the World Health Organization (WHO) and the International Diabetes Federation has recommended hemoglobin A1C

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(HbA_{1C}) as a diagnostic test[6]. Although it is not currently recommended in all but one of the Asia Pacific countries, many physicians globally have taken a liking to HbA_{1C} and this newfound use. Historically, HbA_{1C} has previously only been utilized to monitor glycemic control and guide therapy in those already diagnosed[5,7]. With a strong correlation able to be made between HbA_{1C} and retinopathy, as well as other microvascular complications, the convenience of sampling HbA_{1C} at any time without regard to food ingestion removes the methodological, procedural and practical problems of measuring blood glucose levels[7,8]. This report will further discuss the concepts behind HbA_{1C} and the scientific method of its application, the advancement and validity in its practical implementation, its limits, as well as its usefulness in the detection of millions of people who would otherwise be left undiagnosed, particularly in rural and remote regions of the Asia Pacific.

2. Hemoglobin A1C in clinical practice

2.1. Biochemical basis of HbA_{1C}

The discovery of HbA_{1C} and its association with blood glucose measurements have been rigorously investigated since the 1960s. Rahbar initially identified HbA_{1C} as an "unusual hemoglobin in patients with diabetes"[9]. However, at the same time, despite there being a strong suspicion that hyperglycemia was associated with vascular complications, it was difficult to prove without an objective marker of glucose control[7]. With this purpose and need for a marker in mind, throughout the following two decades, multiple studies were conducted to find the correlation between HbA_{1C} and glucose measurements. It became widely published that HbA_{1C} was the hemoglobin component of an erythrocyte that was composed of glycohemoglobin[9]. With the erythrocyte cell membrane being highly permeable, hemoglobin was easily exposed to intracellular levels of glucose. During these occasions, via nonenzymatic attachment, glucose bound to the N-terminal valine on the β chain of hemoglobin, forming HbA_{1C}[10]. With the attachment of glucose to the hemoglobin remaining there for the lifetime of the erythrocyte, it became apparent that the amount of HbA_{1C} that was formed would reflect the level of glucose exposure. As the life span of an erythrocyte on average is approximately 120 d, blood sample at any given time would include erythrocytes of different ages with varying degrees of exposure to glucose[10]. Despite elder erythrocytes being exposed to more hyperglycemia, younger erythrocytes are more prominent in a blood sample. With approximately 50% of HbA_{1C} representing blood glucose levels over the preceding 30 d, and 10% the previous 90-120 d, the measured HbA_{1C} was able to be extrapolated to provide an estimation of average glucose control over the past 2-3 months[10]. The method selected to measure HbA_{1C} is dependent on the laboratory, with approximately 100 different ways of doing so. The use of antibodies in immunoassays and cation-exchange chromatography are two methods most widely used to efficiently separate the glycated from the non-glycated hemoglobin[7]. Regression equations, developed using data from earlier studies, are then used to generate average blood glucose levels from HbA_{1C}, ultimately aiding in the development of current DM management guidelines[7].

2.2. Application and validity of HbA_{1C}

By the 1980s, the association between glucose control and HbA_{1C} and development of diabetic complications was evident, supporting the implementation of HbA_{1C} to the clinical environment; a recognizable cornerstone in clinical practice[4]. Two studies, the Diabetes Control and Complications Trial and the UK Prospective Diabetes Study, cleverly illustrated that in both type 1 diabetes mellitus (T1DM) and T2DM, intensive blood glucose control, obvious in blood glucose and HbA_{1C} measurements, decreased the risk of microvascular complications[10]. Both studies also demonstrated how the HbA_{1C} result can allow the establishment of specific treatment goals; appropriate lifestyle and medication adjustment[10]. On the basis of the results from these trials, DM organizations globally began and currently still use HbA_{1C} as a significant tool to monitor glucose control and guide management[6]. The current Australian DM guideline outlines that the general HbA_{1C} target in people with T2DM is less or equal to 7%[8]. A result greater than 7% in those without severe hypoglycemia, limited life expectancy, or co-morbidities and who isn't elderly, should prompt more active hypoglycemic treatment as suggested by the International Diabetes Federation[6]. It is further recommended that both those patients with T1DM or T2DM have their HbA_{1C} tested every 3-6 months[10,11]. Although target levels are specified and provide ranges to guide point of intervention, most importantly, as the guidelines state, any significant reduction in HbA_{1C} will improve patient outcomes; with each 1% reduction resulting in a 20% to 40% decrease in risk of developing complications[4].

2.3 Advances in the utilization of HbA_{1C}

To reduce the risk of impact of T2DM, both micro and macrovascular complications, early diagnosis is recognized as the ultimate solution[8]. However, for the presence or absence of a chronic disease to be determined, a diagnostic tool must have a low degree of intra-individual variation[7]. With the fasting plasma glucose and oral glucose tolerance tests both performing poorly on this measure, further use of HbA_{1C} as a diagnostic tool has been pondered for the past decade. In 1997, expert committee on the diagnosis and classification of DM and another group in 2003 failed to recommend the use of HbA_{1C} in the diagnosis of T2DM due to lack of standardization and no consensus on an appropriate cut-off point for DM identification[7]. In 2009 however, another international expert committee examined data on retinopathy prevalence and glycemic measures from nine countries and determined that HbA_{1C} of 6.5% recognizes the

cut-point at which retinopathy begins to occur[6,7]. This finding, together with almost universal standardization of HbA_{1C} measurement as a result of a National Glycohemoglobin Standardization Program, has encouraged the recommendation for HbA_{1C} to be used to diagnose T2DM[8,12]. To date, the American Diabetes Association added HbA_{1C} into its 2010 clinical practice recommendations with a cut-off value of 6.5% or greater alongside the glucose based criteria[3]. Although New Zealand adopted its use[13], other countries in the Asia Pacific region have yet to add HbA_{1C} as a diagnostic tool, but as stated in 2012 Australian guidelines for diabetes management in general practice, it is a policy that maybe adopted in the future[4,8]. In Australia to date, Medicare does not fund HbA_{1C} as a diagnostic or screening test for diabetes, only recognizing its use for those previously diagnosed, and further requiring evidence of such on the request form[3]. A systematic review conducted by WHO, compared fasting plasma glucose and HbA_{1C} with the 10-year incidence of retinopathy. It revealed that HbA_{1C} of 6.5% had a positive predictive value of 15.9%, negative predictive value of 97%, a sensitivity of 7.9% and a specificity of 97%[14]. Therefore, this indicates that as a diagnostic test, when a positive diagnosis is made, it is highly likely to be correct. When practical considerations are considered alongside this finding, such as not requiring the patient to fast or undergo special preparation, allowing more convenient opportunistic screening in the usual clinic setting, and results not being influenced by short term stressors such as hospitalization and acute illness, it seems logical that this advancement in the utilization of HbA_{1C} as a diagnostic tool should be pursued sooner rather than later within the Asia Pacific region[15].

2.4. Practical implementation of HbA_{1C} as a diagnostic tool in remote areas

With an increasing trend of reported T2DM in remote and rural areas of the Asia Pacific region, it is obvious that a diagnostic and monitoring solution that is opportunistic and allows immediate and easily interpretable results is necessary[1,15]. For instance, HbA_{1C} in the form of point of care (POC), testing in Australia's rural and remote Aboriginal and Torres Strait Islander communities seems ideal given the high specificity of the test and recognizing the largely nomadic nature of these communities. A study conducted in a remote aboriginal community in Australia, assessed and compared the accuracy of POC measurements of capillary blood glucose and HbA_{1C} levels. At the conclusion of the study, they found that POC capillary HbA_{1C} testing offered an accurate, practical, community-friendly way of monitoring DM, and illustrated how incorporating HbA_{1C} as a diagnostic tool in these communities would be beneficial[16]. The precision of HbA_{1C} testing was less than 3%, allowing clinically significant changes in serial HbA_{1C} concentrations to be detected. These positive findings were compared to POC capillary glucose testing where conclusions at the end of the study recommended that results be confirmed by a laboratory test of venous plasma if they were likely to significantly influence clinical decisions. This is due to POC and laboratory results for glucose concentration showing a concentration-dependent difference[16]. These findings are particularly relevant when considering the distance between clinical settings and the laboratory in rural and remote communities. The distance patients often have to travel to access health care when there is uncertainty as to whether the patient has fasted, and when often dealing with a population where health is not a major priority. Hence, inclusion of HbA_{1C} in the Australian guidelines outlining the diagnostic criteria for T2DM seems practical in the future, and even more so in rural and remote regions of the Asia Pacific, where early, accurate and on the spot diagnosis is essential[1,2].

2.5. Cost effectiveness of HbA_{1C} as a diagnostic tool

In order to improve population health in the Asia Pacific region where diabetes has reached epidemic proportion, replacement of a cost ineffective intervention to a cost-effective one is often necessary[5]. Hence, before the implementation of HbA_{1C} as a diagnostic tool, various countries performed a cost effective analysis to ensure the highest possible overall level of population health. Using population-based data, a study conducted in Germany compared the cost effectiveness of HbA_{1C}, oral glucose tolerance test (OGTT) and fasting plasma glucose tests in the diagnosis of those with T2DM. It concluded that the most cost-effective diagnostic strategy was HbA_{1C} combined with OGTT. Although costs were lower when attempting diagnosis with fasting plasma glucose combined with OGTT or OGTT alone, these tests detected only about one-third to one-fourth of subjects with previously undiagnosed diabetes[17]. No cost effective analysis has been conducted in Australia to date with regards to HbA_{1C} and the diagnosis of T2DM. However, in 2012, the Australian Diabetes Society and the Royal College of Pathologists of Australasia applied for an analytic protocol that will be used to guide the assessment of the safety, effectiveness and cost-effectiveness of HbA_{1C} in making the diagnosis of T2DM and a listing on the Medicare Benefits Schedule[5]. This analysis is still pending. However, it is interesting to note some of the cost effective proposals listed in the application with regards to HbA_{1C} as a diagnostic test. With HbA_{1C} having the ability to diagnose and assess the severity in one test, this enables the practitioner to initiate management on the confirmatory return visit, resulting in decreased costs as a result of fewer returned general practice consultations[18]. Long-term health costs would also decrease, with early detection enabling early management and reducing risk of developing complications[17]. The HbA_{1C} test is also less time consuming than OGTT, and easier to tolerate orally. Although data available is limited, it is evident from the above study and the suggestions outlined in the Australian proposal, which may also be applicable to other countries in the region. Hence, HbA_{1C} should without doubt be considered a cost beneficial intervention in the diagnosis of T2DM.

2.6. Limitations to the use of HbA_{1C} as a diagnostic and monitoring tool

As with many clinical tools, there are various genetic, hematologic and illness related factors as well as laboratory variances that can influence HbA_{1C} results. Therefore, they are important to be conscious of during analysis and when determining its potential role in the diagnosis and management of T2DM. Studies have demonstrated that the intra-individual variance of HbA_{1C} in patients without DM is minimal, less than 1%[4]. However, there is variance among individuals and this can be attributed to genetic related factors, age and the environment. Studies involving twins with T1DM suggest a strong genetic influence[3]. Approximately 33% of an inherited variance is said to be related to a "glycation gap", which is the difference between the predicted HbA_{1C} and the actual HbA_{1C}[4]. This can be influenced by differences in erythrocyte transmembrane gradient, which will vary the degree of glucose entry into the erythrocyte, as well as diphosphoglycerate and pH levels within the cell[10]. A large amount of evidence is also surfacing to support the idea that race may perhaps affect levels of HbA_{1C}[4,7]. Various studies have reported significant differences in HbA_{1C} concentrations among different racial groups after adjusting for factors likely to influence glycemia. One study by Tsugawa *et al.* illustrated that Mexican Americans and African Americans had higher average HbA_{1C} values compared to white Americans[19]. All this said however, remains unclear whether these reports have clinical significance, and perhaps, as authors speculated, a delay in diagnosis is the reason for different levels of HbA_{1C} between "black" and "white" Americans[19,20]. Given the current variation in HbA_{1C} concentrations is less than or equal to 0.4%, no consensus has been reached regarding different cutoffs of HbA_{1C} for different racial groups[4]. Hematological and other illness related factors, particularly those that alter the normal life span of erythrocytes, such as splenomegaly, rheumatoid arthritis, acute blood loss, iron deficiency anemia and chronic alcoholism, could substantially alter the level of HbA_{1C}, providing an inaccurate estimation of blood glucose control[10]. An important analytical factor to keep in mind is the clinical variances between laboratories and within laboratories given there are over 100 different methods of measurement[3]. With standardization being a major priority in Australia, further improvements are soon to be achieved following a national whole blood external quality control program developed by the Royal College of Pathologists of Australia and the Australian Association of Clinical Biochemists[4].

3. Conclusion

In conclusion, given 7.5% of the Asia Pacific population aged 25 years and older have T2DM and for every person diagnosed or undiagnosed, the role of HbA_{1C} and its possible value in diagnosing this chronic disease earlier is a worthwhile topic to have discussed[2]. With most undiagnosed diabetic patients having recognizable risk factors and 90% of these attending their general practitioner each year, it is apparent that a more simple and efficient diagnostic test is long overdue[15]. Not only have studies illustrated the importance of early diagnosis and immediate effective management to reduce the risk of developing the detrimental sequelae, but they have found that more effective glycemic control early results in long term benefits even if control eventually deteriorates[3]. Unlike America, where diagnostic use of HbA_{1C} in T2DM has already been established, Asia Pacific countries have largely yet to completely recognize and implement such a convenient, accurate and opportunistic way of sampling. Until then, HbA_{1C} remains only to be a form of glucose control monitoring in those already diagnosed. The longer the delay, the more likely those populations at high risk of T2DM in the region continuing to remain undiagnosed. Without regarding to food ingestion in sampling, it makes it more likely that HbA_{1C} will result in detection of millions undiagnosed, making it a cost effective initiative as discussed above. Despite the limitations resulting in HbA_{1C} not being an appropriate test to confirm diagnosis in those with a chronic medical disease, or who have anemia or another abnormality to their erythrocytes, HbA_{1C} can be measured accurately in the vast majority of people[7,11]. Hence overall, HbA_{1C} is a clinical tool whose use needs to be extended from simply monitoring glucose control to the diagnosis of T2DM in order to achieve improved outcomes and ultimately major long term health and cost benefits for the Asia Pacific region.

Conflict of interest statement

We declare that we have no conflict of interest.

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Comments

Background

Diabetes is a significant emergent disease in the Asia Pacific region that requires accurate and timely diagnosis to ensure effective and uniform management. The HbA_{1C} test is now well recognized internationally as an appropriate diagnostic test. The paper examines the appropriateness of widely adopting this test for use in the Asia Pacific region.

Research frontiers

This paper has the potential to catalyse the widespread introduction of HbA_{1C} testing for diabetes diagnosis throughout the Asia Pacific region. The authors have comprehensively researched the auguments for its introduction and have presented these in a clear and compelling form.

Related reports

Prevalence studies of diabetes in China have recently been published by Yang *et al*. It is estimated that over 150 million diabetics reside in the Asia Pacific region with over 95% being T2DM. Other papers cited validate the use of HbA_{1C} as a diagnostic tool and include the advantages over the current methods and known limitations of the test.

Innovations and breakthroughs

This is a novel paper in its approach in that it builds a well-researched and evidenced rationale for the introduction of HbA_{1C} testing as a diagnostic screening tool for diabetes in the Asia Pacific region.

Applications

With the growing and significant number of diabetes cases in the Asia Pacific region, a proven cost effective screening methodology to manage this public health epidemic is required. This paper provides a strong evidence based approach to suggest an appropriate rationale.

Peer review

This is a well-researched and presented paper that will be especially helpful to clinicians and public health administrators tasked with implementing and managing regimes to treat the growing number of diabetic patients along with problems associated with their comorbidities.

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