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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