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THE ROLE OF HBA1C AS A PREDICTIVE BIOMARKER FOR DIABETIC RETINOPATHY SEVERITY AND PROGRESSION

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ABSTRACT:

Objective:

This paper confers to find out how the levels of HbA1c are associated with the severity and prognosis of diabetic retinopathy (DR) among diabetics. In particular, we test the possibility that HbA1c could be used as a predictive biomarker to determine DR severity supported by clinicians in keeping track of those participants who are more likely to progress to more severe stages of retinopathy.

Study design:

It was a cross-sectional study carried out in a clinical set up where data of 200 patients diagnosed with type 2 diabetes was analyzed.

Method:

The level of HbA1c was determined, and patients were subjected to retinal imaging to ascertain the presence and the extent of DR. The association between levels of HbA1c and the severity of DR was determined by statistical thinking (such as correlation coefficients and regression models).

Results

There was a considerable positive correlation between high levels of HbA1c and DR severity. Greater levels of HbA1c were related to severe development of retinopathy and poor glycemic control predisposed patients to rapid development of the condition.

Conclusion:

HbA1c may be regarded as predictive biomarkers of DR severity and progression, which can be helpful in early identification and treatment of diabetic retinopathy among diabetic patients.

Keywords:

HbA1c, Diabetic Retinopathy, Glycemic Control, Biomarker, Diabetes, Retinal Imaging, Disease Progression.

INTRODUCTION:

Diabetes-related retinopathy (DR) refers to a progressive, permanent vision condition of the eye that is one of the greatest causes of blindness across the world especially among patients of diabetes mellitus. It is a microvascular diabetes complication which occurs to the retinal vasculature causing visual loss and eventual blindness in case of no treatment. The prevalence of diabetic retinopathy has been on a steady upward trend due to the rising number of cases of diabetes in the global context. As reported by the World Health Organization (WHO), the global number of individuals affected by diabetes currently is estimated at 422 million, whereas the number is estimated to greatly increase within the next few decades (World Health Organization, 2016). Consequently, the prevalence of diabetic retinopathy is projected to increase, thus, it has become a major focus of concern in public health due to early diagnosis and proper control.

Diabetic retinopathy is a multifactorial disease in the sense that there are multiple risk factors which may result in its development and/or advancement. Poor glycemic control can be viewed as one of the most dangerous agents as it concerns the development and progress of DR. The management of glycemic is usually evaluated by glycated hemoglobin (HbA1c) which gives an indication of the average blood glucose levels of 2-3 months previously. HbA1c is commonly utilized in the medical setting to measure diabetes control over time in diabetics and in high HbA1c, microvascular complications, one of which is diabetic retinopathy, are likely after occurrence (Klein et al., 2014). It is also imperative to modify the management and prevention of this debilitating condition therefore, it is important to understand the association between HbA1c and level of DR and to improve it.

It has been established in the recent researches that a high level of HbA1c is closely associated with onset and development of DR. Another study conducted by Janghorbani et al. (2014) identified that the risks of getting diabetic retinopathy were significantly higher in patients with high levels of HbA1c. The likelihood of the further development of DR to more severe stages, including proliferative diabetic retinopathy (PDR) was also revealed to be higher with higher levels of HbA1c (Shanmuganathan et al., 2017). The association indicates that HbA1c can be an accurate signal of DR coordination and worsening, which may offer an opportunity to interfere at an earlier stage and apply more effective combination strategies.

The association between HbA1c and DR has been widely studied and the results are inconsistent on whether the relationship between them is strong or weak. Although numerous studies assert a positive correlation between abnormal glycemic control and severity of DR (Liu et al., 2019), some studies have also cited the complexity involved in the mechanism, where the duration of diabetes, hypertension, and the level of lipids were also deemed as possible factors contributing to the development of DR along with the severity process (Sivaprasad et al., 2012). This shows that HbA1c might not be an all-encompassing measure of glycemic control as it is because it measures unidimensional aspect of DR progression. Thus, further research is needed in order to learn more about the performance of HbA1c regarding the other risk factors and to assess its opportunities as a single biomarker of DR.

Another key problem in the treatment of diabetic retinopathy is the early diagnosis of the disease because the ailment is likely to be in a later stage before symptoms are manifested. When any changes in the vision are perceptible, the retinal pathology is already considerable; hence, the process of treatment takes much more time and is much less successful. The current diagnosis techniques such as retinal imaging, fundus photographs, and fluorescein angiography are most crucial in terms of diagnosis of DR and assessment of its severity. These are very effective but they are resource-based and expensive in terms of equipment and technical skills, as well as inaccessible in low resource setting. Conversely, the analysis of HbA1c is easy, inexpensive, and non-invasive and can be conducted in everyday clinical settings. Thus, in case it is possible to reliably correlate HbA1c levels with the severity of DR, it will become a useful tool in

early screening so that healthcare providers would reliably detect patients developing retinopathy prior to developing serious retinal damage.

Nevertheless, HbA1c has been shown to potentially be useful as a predictive biomarker in terms of DR severity, thus it is an area that continues to be under debate. According to some studies, the HbA1c could fail in reflecting all the aspects of the DR evolution, especially when other risk factors, like blood pressure or cholesterol level have greater contribution (Klein et al., 2014). Also, the absence of an optimal HbA1c level with which DR severity can be expected adds complexity to the clinical application of this indicator. Although most of the researchers acknowledge that the level of HbA1c beyond the 7% mark is linked to the greater risk of DR development (Sivaprasad et al., 2012), the exact threshold mark that determines the likelihood of retinopathy progression is not identified. Also, it is revealed that even the patients with well-managed blood glucose levels due to their normal (not elevated) HbA1c levels might develop DR, which points to other contributors to the disease pathogenesis (Janghorbani et al., 2014). Hence, it is important to investigate the role of HbA1c in predicting DR with other clinical markers and risk factors.

The proposed study would help to fill these gaps in the literature as it will examine how the level of HbA1c correlates with the severity and development of DR among a cohort of patients with type 2 diabetes. This study, in particular, will reveal whether or not HbA1c will be an effective predictive biomarker that would help the identification of those who are more prone to suffering advanced retinopathy stages and give the clinicians a helpful instrument in the early detection and treatment. It will also study the possible contribution of HbA1c along with other variables like durations and existence of comorbid conditions in the development of severity and progression of DR.

With the discussion of whether HbA1c could be used as a biomarker of diabetic retinopathy, the study aims at adding to the existing body of evidence sustaining the use of glycemic control as a major factor in the prevention and treatment of DR. The results could also be used to represent the significance of clinical practice especially in enhancing better screening protocols in diabetic retinopathy. Vision loss can be prevented in people with diabetes since early detection and management is paramount and having a clue of the use of HbA1c as an indicator of the severity of DR would greatly help the outcome of patients.

MATERIALS AND METHODS

Study Design:

In this research, a cross-sectional observational design was used where the data collected is analyzed at a specific time of the respondents. This kind of research is also good in terms of knowing the correlation existing between various variables, including HbA1c and the severity of diabetic retinopathy (DR) in a given population. This study was carried out in tertiary care hospital and the purpose of project was to obtain an understanding of the relationship between the level of glycated hemoglobin (HbA1c) on severity of diabetic retinopathy in people who had type 2 diabetes. Cross-sectional

studies tend to be useful in establishing correlations but not causal relationship given that the changes are not followed as time moves (Jiang et al., 2015).

In the case study under discussion, the aim was to see whether HbA1c can be the biomarker to assess the severity of DR, a significant complication of diabetes because of which individuals can become blind. Utilization of the cross-sectional data also gave insight into the association between the two factors at the particular moment, though it was possible to determine the importance and strength of the relationship between glycemic control in patients and their retinal well-being.

The number of participants entered into the research was 200; they all were diagnosed with diabetes of type 2. The sample was identified in a group of patients who use the diabetes care center of the hospital. Those who met the inclusion criteria of the study had to be adults aged 40 to 70 years with diabetes of type 2, diagnosed at least five years. This period was selected as the prevalence of microvascular problems including DR rise with chronic diabetes and the patients with a longer history of the disease demonstrate higher chances of retinopathy demonstration (Sivaprasad et al., 2012). Moreover, subjects in this age bracket were prone to attain age-related alterations in the retina, which might combine with the impacts of diabetes on the retina conditions.

People who had any form of ocular ailment other than DR, including glaucoma, age-related macular degeneration, or cataracts, were excluded in the exclusion criteria since those diseases could complicate the diagnosis of diabetic retinopathy. Besides, the subjects with diseases that might have the potential to affect the health of the retinas such as high blood pressure and high cholesterol have been also excluded. The risk of developing DR is also a known risk factor of high blood pressure (Chatziralli et al., 2016); hence it may influence the results obtained in the study because it would be hard to estimate the level of DR worsening exclusively on glycemic control of study participants. The other disorder that might worsen the effects of the microvascular damage of diabetes is hyper lypidemia, or elevated amounts of lipids in blood (Hussain et al., 2018). Hence, such comorbidities made it impossible to include participants with such conditions in order to rule out the influence of these other risk factors.

The data collected was broken down into two major samples: Measurement of HbA1c and imaging of the retina.

HbA1c Measurement:

HbA1c is one of the high powered biomarkers useful in evaluation of long term glycemic control in diabetic patients. HbA1c was analyzed in this research protocol by high-performance liquid chromatography (HPLC), a well-established technique to directly determine the quantity of hemoglobin glycated in principle blood samples productively (Levy et al., 2014). The HPLC method was selected because it is accurate and separates the HbA1c species with other hemoglobin forms, and therefore, no incorrect value will be reported and only glycated fraction will be measured. The technique enables clinicians to determine the state of glycemic control of the patient by having a clear indication on average blood glucose levels over the last 2- 3 months. HbA1c results were defined using typical clinical cut points where values above that of 7 percent may be an

indication of a suboptimal level of glycemic management (American Diabetes Association, 2020).

Retinal Imaging:

Fundus photography was performed to acquire retinal images; the process is non-invasive, and tissue is not damaged because the procedure permits the retinal vasculature to be viewed. The presence and the extent of diabetic retinopathy were determined in terms of the retinal images analysis. Although the retina imaging blueprint is essential in the clinical practice and determination, ocular fundus photography has been viewed as the gold standard in imaging retina and shall be used in the detection and monitoring of DR (Bressler et al., 2017). In the current study, the intensity of DR was determined on Early Treatment Diabetic Retinopathy Scale (ETDRS), and retinopathy may be ranked in five degrees, namely no retinopathy, mild non-proliferative diabetic retinopathy (NPDR), moderate NPDR, severe NPDR, and proliferative diabetic retinopathy (PDR). ETDRS is one of the most popular scales used in clinical practice and research and enables making a standardized evaluation of the degree of retinopathy (Early Treatment Diabetic Retinopathy Study Research Group, 1991).

Data Analysis:

Data obtained was exploited with SPSS version 26 to determine the correlation between the level of HbA1c and the degree of diabetic retinopathy. The data analysis was carried out upon several statistical means:

Descriptive statistics was performed to describe the characteristics of the participants in the study like age, gender, length of diabetes, and levels of HbA1c. To present the overview of demographic and clinical characteristics of the cohort, the variables were averaged, standard deviation, and frequency distributed to determine the mean, standard deviation, and frequency distribution of the variable.

A Pearson correlation coefficient was determined to analyze the connection between the amounts of HbA1c and the level of diabetic retinopathy. This statistical procedure was used to gauge the strength and direction of a linear relationship between two continuous measurements (HbA1c and severity of DR) (Field, 2013). The positive correlation would mean the higher the HbA1c level, the higher the severity of DR and vice versa would imply a negative correlation.

A regression model was utilised to see whether the increase of retinopathy could be predicted by HbA1c. The present model evaluated the possibilities of use of HbA1c as a predictive biomarker of DR severity, with consideration of the connection between HbA1c and retinopathy severity stages. The confounders, which were possible, were the age, gender, and duration of diabetes, which were adjusted in the regression model. The relevance of this analysis was because it wanted to establish the possibility of utilization of HbA1c as a clinical instrument in predicting the occurrence of DR (Sivaprasad et al., 2012). The output of the regression analysis was given in odds ratios, 95% confidence interval and p value of < 0.05 was significant.

The ethical standards in this study were observed as the research was approved by the institutional review board (IRB) of the hospital; this ensures that any medical research conducted on human subjects is ethical. All the participants were informed of what they consented to prior to their participation in the research. Study intentions, methods, potential problems, and benefits were explained to create awareness among the participants. Their participation in the study was promised to be voluntary and they could leave it at any moment without any penalty. In addition, all the collected data were confidential and their personal identifiers have been eliminated so that the identity of the participants is not revealed.

The ethical considerations were adhered to during the study. The anonymity of health data of the participants was observed, and the data were accurately stored. The research was also ethically sound since it was conducted in line with the declaration of Helsinki (World Medical Association, 2013) which stipulates ethical principles of medical research conducted on human participants.

RESULTS

The samples payoff was 200 people, by 120 men (60%) and 80 women (40%), of which average age was 56 years (SD = 8.3). Their age group was between 40-70 years; hence, the study included members in the age group most likely to suffer diabetic retinopathy (DR). The choice of this population is quite specific because they are supposed to represent individuals who have had a type 2 diabetes long enough because a longer diagnosis with diabetes is known to increase the possibility of developing DR (Klein et al., 2014). The average length of diabetes among the study population was 10.3 years (SD =3.2) as opposed to the average time it takes DR to develop in a person with long-term diabetes (Sivaprasad et al., 2012).

The mean HbA1c was 8.1 percent (SD = 1.3), implying that there was a higher risk of having poor glycemic control with an ideal glycemic level of 7 percent for those with diabetes (American Diabetes Association, 2020). HbA1c which is at an increased level means that the control of blood glucose has not been maintained over a long period and was in the past shown to be related to the higher chances of developing microvascular complications including DR (Sivaprasad et al., 2012). The variety of HbA1c values among the participants also made it possible to determine the dependence of the presence of different levels of glycemic control and the presence of DR.

All 200 participants had their retinal imaging done via the use of fundus photography to determine whether they had diabetic retinopathy and to what extent. Fundus photography is the established optical procedure that lets visualize the retina and helps diagnose DR with the high sensitivity and specificity (Bressler et al., 2017). The retinal images were graded as per the Early Treatment Diabetic Retinopathy Study (ETDRS) scale that divides DR into five levels that include: no retinopathy, mild non-proliferative diabetic retinopathy (NPDR), moderate NPDR, severe NPDR and proliferative diabetic retinopathy (PDR) (Early Treatment Diabetic Retinopathy Study Research Group, 1991).

The data showed that 45 percent of the respondents (n = 90) did not show any signs of retinopathy due to which it can be stated that almost the half of the participants in this

research either had concentrated levels of glucose in their blood or early stages of diabetes. No observable alteration of retinal vasculature was made by these people. Nevertheless, the other 55 percent of the respondents showed the presence of retinopathy in different levels. Out of them, 35% (n = 70) had non-proliferative retinopathy and it is defined by the distinctive alterations of the microvessels (management and treatment of retinal hemorrhages, microaneurysms, and hard exudates) but not the more severe changes of the proliferative process. The other 20 percent (n = 40) presented with proliferative diabetic retinopathy (PDR) or worsened form of DR due to the branching of new vesicles of weak blood vessels around the retina and frequently requiring severe vision loss and high risk of blindness occurrence (Sivaprasad et al., 2012).

One of the main notes within the imaging outcomes was that most people with NPDR and PDR had HbA1c elevations greater than 8%, and it can be correlated with the previous literature that has demonstrated a significant association between high levels of poor glycemic control and the risk of developing DR (Janghorbani et al., 2014). Namely, 72 percent of the participants with NPDR and 85 percent with the PDR had HbA1c levels of greater than 8 percent, which proves the assumption that the persistent hyperglycemia also has an impact on the advancement of the diabetic retinopathy (Klein et al., 2014). These results support the need to keep glycemic levels at the optimal level to reduce the risk of developing and treat DR.

Data analysis was conducted in SPSS version 26, and target of analysis concentrated on investigating the connection amid the level of HbA1c and the level of diabetic retinopathy. Descriptive statistics were used in the early stage to summarise the demographic and clinical makeup of the study participants.

The correlation between the level of HbA1c and the level of DR severity was performed with Pearson correlation coefficient. The assessment indicated that there was indeed a positive correlation between the level of HbA1c and severity of diabetic retinopathy as the correlation coefficient (r) was found to be 0.58 ($p < 0.01$). This outcome demonstrates that the relationship between the high HbA1c levels and worse stages of DR is positive and moderate-to-strong. That is to say that the higher the level of HbA1c was, the higher the severity of DR was, and those with a stronger HbA1c had more chances of being categorized as someone with NPDR or PDR. Earlier studies have also been able to exemplify a strong correlation that exists between inadequate glycemic management and advancing DR (Klein et al., 2014), corroborating the plausibility of these results.

The regression test was conducted in order to consider the question of the possibility to use HbA1c as the predictive factor in the development of DR. It was estimated by the odds ratio of the likelihoods of having advanced DR (NPDR or PDR) with each 1 percent increase in HbA1c. The results showed that an increment of HbA1c by 1% raised the odds of getting advanced DR by 1.5 times (OR= 1.5, 95% CI: 1.2-1.8, $p < 0.05$). The finding suggests that HbA1c is a significant predictor of the development of DR and

ensuing higher concentrations of HbA1c are tremendously connected with increased risk of moving towards more severe versions of the condition.

The statistical findings confirm the assumption that HbA1c at a high level is a vital element in the development and the development of diabetic retinopathy. The odds ratio shows that people with increased HbA1c levels are significantly more prone to developing more serious retinopathy, which can be compared to the results of the previous studies that identified the importance of glycemic control in the management of the development of DR (Sivaprasad et al., 2012). Besides, the association between the two parameters DR severity and HbA1c was strong indicating the value that monitoring of HbA1c would be in complete management of diabetes.

With a p-value < 0.01, one can say that the correlation between HbA1c and DR severity is significant, i.e. not likely to have come up by chance alone. It adds weight to the contention that HbA1c is a predictive factor of the occurrence and occurrence of DR. Also, on odds ratio, the 95 percent CI (1.2-1.8) implies that the relation between HbA1c and the severity of DR is reliable and consistent throughout the study population.

Subgroup analyses were further performed to determine whether or not any other variables including age and duration of diabetes had any effect on the connection between HbA1c and DR severity. These factors are found to increase the risk of DR (Sivaprasad et al., 2012), and their effect investigation might gain more insight into factors that increase the risk of developing the condition.

Age was not an important modulator of the relationship between HbA1c and the severity of DR which was observed in the analysis. Nonetheless, longer development of diabetes (over 10 years) was also observed to have greater connection between the HbA1c level and the severity of DR. This indicates that the presence of diabetes over time increases the effect on glycemic control on retinal health, which can be a reason why early treatment and intervention of glycemia control are critical in the early years of diabetes (Janghorbani et al., 2014).

CONCLUSION

Diabetic retinopathy (DR) is one of the major causes of visual impairment and blindness all over the world and specifically among patients who have diabetes mellitus. Considering the drastic effect of DR on the quality of life of diabetic patients, establishment of credible biomarkers to monitor the severity and progression of DR is paramount in effective management and intervention. The findings of this research paper outline strong pieces of evidence on the hypothesis that glycated hemoglobin (HbA1c) is an effective predictive biomarker of the intensity and course of DR. In particular, our results show that an increase in HbA1c level significantly correlates with severe DR stages, and poor glycemic control correlates with the quicker DR progress. This conclusion highlights the possible benefits of using HbA1c as an efficient, economical, and non-invasive method to screen the people who have a high risk of DR development.

The findings of this and other prior studies show that hyperglycemia expressed in terms of high HbA1c is a significant risk factor promoting the occurrence and worsening of DR

(Klein et al., 2014). HB1c elevation, indicating prolonged hyperglycemia (3 months), contributes to structural damage of the small vessels of the retina causing the characteristic manifestations of DR related to microaneurysms, retinal hemorrhages, and ultimately the proliferant retinopathy (Janghorbani et al., 2014). This positive relationship between HbA1c level and the intensity of DR shows that HbA1c level is a good indicator of determining the complication and risk of DR of diabetes.

With the results of the regression analysis, it is especially interesting to note that this qualification is an additional evidence that every 1% rise in A1c is associated with a 1.5 times higher potential of developing more developed DR, including proliferative diabetic retinopathy (PDR). This observation is in line with earlier research which has documented that poor glycemic control had a significant connection with the occurrence of worse manifestations of DR (Sivaprasad et al., 2012). It brings out the promise of using HbA1c as a predictive marker that has the ability to help clinicians focus on patients at least risk of developing advanced forms of DR and by so doing take the advantage of early intervention measures.

Detecting patients who are at increased risk of getting DR enables clinicians to act faster and help them avoid the deterioration of the condition. Careful diagnosis and initial intervention is of primary concern to avoid irreversible blindness in diabetic patients. Glycemic control is also critical to the extent that lower HbA1c levels will decrease the chances of progression of DR. The current clinical practice guidelines are to keep the HbA1c of persons with diabetes below 7% to minimize the risk of several microvascular complications, including DR (American Diabetes Association, 2020). Nevertheless, our results point to higher risks of developing more advanced forms of DR at only moderately higher HbA1c levels (i. e., above 8%), which demonstrates the significance of prompt and long-term glycemic control.

HbA1c as a screening method may be especially useful in the primary care where special retinal imaging techniques are not affordable or accessible by the reason of cost or absence. The HbA1c testing is a common diabetes management procedure and is accessible with frequency, which makes it a perfect indicator of detecting risk of DR before severe harm to the retina takes place. With the inclusion of HbA1c levels in regular screenings, the medical care professionals would know patients needing more intense eye examination or other measure that would prevent the development of DR. When DR is detected early, especially in people with higher levels of HbA1c, it is possible to intervene with laser therapy, anti-VEGF injections, or some other treatment that may prevent blindness (Bressler et al., 2017).

Nonetheless, although HbA1c has been proven to be a powerful prognosticator of the development of DR, it is critical to remember that it lacks perfection as a biomarker. A number of factors complicate the correlation between HbA1c and DR, such as length of diagnosis period, the occurrence of hypertension or hyperlipidemia, and genetics. As an example, investigations revealed that period of diabetes is a major determinant of the occurrence of DR with greater diagnosis period giving an increase in chances of obtaining late stages of the illness (Sivaprasad et al., 2012). Also, the developing of

comorbidities, like hypertension and hyperlipidemia, can enhance the consequences of hyperglycemia on the retina and contribute to the advancement of the disease (Chatziralli et al., 2016).

Thus, although HbA1c has high value as the indicator in predicting the degree of severity of DR, it must be applicable alongside with other clinical indicators and evaluation. An effective management plan of DR must incorporate routine eye assessment, blood pressure maintenance, management of lipids, and lifestyle changes among others besides attending to glycemic control. The combination of the prevention and management strategies will allow it to provide a wider perspective of the prevention and management of DR in diabetic individuals.

Though the study at hand is truly convincing in the predictive nature of HbA1c in the development of DR, there are still some crucial questions to solve, and further studies are necessary to elaborate these data. The influence of longitudinal data in comprehending the long-term association between HbA1c and DR is one of the areas that should be further researched. A longitudinal study design would give investigators an opportunity to monitor variations in HbA1c overtime and analyze how DR develops in accordance with the different ranges of glycemic control. These studies can offer excellent guidance regarding the benefits of consistent long-term blood glucose control as associated with lowering the risk of progression of DR, particularly on those who might have suffered seemingly poor glycemic control previously.

There is also a need to conduct a research to identify the potential of HbA1c variability in predicting DR. The variability of HbA1c, i.e., the variation of the blood glucose control over a period of time, has been found to have a significant influence on microvascular complications development, in particular DR (Monnier et al., 2013). Examining the correlation between HbA1c variability and DR may help us narrow down our knowledge about the importance of glycemic control for the prevention of DR and give more precise treatment advice.

Application of additional biomarkers together with HbA1c to determine severity of DR and its progression is another area of interest. Although HbA1c is a valuable measure of glycemic management, other biomarkers exposed as playing a role in the pathogenesis of DR, like cytokines in the serum, advanced glycation end-products (AGEs), and vascular endothelial growth factor (VEGF), can offer further information (Liu et al., 2019). The study of the synergism of a number of biomarkers can help to give rise to more adequate and individual models of prediction of the risk of developing DR and its evolution.

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