

## Glycosylated Hemoglobin and its Role as a Marker of Mortality in Severe Pneumonia by Covid-19

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### Abstract

Since the onset of the covid-19 pandemic in 2020, several aspects have been investigated to predict the prognosis of this disease, including glycosylated hemoglobin (HbA1c). Glycosylated hemoglobin has been studied as a prognostic value for different diseases, initially diabetes, cardiovascular problems, gestational diabetes and nowadays covid-19 pneumonia, HbA1c has been useful to prevent and predict possible complications and the risk of death in patients with covid-19. It has been described that patients with glycosylated hemoglobin values higher than 7% tend to have a higher risk, thus noting that HbA1c may be useful as a prognostic factor for severity and mortality in patients with poor glycemic control and Covid-19 pneumonia.

**Keywords:** Covid 19, Glycated Hemoglobin, Mortality

### Introduction

At the end of 2019, the World Health Organization reported several cases of unknown pneumonia in Wuhan China. Different PCR tests were performed, identifying a new type of coronavirus, which causes severe acute respiratory syndrome, which is why it was called Sars cov -2 and the disease that causes covid-19, from Wuhan, spread rapidly to different areas of China, with subsequent spread to various parts of the world resulting in an epidemic initially in China, followed by a major pandemic and current health emergency, Since then, efforts by the World Health Organization have been focused on creating a vaccine, promoting self-care, and improving the clinical management of covid19 [1-3, 5, 6].

Regarding the clinical characteristics, it generally has symptoms similar to those of the flu such as fever, myalgia, respiratory symptoms and in the most serious cases progress to pneumonia, leading to episodes of severe respiratory distress requiring hospitalization, even reaching intensive care [1, 4, 6, 9].

Most fatal cases have been reported in patients with various risk factors such as advanced age, underlying medical comorbidities such as cardiovascular disease, diabetes, mellitus, chronic lung disease, high blood pressure, and cancer [6].

In addition to the clinical factors of relevance, emphasis has also been placed on Investigating what are the prognostic factors or

what types of laboratory studies could help us establish a prognosis of severity in terms of covid-19 using methods such as radiological studies, quick sofa score, biomarkers such as troponin, natriuretic peptide, urea nitrogen, serum electrolytes, glycosylated hemoglobin, to establish prognoses of severity and / or mortality [5, 6, 9].

Glycosylated hemoglobin (HbA1c) is considered the Gold standard for evaluating blood glucose levels in three months. It should be noted that an elevated HbA1c level is related to an increased risk of complications in diabetic patients, little information is available about the increase in HbA1c levels and its relationship with hypercoagulable states and inflammation and mortality in patients with covid-19, the objective of this study is to describe the prognostic role of glycosylated hemoglobin in patients with covid-19 [2, 7, 8, 10, 11].

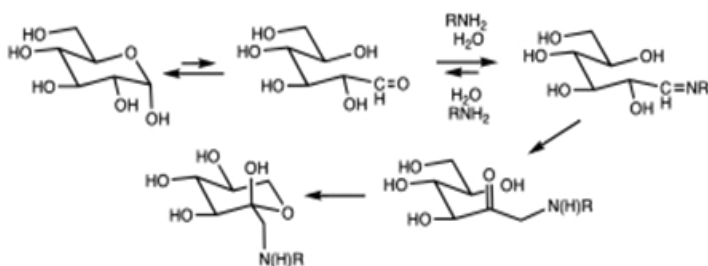
## Materials and Methods

A bibliographic search was carried out in databases such as PUB MED, SCIENCE DIRET, SCIELO from 2015 to 2021, using as keywords: glycosylated hemoglobin, Covid 19, prognosis, HbA1c, the initial search yielded a total of 97 articles, they were excluded those studies published in a language other than English or Spanish and those that did not have a full text available, leaving a total of 15 articles available for our review, including reviews, meta-analyses, clinical trials, then a careful reading of the information obtained was carried out in the studies found, in order to describe physiological aspects about HbA1c, its predictive value for the prognosis of various diseases and its relationship with poor prognosis in patients with Covid-19 pneumonia.

## Results

### Glycated Hemoglobin (Hba1c)

Hemoglobin is a protein found in red blood cells which is made up of two globin dimers associated with a heme group, hemoglobin represents different names depending on the dimer that makes up the molecule, having subtypes such as HbA, HbA2 HbF being the most important HbA [7].



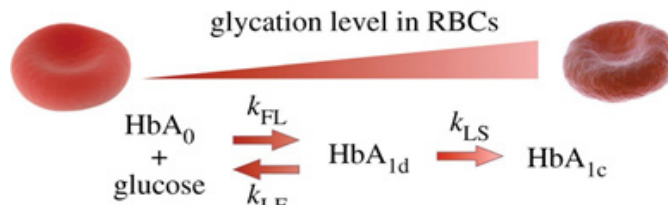
**Figure 1:** Chemical structure of HbA1c

The Hb components were identified and classified as A0, A1 and 1B and 1C. We have that glycosylated hemoglobin is important to predict the prognosis of various diseases such as diabetes mellitus, now glycosylation refers to the process of enzymatic alteration that changes the protein function, the half-life or the interprotein interactions of various proteins [7, 8].

Glycosylation refers to the non-enzymatic binding of glucose to an amino group of a protein, such as glycosylated hemoglobin,

albumin, fructosamine, among others [7, 8].

The first step in the glycosylation process refers to the condensation between the carbonyl group of glucose and the free primary amine of hemoglobin, achieving the formation of a schiff base or also called the early Maillard reaction [7, 8].



**Figure 2:** Simplified Scheme of Hemoglobin Glycosylation

In the case of HbA1c, glucose binding is achieved in covalent form with terminal valine residue Nh2 in the beta chain of HbA, glycosylation occurs at various sites, such as in the valine residue of the alpha chain in allisin of the chain alpha or beta as well as some types of hexoses such as fructose 1,6 bisphosphate or glucose 6 phosphate [8]. (table 1)

**Table 1: Types and components of HbA**

Types	Amine	Carbonyl
A1a1	Chain $\beta$	Fructose 1,6-diphosphate
A1a2	Chain $\beta$	Glucose 6-phosphate
A1b	Chain $\beta$	Pyruvate
A1c	Chain $\beta$	Glucose

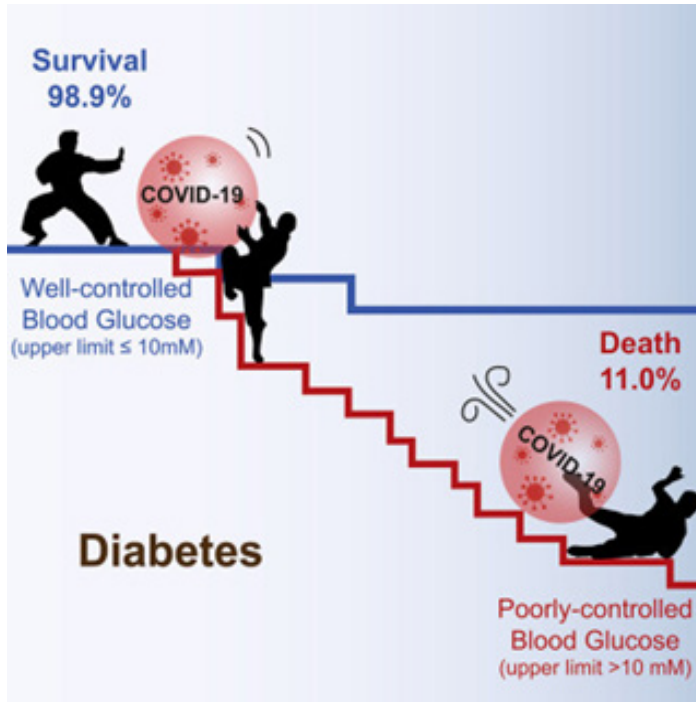
Hba1c as a Prognostic Factor in Patients with Covid 19 Pneumonia Glycosylated hemoglobin has been studied for many years to try to prevent and guarantee absolute protection against late complications of different diseases, the best known so far has been type 2 diabetes mellitus, so much so that there is registered evidence where it is established that HbA1c can help prevent complications such as retinopathy and diabetic nephropathy, this by analyzing HbA1c levels higher than 8% where it is considered a very high risk to suffer these complications [2, 5, 7, 10].

It should be noted that reference values have been established for HbA1c in terms of diabetes, we have that for non-diabetic people the normal is less than 5.7%, people with prediabetes within 5.7 to 6.4% and people with diabetes generally find between 6.5 or higher [10].

Finding that glycosylated hemoglobin values lower than 7% there is an evident decrease in the incidence of microvascular events such as acute myocardial infarction, non-fatal stroke and cerebrovascular accident, it should be noted that the literature reflects what if there is a 1% rise in HbA1c there is an 18% increase in cardiovascular disease [11].

Therefore, the association that exists between glucose and hemoglobin control with the possibility of adverse outcomes and death in patients with COVID-19 pneumonia has been written.

In addition, current scientific literature shows that the presence of type 2 diabetes mellitus is a risk factor for unfavorable results of covid-19, in addition to this it is established that better glycemic control in patients with pre-existing type 2 diabetes is directly associated with a significant reduction in adverse effects of covid-19 such as pneumonia, respiratory distress and death [10, 11, 12]. (fig 3)



**Figure 3:** Association scheme between glycemic control and complications of Covid 19

It is important to recognize that patients hospitalized in intensive care units with a diagnosis of covid-19 and in addition to this have associated diabetes mellitus or cardiovascular disease, high levels of glycosylated hemoglobin, have a greater risk of requiring mechanical ventilation or death, in addition, elevated HbA1c levels are associated with hypercoagulable states, inflammation, and decreased oxygen saturation level in patients with covid-19, another important fact, evidenced in the study carried out by Wang et al, where they were in charge of studying the predictive value of HbA1c for adverse prognosis in covid 19, finding that the association between elevated HbA1c referred to as a continuous variable and the adverse prognosis of Covid-19 was not significant, however, higher HbA1c levels considered as a dichotomous variable contributed to an increase in the mortality of patients with covid-19, noting that prolonged uncontrolled hyperglycemia increases the risk of adverse prognosis in covid 19, which means that patients with higher HbA1c must be strictly monitored to minimize the risk of adverse prognosis in covid 19 [10-12].

For this reason, emphasis is placed on glycemic control, which corresponds to a glycosylated hemoglobin of less than 7% since current evidence reveals that it could prevent the risk of infection by Covid -19 and its severity [10, 14].

## Discussion

The present study aims to describe glycosylated hemoglobin and its role as a marker of mortality in severe pneumonia due to COVID-19. Finding that the evidence currently recorded gives us to understand that today the diagnostic utility that glycosylated hemoglobin represents is directly related to diabetic patients, and it has also been determined that its increase is of utmost importance to predict mortality in patients who undergo with Covid -19 infection, different authors have investigated what other markers can be used to predict mortality in patients with Covid-19, such as the authors Ocampo et al. Conducted a review of the topic in 2020 about the prognostic value of cardiac biomarkers in Covid-19 disease, finding a total of 22 bibliographies, including observational studies and original articles, where they describe the clinical relationship and alteration of cardiac biomarkers and their relationship with the clinical evolution of patients with Covid-19. That it is reasonable to consider the use of biomarkers in risk stratification in patients with Covid-19 and established cardiovascular disease since troponin and natriuretic peptide behave as independent risk factors for clinical compromise. Severe requirement of ventilatory and hemodynamic support, stay in intensive care unit and increase of mortality in patients with Covid-19 and preexisting cardiovascular compromise [9, 15].

On the other hand, the work carried out by Wang and collaborators where they studied the association between glycosylated hemoglobin with systemic inflammation, hypercoagulability and prognosis of patients with Covid-19, where they additionally analyzed the levels of pcr, vsg, Il-6, ferritin, serum and oxygen saturation, finding that in those patients who had high glycosylated hemoglobin, the levels of Il-6, serum ferritin, pcr and vsg were also significantly elevated, but on the contrary the oxygen saturation was below the normal ranges, thus evidencing that a high level of glycosylated hemoglobin is associated with a state of inflammation, hypercoagulability and low oxygen saturation in patients with covid-19, thus increasing the mortality rate around 27.7% in patients with diabetes mellitus [10].

It is important to highlight that glycosylated hemoglobin is not only useful in patients with diabetes mellitus, but recent research has been responsible for studying the relationship of glycosylated hemoglobin with other diseases, among these we have the study carried out by Ling and collaborators, where they inquired about the impact that glycosylated hemoglobin had on the prognosis of patients with ischemic stroke treated with arterial thrombolysis, finding that In those patients where glycosylated hemoglobin levels were around 6.5, they showed a clinical improvement at the neurological level, verifying that the hemoglobin level glycosylated is directly associated with a neurological function with progressive improvement in patients with ischemic stroke treated with arterial thrombolysis and can be used as a serological indicator of poor prognosis for patients in these cases, giving important contribution about a of the utility as a prognostic factor of glycosylated hemoglobin in different pathologies, which provides us with valuable information about the prognostic utility of HbA1c in different pathologies, including Covid-19 pneumonia, Diabetes Mellitus, Acv, Cardiovascular disorders, which is consistent with the information obtained in our review [12, 13].

## Conclusion

Currently there is little information about the role of glycosylated hemoglobin as a prognostic factor for mortality in patients with covid-19, however it was found that different markers have been studied to establish a prognosis of mortality in patients with covid-19 as troponin, natriuretic peptide, in addition to glycosylated hemoglobin can serve as a prognostic factor for neurological deterioration in patients with stroke treated with arterial thrombolysis and as a prognosis of complications in patients with diabetes mellitus, it also has a direct association with states of inflammation and hypercoagulability, However, life found shows us which high levels of glycosylated hemoglobin are associated with higher mortality, exacerbation of clinical manifestations, supplemental oxygen requirement in patients with covid-19 pneumonia and associated risk factors, future research is recommended to complement the result ados obtained in our study.

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