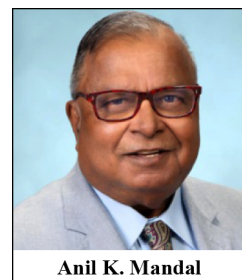


Diagnosis and Management of Diabetes and the Relationship of dGlucose to Kidney Function

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Abstract: This article reviews different glycemetic parameters and is aimed to clarify the most dependable glycemetic parameter that predicts renal preservation. Glycosylated hemoglobin (HbA1c) and fasting blood glucose (FBG) are the most commonly ordered tests for the diagnosis of diabetes and are also used to indicate prevention of microvascular complications associated with diabetes. Some experts have concluded that HbA1c remains the only test that can predict microvascular complications but HbA1c is misleading with anemia. Other experts have reported that elevation of 2 hour postprandial glucose (2hPPG) or postprandial hyperglycemia is critical for the development of diabetic complications

Measurement of parameters under fasting conditions is convenient in both clinical and research settings and are used to establish clinical guidelines for diabetes management and for rating efficacy of management. Despite the use of these diagnostic markers and a plethora of oral antidiabetic agents to treat diabetes, diabetic complications namely; cardiovascular disorders (CVD), end stage renal disease (ESRD) and amputation are on the rise.

Although affirmative data on many of the complications are not available, the United States Renal Data System on ESRD is a testimonial to poor diabetes care. We have innovated dglucose (2hPPG-FBG) and found that dglucose relates significantly to renal function change measured by serum creatinine levels or estimated glomerular filtration rate. Our current study on dglucose confirms our previous finding and validates the importance of dglucose to aid in the management of diabetes and prevents diabetic complications.

In conclusion, the new finding in this study is dglucose (2h-postprandial glucose-Fasting glucose) which convincingly relates to renal function changes. Since dglucose is a product of 2hPP glucose, keeping 2hPPG under tight control with intensive insulin therapy is fundamentally important. Further blood pressure control avoiding the use of renin-angiotensin inhibitor therapy is additive to renal protection in diabetes.

Keywords: Diabetes, kidney disease, dglucose, HbA1c, postprandial glucose, insulin, renal protection.

1. INTRODUCTION

Glycemetic parameters consist of fasting blood glucose (FBG), 2-hour postprandial glucose (2hPPG), in a random fashion or in a 4-hour oral glucose tolerance test (OGTT), and glycosylated hemoglobin (HbA1c). Results from these glycemetic parameters have been analyzed to determine which parameter is most sensitive for the diagnosis of diabetes. However, of greater importance is how well the parameter used for diagnosis and progression related to outcome measures of nephropathy, retinopathy or myocardial infarction. Our focus here is to weigh the validity of each glycemetic parameters in predicting the outcome measures and make recommendations to use a glycemetic parameter which will best predict changes in microvascular complications associated

with diabetes. It is important for the patients and treating doctors to understand that a high blood glucose level, equal to or above 200mg/dL (11.1 mmol/L), is alarming and it becomes essential for treating doctors to reduce the elevated glucose to reduce the anxiety of the patients. Which glycemetic parameters will the treating doctors order that best convince the patients that the glycemetic level is such that it does not increase the risk of developing complications such as retinopathy, neuropathy or nephropathy? This is the subject of discussion in this article. Let us now examine each of the glycemetic parameters separately to reach a decision.

2. GLYCOSYLATED HEMOGLOBIN (HBA1C)

In the clinical practice of diabetes, the conventional wisdom is to order HbA1c every 3months to monitor glycemetic control and adjust the therapy. The test is readily available, found to be reliable and correlates well with the risk of microvascular complications [1]. A recent opinion piece in the Journal of the American Medical Association concluded that HbA1c remains the only test that can predict the microvascu-

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lar complications of diabetes. HbA1c provides valuable information to help guide treatment decisions [2].

Despite the novelty of HbA1c in the diagnosis and prognostication of diabetes, advanced by some authors, shortcomings exist which reduces the validity of this test. For example, in a study comparing HbA1c screening with both FBG and 2-hour PPG, HbA1c had low sensitivity and high specificity for identifying diabetes and prediabetes. The authors concluded that the data supported greater use of OGTT and both FBG and 2hPPG values for diagnosis of diabetes and prediabetes [3]. Further, investigators wishing to determine the distribution of normal versus increased HbA1c levels in individuals who had undergone a 2-hour OGTT, found that nearly two-thirds diagnosed with diabetes *via* OGTT had normal HbA1c level [4]. Among Filipino-American, Japanese-American and native Hawaiians the use of HbA1c resulted in lower sensitivity and was estimated to have missed the diagnosis in 60% of those newly diagnosed with diabetes when compared with OGTT [5]. HbA1c can be misleading in patients with anemia including those with chronic kidney disease. Data from NHANES showed that in patients with high or low hemoglobin concentrations, HbA1c should be used with caution to diagnose diabetes or prediabetes, since changes in erythrocyte turnover may alter test results [6].

3. RELATIONSHIP OF GLYCEMIC PARAMETERS TO OUTCOME MEASURES

Let us examine the relationship of different glycemic parameters with outcome measures. A study of 26,543 women showed that baseline HbA1c is a good predictor for Type 2 diabetes, but not for cardiovascular health in middle-aged and older women [7].

Once again let us review how HbA1c and FBG, two most commonly ordered tests, predict outcome measures in diabetes. Pharmacologic interventions in diabetes are most commonly directed at lowering FBG and HbA1c. The reasons for that are historical. Testing under fasting conditions are convenient in both the clinical and research settings and have been used to establish clinical guidelines for diabetes management and for rating efficacy of management. Thus FBG and HbA1c have been the primary endpoints in landmark studies of diabetes. In 1995, the authors of the landmark Diabetes control and complications trial wrote: "Mean HbA1c is not the most complete expression of the degree of hyperglycemia. Other features of diabetic glucose control, which are not reflected by HbA1c, may add to or modify the risk of complications. For example the risk of complications may be more highly dependent on the extent of postprandial glycemic excursion [8]".

Another study examined systemically the relationship of all three glycemic parameters (FBG, 2h PPG and HbA1c) to two outcome measures consisting of retinopathy and nephropathy in Pima Indians in Gita River Indian Community, Arizona, USA [9]. The subjects were followed up for only five years. The development of complications within this time period suggests that the degrees of glycemia defined in this study also have long term prognostic relevance. Retinopathy and nephropathy have been shown to be strong predictors of the progression of diabetic complications including proliferative retinopathy, end stage renal disease

(ESRD), cardiovascular disease, amputation and mortality. This study encompassing the value of three glycemic parameters in predicting retinopathy and nephropathy is based on mainly complex statistical analysis. In general, longitudinally each of the three measures of glycemia significantly predicted the development of retinopathy ($P < 0.0001$) and nephropathy ($P < 0.05$). However, the authors concluded that HbA1c or FBG alone, may be acceptable alternatives to 2-h post challenge glucose [9].

4. POSTPRANDIAL HYPERGLYCEMIA

Fasting blood glucose (FBG) $> 126\text{mg/dL}$ (7mmol/L) and or HbA1c $> 6.5\%$ have traditionally been used as markers for the diagnosis and management of diabetes.

Despite the use of these diagnostic markers and a plethora of oral antidiabetic agents to treat diabetes, diabetic complications, namely, cardiovascular disorders (CVD), ESRD and lower limb amputation are on the rise. Although the affirmative data on many of the complications are not available, results from the United States Renal Data System on ESRD is a testimonial to poor diabetes care (Figs. 1 and 2). Therefore one can surmise that either the definition of diabetes or the prevalent therapy with oral antidiabetic agents or both are faulty [10].

Fig. (1) shows that in 1980, 1 in 11,000 new patients received dialysis compared to 1 in 2,800 patients in 2011. In 2011, eleven times more patients were treated with dialysis than in 1980. Fig. (2) shows that diabetes remains the most common cause of dialysis by counts and rates.

Abundant literature is available supporting the importance of postprandial hyperglycemia in the diagnosis and therapy of diabetes with a goal to prevent diabetic complications. The authors own studies have added further weight to the volume and novelties of postprandial hyperglycemia to improve diabetes care and reduce the risk of diabetes complications. Here are the key findings of some of the studies on postprandial hyperglycemia.

- Emerging evidence suggests that postprandial glucose levels may be better indicators of overall glucose homeostasis than fasting glucose levels. At least half, if not the majority of the 24-hour day, is spent in the postprandial period. Thus PPG levels best characterize overall glucose control [11].
- With regard to overt diabetes the Honolulu Heart study revealed a linear correlation between the 1-hour post challenge glucose level and risk of coronary heart disease [12].
- Similarly, the Diabetes Intervention study showed an association between 2-hour PPG values and an increased risk of death that was independent of fasting glucose [13].
- The Diabetes Epidemiology: Collaborative Analysis of Diagnostic criteria in Europe (DECOD) study, a retrospective analysis of about 25,000 patients with Type 2 diabetes throughout Europe, revealed a significant association between the 2-hour PPG and cardiovascular mortality. No relationship was seen between cardiovascular death and FBG [14].

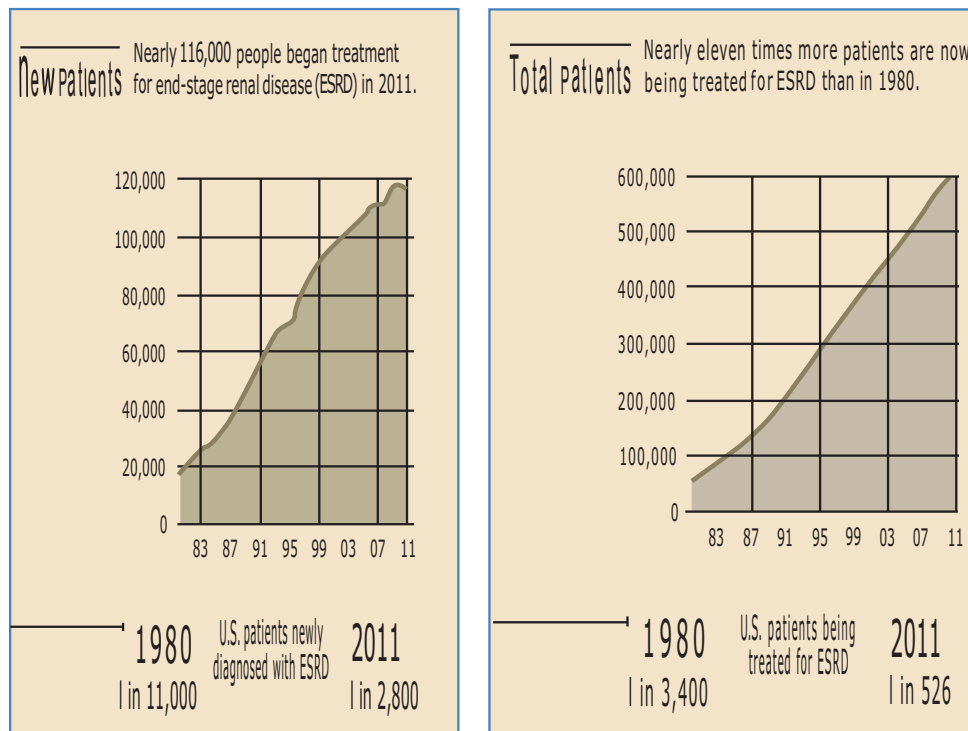


Fig. (1). End Stage Renal Disease in the United States.

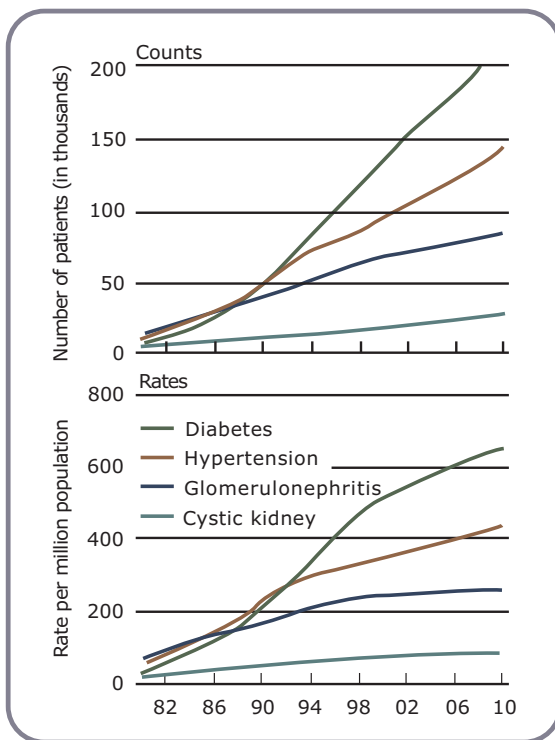


Fig. (2). US Renal Data System- Incidence of ESRD by Primary Diagnosis.

e. From a clinical standpoint, a 30 year study by Hass Lacher and associates showed a significant relationship between PPG levels and the time to development of nephropathy in 52 patients with Type 1 diabetes [15].

f. Lebovitz has put into perspective the pathogenesis and importance of postprandial hyperglycemia [16]. He stated that the initial consequence of insufficient insulin secretion in humans is deficient uptake and utilization of glucose by muscle. Muscle glucose uptake is the major mechanism by which postprandial plasma glucose is cleared. Thus the earliest abnormality of intermediary metabolism, which occurs in diabetes, is postprandial hyperglycemia. Approximately 50% of individuals with undiagnosed diabetes in the US have fasting plasma glucose which exceeds 11.1mmol/L. It is estimated that postprandial hyperglycemia persists for several years before fasting hyperglycemia occurs. He has stressed that regulating glycemic control by monitoring PPG is likely to achieve the best results. Further, correction of postprandial hyperglycemia appears likely to provide very significant benefits in reducing chronic diabetic complications [16].

g. In an article on “Postprandial hyperglycemia and glycemic variability: should we care?” by E. Standl and colleagues examined risk measures of postprandial hyperglycemia and glycemic variability on mainly cardiovascular complications of diabetes in 15 epidemiological studies. They concluded that the net balance of attained evidence is not in favor of the hypothesis that postprandial hyperglycemia is an important variable in the diagnosis and monitoring of cardiovascular complications associated with diabetes. In other words, we don’t need to worry about postprandial hyperglycemia [17]. There are two important shortcomings in this article stated in another article [18] which had stated that the alarmingly suggestive body of evidence for harmful effects of postprandial hyperglycemia on diabetes compli-

cations has been sufficient to influence guidelines from key professional societies. He went on to say that correcting postprandial hyperglycemia may form part of the strategy for the prevention and management of CVD in diabetes [18]. Thus the author himself contradicted his data and conclusions [18].

The greatest deficiency in all these articles including the epidemiological studies [17] is the total lack of information on pharmacologic interventions for diabetes used in these studies. No information was given as to how patients were treated in these studies. Unless postprandial hyperglycemia is treated adequately with insulin to reduce glucose levels, it will be most difficult to determine the uniformity of the harmful effects of uncontrolled postprandial hyperglycemia. In that regard, the key factor responsible for postprandial hyperglycemia is impaired early insulin secretion, however therapies are now available that specifically target postprandial hyperglycemia by improving early postprandial plasma insulin levels [19].

5. OUTCOME MEASURES

Outcome measures have focused on CVD associated with postprandial hyperglycemia. However, there is a paucity of data on the relationship between postprandial hyperglycemia and renal function changes. The aim of the authors' studies is to determine which of the glycemic parameters relates best to renal function changes and how will therapeutic interventions favorably affect this relationship.

- A single study from Italy confirmed that 2hPPG greater than 200mg/dL and HbA1c above 8% (established diabetes) is closely linked to a rapid decrease in GFR, whereas 2hPPG of less than 200mg/dL and HbA1c of less than 8% is associated with trivial or no change in GFR [20].
- Prevalent studies in diabetes have reported that intensive insulin therapy retards or prevents diabetic microvascular complications or diabetic nephropathy [21, 22]. Diabetic nephropathy is typically defined by proteinuria. The authors did not specify renal function changes determined by serum creatinine (Scr) or any measure of GFR. Currently GFR is an estimated GFR called eGFR. eGFR > 60ml/min is normal and <60 ml/min is abnormal or considered renal failure.
- Authors own studies.** Thus far, convincing evidence is lacking concerning the validity of any of the glycemic parameters including FBG, HbA1c or 2hPPG in predicting prevention of progression of diabetic nephropathy to ESRD. In order to obviate the dilemma concerning the validity of blood glucose levels between F and 2hPP, we have developed a novel approach with the introduction of dglucose, which is the difference between 2hPP and fasting glucose levels (2hPP-F). In order to relate the results of dglucose to renal function tests, we have correlated glucose with the same calculated difference for blood urea nitrogen (BUN or dBUN), Scr or dScr, and eGFR or deGFR [23]. Fifty-six adults with diabetes (29 females and 27 males) were studied. Ages ranged from 19 to 91 years with a mean of 68.7 + 13.5 years. F and

2hPP glucose levels and renal function panel, which included BUN, Scr and eGFR were prospectively obtained as part of the routine laboratory tests for regular office visits. eGFR was calculated from the modifications of diet in the renal disease equation as recommended by the National Kidney Foundation. [24]. All patients were treated with a combination of short-acting insulin, on a sliding scale and long acting insulin either NPH or Lantus. All patients monitor blood glucose levels at home; most patients check blood glucose before breakfast and dinner. A few check their blood glucose three to four times a day. For brevity, no distinction was made as to whether a patient has Type 1 or Type 2 diabetes, as in previous reports [25, 26]. Hypertension was treated with one or more drugs from a variety of different antihypertensive drug groups. These groups are beta blockers, namely atenolol or metoprolol; second generation dihydropyridine calcium channel blockers, namely amlodipine or isradipine; sympathetic inhibitors, namely clonidine; central inhibitors, namely alpha methyldopa; and the diuretic, chlorthalidone. The most common combination used was atenolol and amlodipine. Angiotensin converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) were not used in any patient. Pearson correlation coefficients were calculated to describe the relationship between F, 2hPP, or 2hPP minus F glucose levels (dglucose) and differences in F, 2hPP, or 2hPP minus F (d) BUN, Scr or eGFR. As well, Pearson correlation coefficients were used to describe relationships between HbA1c or average glucose and F, BUN, Scr or eGFR in 42 patients. All inferences were made where $P < 0.05$ was considered statistically significant. The correlation between dglucose and dBUN was not statistically significant. The correlation coefficients between dglucose and dScr ($r = 0.420$) and between dglucose and deGFR ($r = -0.434$) were statistically significant, $p = 0.0013$ and 0.0008 respectively.

The regression between dglucose and dScr and dglucose and deGFR are presented in Figs. (3A) and (3B). For every 100 mg/dL increase in dglucose, the dSCR increased by 0.08 mg/dl and deGFR decreased by 2.73 ml/min. In addition, the values for dglucose and dSCR and eGFR were divided based on whether the 2hPP glucose values were greater than 200 mg/dl or less than 200 mg/dL and correlation coefficient were calculated. As shown in Fig. (3A), a strong positive correlation is seen between dglucose and dSCR when 2hPP glucose was greater than 200 mg/dL ($r = 0.523$; $P = 0.0018$) but not in patients whose 2hPP glucose was less than 200 mg/dL. ($r = 0.142$, $p = 0.5180$) Fig. (3A). Similarly, a strong negative correlation is seen between dglucose and deGFR in patients with dglucose greater than 200 mg/dL ($r = -0.513$, $p = 0.0023$) but not in patients with 2hPP glucose less than 200mg/dL ($r = 0.064$; $p = 0.7723$) (Fig. 3B).

Average glucose and HbA1c were poorly correlated with fasting renal function parameters and showed low r and non-significant p values (Table 1).

Thus our studies demonstrate that 2hPP glucose levels can be used as an important marker to predict renal function changes in diabetes. We have enhanced the value of 2hPP

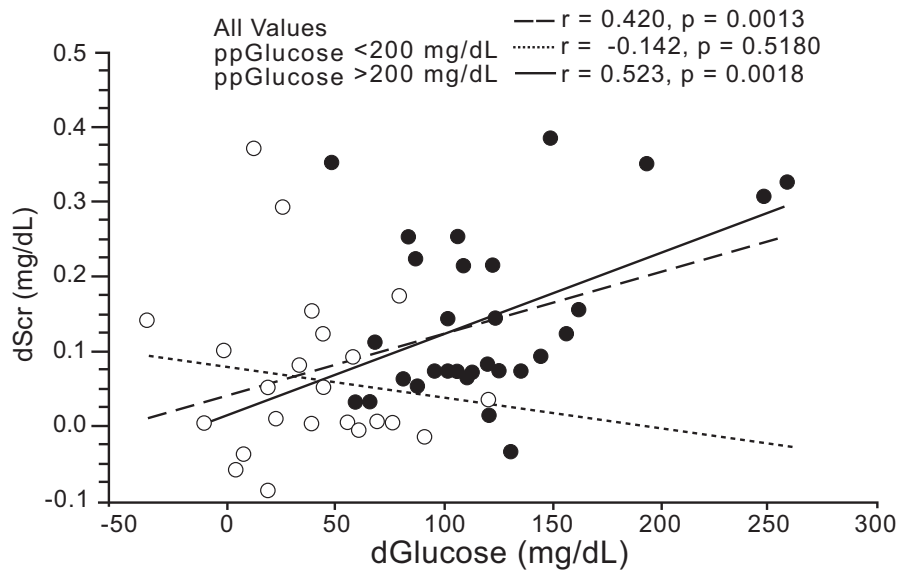


Fig. (3A). Regression between dglucose and dScr.

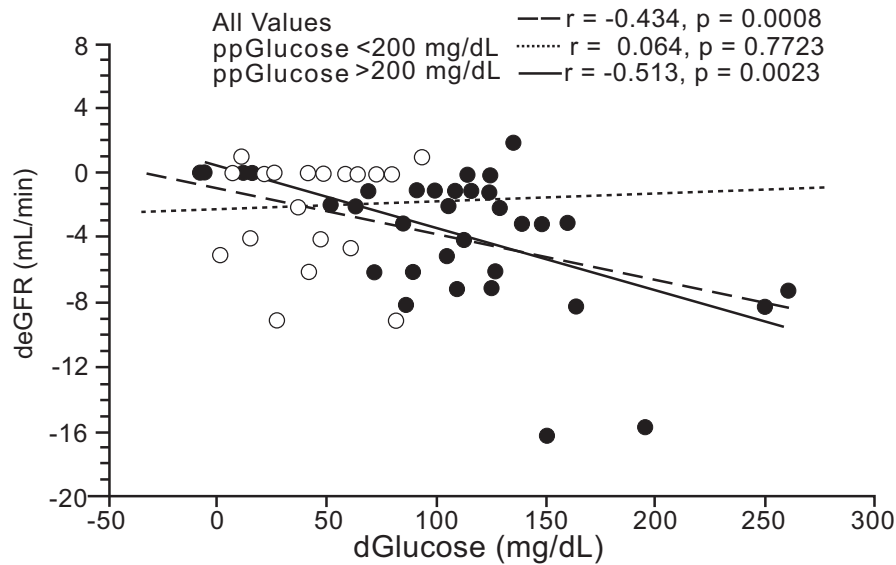


Fig. (3B). Regression between dglucose and deGFR.

Table 1. Correlation coefficients and p values for HbA1c or average glucose and fasting BUN,Scr and eGFR,

	HbA1c		Average Glucose	
	Correlation Coefficient (r)	p Values	Correlation Coefficient (r)	p Values
F BUN	0.137	0.3987	0.135	0.4455
FScr	0.233	0.1485	0.275	0.1152
F eGFR	-0.127	0.4360	-0.69	0.3401

F- Fasting, Scr- Serum Creatinine, eGFR-estimated glomerular filtration rate.

glucose by innovating dglucose (2hPPG-FBG). Our current study is an expanded study consisting of more patients and longer duration of follow-up (26months). All patients in the current diabetes cohort are treated with a combination of Glargine or detemir insulin and aspart or regular insulin. The current study shows that dglucose is significantly reduced in

these diabetes cohorts and dglucose significantly relates to dScr as before when dglucose is greater than 50 mg/dL (un-published data).

Thus, when considering glycemic parameters such as HbA1c, FBG, 2hPP glucose and dglucose, elevated dglucose may be most predictive of progression to kidney failure. An

important question is how one can reduce dglucose. Dglucose levels will be higher if 2hPP glucose is much higher than FBG. Thus the quintessential goal is to reduce 2hPPG which can be achieved with insulin but not metformin (unpublished data).

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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