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Co-Relation Between Level of HbA1c and Depth of Diabetic Foot Ulcer

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Abstract **Original Research Article**

Background: Diabetic foot is a common complication of diabetes mellitus (DM). The Wagner classification is mostly used to grade its severity. Diabetic peripheral neuropathy (DPN) a disease often associated with neuropathic pain, foot ulceration and lower extremity amputation, which can significantly affect the quality of life of patients. To determine the severity of diabetic foot ulcer at various level of HBA1C and determine the association. ***Methods:*** An observational cross-sectional study was carried out at Department of surgery, Rangamati Medical College, Rangamati, Bangladesh from January to December 2022 with 100 diabetic patients who after giving consent filled questionnaires. The relationships between the HbA1c levels of the patients with the Wagner and PEDIS (Perfusion, Extent, Dept, Infection, Sensation) classification system grades, and the surgical procedures performed were analyzed and the treatment outcomes were evaluated. ***Results:*** The study included Sample size of 100 Patients. Here in the study mean age for group A was 41.2 years, for group B it was 29.6 years and for group C it was 25.8 years. There was significant difference found between these groups as p value was <0.05. It was observed that all the patients in group A were overweight. In group B majority 44.6% patients normal followed by 44.4% obese patients and 13.8% overweight patient. In group C we found that majority 48.5% patients were normal followed by 31.9% obese patients. Majority 40% patients in group A had T2DM. In group B we found that 52% patients had T2DM followed by 48% patients with T1DM. In group C we found that majority 67% patients had T2DM. It was observed that majority 60% patients in group A had no vasculopathy followed by 40% patients with post tibial art vasculopathy. We found that site of ulcer was improving with increasing duration of follow up. Initially we found 30% patients with infection at dorsum aspect of foot. After follow up day 6 we found improvement in ulcer infection. ***Conclusions:*** This research further supplemented an already strongly established association between uncontrolled diabetes and diabetic foot ulcer. We focused on specifically HBA1C and how increased lab values are linked with different grades of Diabetic Foot ulcer and found a strong association demanding a proactive approach towards patient care and education. HbA1c has a linear relationship with the grades of Wagner classification of diabetic foot.

Keywords: Glycated Hemoglobin, Foot ulcer, Diabetes.

INTRODUCTION

Diabetic foot is a common complication of diabetes mellitus (DM). The Wagner classification is mostly used to grade its severity [1]. Diabetic peripheral neuropathy (DPN) a disease often associated with neuropathic pain, foot ulceration and lower extremity amputation, which can significantly affect the quality of life of patients [2,3]. The most frequent type of neuropathy associated with diabetic foot complications is the distal symmetric sensorimotor polyneuropathy, and, along with peripheric vascular disease, it is a major contributing factor to the formation of foot ulcers [3]. According to the American Diabetes Association (ADA), a glycated hemoglobin (HbA1c) level ≥6.5% is recommended for diagnosis of diabetes, while pre-diabetic patients could be diagnosed with HbA1c levels in the range of 5.7% to 6.4%. Typically, diabetic foot syndrome is characterized by foot infection, ulceration, or destruction of deep tissues in association with neurological abnormalities and divergent levels of peripheral vascular insufficiency. Diabetic foot ulcer and infections are associated with substantial morbidity and mortality. An estimated 2.5% of diabetics develop

diabetic foot ulcers each year, and 15% develop diabetic foot during their life time [4-6]. A healthy, intact diabetic foot is indeed best maintained by a consistent and recurrent preventive treatment strategy accomplished through a multidisciplinary approach that encompasses instruction in Glucose assessment, insulin and other diabetes medication administration, regarding medical surveillance, a common strategy to evaluate the effectiveness of DM treatment is the use of a biomarker. A biomarker is a "characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes or pharmacological responses to a therapeutic intervention" [7]. Specifically, for the case of DM, the levels of glycated hemoglobin (HbA1c or hemoglobin A1c) are periodically measured, as glycemic variability has been recognized as the most important risk factor for DPN. Management of diabetic foot ulcers. The gold standard for diabetic foot ulcer management includes prevention, patient and caregiver education, glycemic control, debridement of the wound, management of any infection, revascularization procedures when indicated, off-loading of the ulcer and reconstructive surgery if needed. HbA1c can be used as a diagnostic test for diabetes providing that stringent quality assurance tests are in place and assays are standardized to criteria aligned to the international reference values, and there are no conditions present which preclude its accurate measurement. An HbA1c of 6.5% is recommended as the cut point for diagnosing diabetes. A value of less than 6.5% does not exclude diabetes diagnosed using glucose tests. After that discovery, numerous small studies were conducted correlating it to glucose measurements resulting in the idea that HbA1c could be used as an objective measure of glycaemic control. HbA1c was introduced into clinical use in the 1980s and subsequently has become a cornerstone of clinical practice [8]. HbA1c reflects average plasma glucose over the previous eight to 12 weeks [9]. It can be performed at any time of the day and does not require any special preparation such as fasting. These properties have made it the preferred test for assessing glycaemic control in people with diabetes. More recently, there has been substantial interest in using it as a diagnostic test for diabetes and as a screening test for persons at high risk of diabetes [10]. Owing in large part to the inconvenience of measuring fasting plasma glucose levels or performing an OGTT, and day-to-day variability in glucose, an alternative to glucose measurements for the diagnosis of diabetes has long been sought. HbA1c has now been recommended by an International Committee and by the ADA as a means to diagnose diabetes [10-13]. Although it gives equal or almost equal sensitivity and specificity to a fasting or post-load glucose measurement as a predictor of prevalent retinopathy, it is not available in many parts of the world. Also, many people identified as having diabetes based on HbA1c will not have diabetes by direct glucose measurement and vice versa. The relationship between HbA1c and prevalent retinopathy is similar to that of plasma glucose, whether glucose and HbA1c are plotted in deciles, in vigintiles or as continuous variables. These analyses were designed to inform current deliberations on possible revisions to the diagnostic criteria for diabetes.

METHODS

An observational cross-sectional study was carried out at Department of surgery, Rangamati Medical College, Rangamati, Bangladesh from January to December 2022 with 100 diabetic patients who after giving consent filled questionnaires. The relationships between the HbA1c levels of the patients with the Wagner and PEDIS (Perfusion, Extent, Dept, Infection, Sensation) classification system grades, and the surgical procedures performed were analyzed and the treatment outcomes were evaluated.

Inclusion Criteria

The inclusion criteria were: association between HBA1c, DPN and diabetic foot complications, HBA1c levels between groups with and without DPN and diabetic foot complications and age of the patient.

Exclusion Criteria

Exclusion criteria were; juvenile diabetes, patients with inflammatory or infectious diseases, autoimmune and rheumatic diseases, cancer, hematological diseases and those who were under treatment with anti-inflammatory drugs, pregnant and lactating female were excluded. Patient with recent venous thromboembolism.

Procedure

All the patients having diabetes with foot ulceration in the department of surgery at CMC Hospital were taken into the research study. Foot ulcer was defined as a full-thickness skin defect that required. Then Clinical Examination was done with focus on General, Regional and Local Examination of the ulcersite. The laboratory investigations include testing for random blood glucose for diabetic patients. Differential diagnosis was established and patients were categorized into diabetic and non-diabetic patients. Study design was observational cross-sectional study and study variables includes age, gender, HbA1c, CBC, serum glucose, electrolytes. Urea and creatinine level, gram stain, culture and sensitivity, type of ulcer, length of hospital stay and mortality. Clinical assessment for signs of infection (swelling, exudates, surrounding cellulitis, odour, tissue necrosis, crepitation, pyrexia). Ulcer size was determined by multiplying longest and widest diameters and expressed in centimetres square.

General examination includes assessing the general condition of the patient which includes general appearance of the patient, lymph nodes, checking vital signs such as pulse, blood pressure, respiration rate. Systemic examination includes examining cardio-vascular system, respiratory system, digestive system, excretory system and nervous system.

Examination of abdomen was done to rule out any lump, any free fluid or organomegaly. Co Morbidity was looked for Diabetes Mellitus which can be controlled or uncontrolled, nephrotic syndrome, transplanted patient, obesity on immune suppression and on corticosteroid. Local examination of the ulcer: Wound colour, Type of ulcer, Local edema, Discharge colour, Discharge amount, Smell and Content.

Wound was graded and staged at time of hospitalization according to University of Texas Wound classification system as grade 1 (superficial wound not involving tendon, capsule or bone), grade 2 (wound penetrating to tendon or capsule) and grade 3 (wound penetrating bone or joint) three groups of patients were made: Group A with HBA1c upto 6, Group B with HbA1c upto 7, Group C with HBA1c more than 7. Diabetic peripheral neuropathy was seen for the symptoms whether it is sensory motor or autonomous.

Data Analysis

Data were entered and analyzed using SPSS Version 20 (IBM Corp., Armonk, NY, USA). Mean and the standard deviation were calculated for age and HbA1c level. Frequency and percentage for range of age, range of HbA1c, gender, duration of DM, grades of Wagner classification, and other risk factors of foot ulcers (foot abnormalities, nephropathy, neuropathy, hypertension, retinopathy, foot ulcers/toe amputation, cognitive deficit, and cardiovascular diseases) were also calculated. Correlation of HbA1c with Wagner classification was also calculated, the chi-square test was applied, and $p \leq 0.05$ was considered as significant.

RESULTS

The study included Sample size of 100 Patients. It was observed that mean age for group A was 41.2 years, for group B it was 29.6 years and for group C it was 25.8 years. There was significant difference found between these groups as p value was <0.05. It was observed that all the patients in group A were overweight. In group B majority 44.6% patients normal followed by 44.4% obese patients and 13.8% overweight patient. In group C we found that majority 48.5% patients were normal followed by 31.9% obese patients.

Table 1: Distribution of patients according to age

Age (years)	Group A (HbA1C <7)		Group B (HbA1C (7-8)		Group C (HbA1C >8)	
	N	%	N	%	N	%
25-40	2	50.00	11	30.5	10	16.6
41-55	2	50.00	14	39.0	18	30.0
>55	0	0.00	11	30.5	32	53.4
Total	4	100.00	36	100.00	60	100.00
Mean±SD	41.2±12.04		29.6±0.5		25.8±1.09	
p value	<0.0001					

Table 2: Distribution of patients according to BMI

BMI	Group A (HbA1C <7)		Group B (HbA1C (7-8)		Group C (HbA1C >8)	
	N	%	N	%	N	%
Overweight	4	100.00	5	13.8	12	20.0
Obese	0	0.00	15	41.6	29	48.4
Normal	0	0.00	16	44.4	19	31.9
Total	4	100.00	36	100.00	60	100.00
p value	0.13					

Table 3: Distribution of patients according to duration of diabetes mellitus.

Parameter	Group A (HbA1C <7)		Group B (HbA1C (7-8)		Group C (HbA1C >8)	
	Mean	SD	Mean	SD	Mean	SD
Duration of diabetes mellitus	15	0	14.2	5.4	15.04	4.8
p value	0.04					

Table 4: Distribution of patients according to grades

Grades	Group A (HbA1C <7)		Group B (HbA1C (7-8)		Group C (HbA1C >8)	
	N	%	N	%	N	%
One	0	0.00	2	5.5	2	3.3
Two	0	0.00	4	11.0	5	8.3
Three	0	0.00	9	25.0	21	35.0
Four	4	100.00	14	38.8	16	26.6
Five	0	0.00	7	19.4	16	26.6
Total	4	100.00	36	100.00	60	100.00
p value	0.47					

Table 5: Distribution of patients according to neuropathy

Neuropathy	Group A (HbA1C <7)		Group B (HbA1C (7-8)		Group C (HbA1C >8)	
	N	%	N	%	N	%
Motor neuropathy	4	100.00	7	19.4	19	31.6
No neuropathy	0	0.00	10	27.8	13	21.6
Sensory neuropathy	0	0.00	19	52.8	28	46.8
Total	4	100.00	36	100.00	60	100.00
p value	0.2					

It was observed that mean duration of diabetes mellitus for group A, group B and group C was 15 years, 14.2 years and 15.04years. There was significant difference found between these group as p value was patients had sensory neuropathy followed by 31.6% patients with motor neuropathy.

Table 6: Distribution of patients according to vasculopathy

Vasculopathy	Group A (HbA1C <7)		Group B (HbA1C (7-8)		Group C (HbA1C >8)	
	N	%	N	%	N	%
Ant tibial art vasculopathy	0	0.00	9	25.0	13	21.6
Post tibial art vasculopathy	2	50.00	22	61.1	30	50.0
No vasculopathy	2	50.00	5	13.9	17	28.4
Total	4	100.00	36	100.00	60	100.00
p value	0.05					

Table 7: Distribution of patients according to chronic kidney disease

Vasculopathy	Group A (HbA1C <7)		Group B (HbA1C (7-8)		Group C (HbA1C >8)	
	N	%	N	%	N	%
Ant tibial art vasculopathy	0	0.00	9	25.0	13	21.6
Post tibial art vasculopathy	2	50.00	22	61.1	30	50.0
No vasculopathy	2	50.00	5	13.9	17	28.4
Total	4	100.00	36	100.00	60	100.00
p value	0.05					

It was observed that majority 50% patients in group A had no vasculopathy followed by 50% patients with post tibial art vasculopathy. In group B we found that 61.1% patients had post tibial art vasculopathy followed by 25% patients with ant tibial art vasculopathy. In group C we found that majority 50% patients had post tibial art vasculopathy. It was observed that 50% patients in group A, 61.1% patients in group B and 50% patients in group C had chronic kidney disease.

Table 8: Distribution of patients according to wound infection

Wound infection	Group A (HbA1C <7)		Group B (HbA1C (7-8)		Group C (HbA1C >8)	
	N	%	N	%	N	%
Mild	2	50.00	7	19.4	13	21.6
Moderate	2	50.00	17	47.2	39	65.0
Severe	0	0.00	12	33.4	8	13.4
Total	4	100.00	36	100.00	60	100.00
p value	0.04					

There was significant difference found between these group as p value was <0.05. It was observed that in group A 50% patients had moderate type wound infection followed by 50% mild infection. In group B we found that majority 47.2% patients in group B had moderate infection followed by 33.4% patients had severe infection. In group C we found that majority 65% patients were of moderate infection followed by 21.6% patients of mild infection.

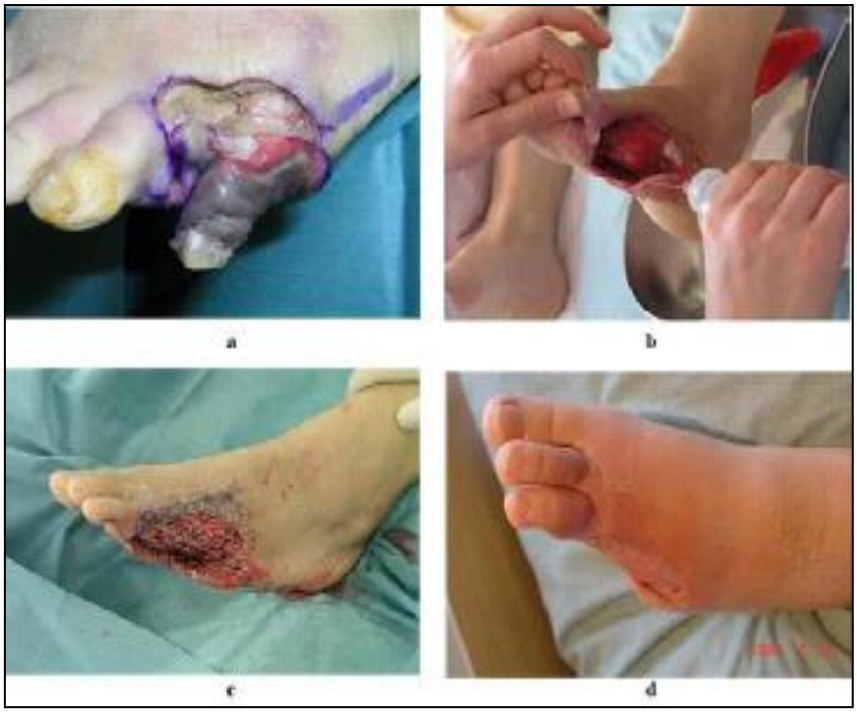

Figure 1: A view of diabetic foot gangrene with a) osteomyelitis of the fifth toe, b) After fourth and fifth toe amputation, cleansing was performed for 2 weeks, c) Intraoperative view showing free skin grafting on the wound, d) A view of the foot 1 month after surgery showing favorable coverage of the wound.

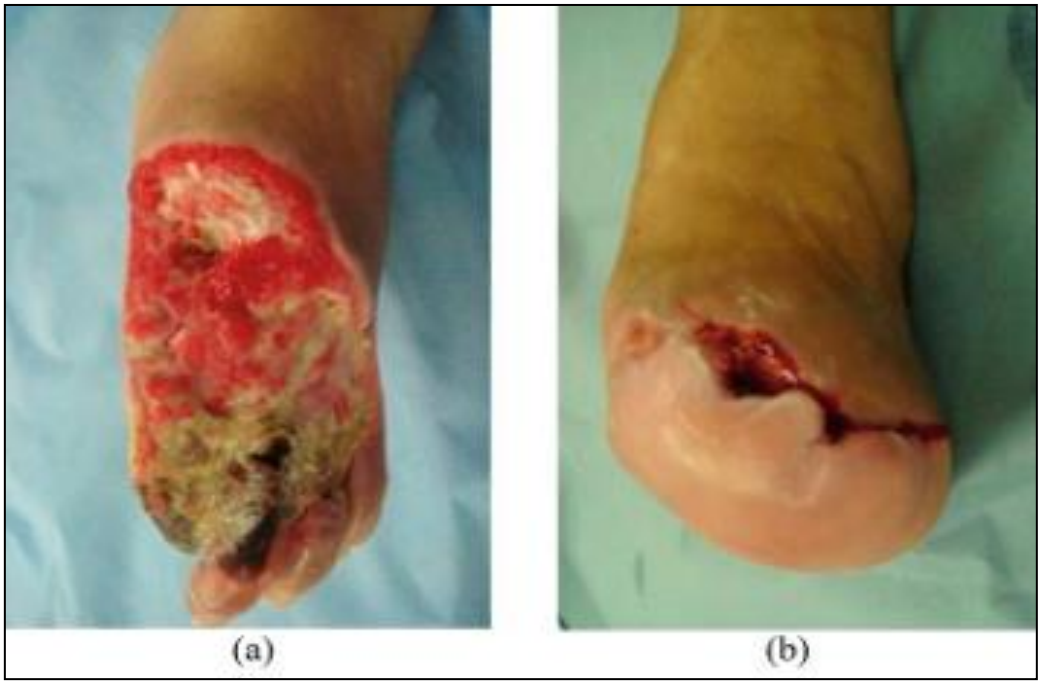

Figure 2: A view of diabetic gangrene extending the first and second metatarsal bones, a) After removal of the necrotic bone, the navicular was exposed, b) Intraoperative view of Chopart amputation followed by resurfacing with a local flap of the sole.

There was significant difference found between these group as p value was<0.05. It was observed that majority 100% patients in group A had gangrene. In group B we found that 58.6% patients had gangrene. In group C we had seen gangrene in 57.7% patients (Figure 1-2).

DISCUSSION

Mobility-limiting diabetic foot is characterized by ulcers, infections, and foot ischemia, making it the most common cause of hospitalization and amputation in patients with DM. In addition, 20% of DFUs do not heal within one year [15], and even if healing is achieved, an

average of 40% of cases recur within one year [16]. Thus, diabetic foot has a variety of effects on patients and increases healthcare costs [17]. The progression of diabetic foot highlights the challenges of clinical management, complex patient management, and sustained protective care. Poor glycemic control can impair all stages of physiological wound healing, complicate wound healing, and lead to chronic wounds. Therefore, the standard approach to the care and treatment of patients with diabetic foot aims to prevent infection and other complications through glycemic control [18, 19]. Furthermore, peripheral nerve dysfunction is often associated with peripheral arterial disease, which can lead to inadequate blood supply to the limbs, a condition known as diabetic vasculopathy, and lead to the development of diabetic foot. Yes, people with diabetes can suffer from neuropathy, nerve ischemia, or ischemia of the foot alone [9]. Diabetic foot syndrome includes several diabetic foot pathologies, including infection, neuropathic osteoarthritis, and diabetic foot ulcers. Diabetic foot accounts for approximately 15% of these cases and is expected to reach up to 25% of cases, making it the most dangerous condition that can lead to amputation [20]. HbA1c has received particular attention from researchers and has been studied extensively in relation to diabetic foot ulcers, gangrene, and amputation. HbA1c reflects glycemic control over the past 2-3 months, and its role in diabetes management is well established [21]. In preliminary studies, controlling HbA1c to 6.5 was associated with macrovascular and microvascular complications, which dramatically reduced symptoms. Although previous studies have suggested that lower baseline HbA1c correlates with wound healing progression, most studies have found that baseline HbA1c is not associated with wound healing in the lower extremities of diabetic patients [22]. Baseline HbA1c values were described by Fesseha *et al.*, Based on analyses using various adjustment models, dividing the described values by 8.0%, initial blood glucose levels showed no association with wound healing [23]. Our study showed similar results. DFUs are characterized by poor healing outcomes, and hyperglycemia was identified as a cause of impaired wound healing. The main causes of delayed wound healing are pre-existing diabetic vasculopathy and neuropathy due to previous exposure to hyperglycemia. Moreover, the current burden of hyperglycemia is also associated with impaired wound healing processes. Accumulating evidence indicates that hyperglycemia-associated advanced glycation end products play a key role in disrupting the normal wound healing process, with underlying mechanisms including increased oxidative stress, altered cell proliferation and apoptosis, and altered cell-extracellular matrix interactions playing a role [24,25]. The existence of foot ulcers attracts more attention to hyperglycemia. Research by Fesseha et al showed that increase of HbA1c during the treatment compared to admission was associated with a hazard ratio (HR) of nearly 2 for wound healing in DFU patients with baseline HbA1c< 7.5%, while no associated benefit was observed for DFU patients with baseline HbA1c over 7.5%. For the purpose of wound healing, this demands that blood glucose be controlled at higher levels if the initial HbA1c value is less than 7.5%. In our study, HbA1c controlled within 7.0-8.0% during DFU treatment is beneficial for wound healing; this advantage was even more evident in DFU patients with baseline HbA1c less than 8.0%. Additionally, in contrast to those with HbA1c controlled at less than 7%, the wound healing rate was almost the same or slightly better in DFU patients with HbA1c higher than 8.0% during DFU treatment. Tight blood glucose control characterized by lower HbA1c level often leads to more frequent episodes of hypoglycemia as some large clinical trials demonstrated [26-30]. For elderly diabetic patients with long diabetes duration, such as patients with DFU, fluctuation of blood glucose is relatively more prevalent. In general, mortality rate increases as the glycemic level elevates for patients with diabetes. However, the mortality pattern was different in various disease statuses of diabetes. For older patients with diabetes, mortality risk was significantly higher in those with an HbA1c > 8.0% compared with those with an HbA1c >8.0% compared with those with an HbA1c <6.5%.24 For patients with diabetes and chronic kidney disease, a U-shaped relationship between HbA1c and mortality was observed; HbA1c <6.0% and ≥9.0% were associated with higher risk of death [31,32].

DFU patients, who are in an advanced stage of diabetes, are significantly different from normal diabetic patients. The association between HbA1c and mortality may be specific to DFU patients. Currently, there are no relevant studies on the relationship between blood glucose levels and mortality in DFU patients. According to the 1-year follow-up results, mortality was not significantly associated with the level of glycemic control [33–35]. Several limitations of our study should not be ignored. First, this is a single-center observational study. All participants were admitted to the hospital, which inevitably resulted in selection bias. Second, the subjects of this study were hospitalized patients with relatively poor conditions. Clinical patients with small wounds and good general condition were not included. Therefore, the results cannot be generalized to the general population with diabetic foot ulcers. Third, the follow-up period was not long enough, making it impossible to observe longer-term results.

CONCLUSIONS

Because HbA1c is linearly associated with the Wagner grade of diabetic foot, HbA1c can be used as a screening tool to predict the occurrence of HbA1c in the above diabetic patients at high risk for diabetic foot. Patients at high risk for diabetic foot include older patients, male patients, patients with a long duration of DM, elevated HbA1c, and patients with existing foot abnormalities. This is important to prevent diabetic foot and its associated complications such as amputation,

infection, disability, and death through improved HbA1c control and awareness of proper foot care, as strict glycemic control reduces diabetic neuropathy and vascular complications. It helps to reduce the frequency of the disease. However, further large-scale studies are needed to clarify the true relationship between HbA1c and Wagner classification.

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