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Research Article

PREVALENCE AND PREDICTORS OF DIABETIC RETINOPATHY WITH SPECIAL EMPHASIS ON HIGH URIC ACID AMONG TYPE 2 DIABETIC PATIENTS

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A R T I C L E I N F O

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A B S T R A C T

Background: Diabetic retinopathy is the most common microvascular complication of diabetes. It is leading cause of preventable blindness in all age-groups and put a significant burden on health services. Evidence suggests the role of uric acid in diabetic retinopathy. **Objectives:** To estimate the prevalence and define the risk factors, particularly high serum uric acid of diabetic retinopathy among type 2 diabetic patients.
Methods: This is a retrospective cross sectional study performed on type 2 diabetic patients at the University Diabetes Center, King Abdul-Aziz University Hospital, Riyadh, Saudi Arabia, and the laboratory work was done at Strategic Center for Diabetes Research, King Saud University. **Results:** The study included 433 type 2 diabetic patients. Most of them (78.5%) aged over 50 years. Females represent 56.1% of the patients. The prevalence of diabetic retinopathy was 47.3%. Multivariate logistic regression analysis revealed that compared to patients aged 50 years or less, those aged more than 50 years were at 55% less risk to develop DR (Adjusted odds ratio "AOR"=0.45; 95% confidence interval "CI": 0.24-0.83, p=0.010). Compared to patients treated with oral hypoglycemic only, those treated with insulin only or both oral hypoglycemic and insulin were at increased risk for DR (AOR=4.68; 95%CI: 1.89-11.53, p=0.001 and AOR=3.71; 95%CI: 2.09-6.59, p<0.001, respectively). Those with hypertension were at higher risk for DR compared to those without it (AOR=1.69; 95%CI: 1.01-2.92, p=0.049). Patients with other chronic diseases were at higher risk for DR than others (AOR=1.93; 95%CI: 1.04-3.59, p=0.038). Considering patients without diabetic neuropathy or nephropathy as reference categories, those with diabetic neuropathy or nephropathy were at almost double risk of developing DR (AOR=1.85; 95%CI: 1.15-2.97, p=0.010 and AOR=1.78; 95%CI: 1.04-3.04, p=0.035, respectively). Increase in the levels of creatinine or HbA1c% by one unit was significantly associated with increase in the risk of DR (AOR=1.13; 95%CI: 1.01-1.28, p=0.047 and AOR=1.15; 95%CI: 1.01-1.33, p=0.049, respectively). High serum uric was not significantly associated with DR, after controlling for confounding effect. **Conclusion:** Diabetic retinopathy is prevalent among type 2 diabetic patients attending the University Diabetes Center, King Abdul-Aziz University Hospital, Riyadh, Saudi Arabia with some identified determinants; however, association with serum uric acid is not conclusive.

INTRODUCTION

Diabetes mellitus is common chronic endocrine problem and one of the most fast-growing health problems in the world, and is now reaching to epidemic proportion in Saudi Arabia [(1)].The prevalence of diabetes in Saudi Arabia (23.9%) at 2013, So Saudi Arabia at the Top 10 countries with higher prevalence of diabetes and the number of patients with diabetes are increasing in every country within time [(2)].

Diabetic retinopathy is the most common microvascular complication of diabetes. It is leading cause of preventable blindness in all age-groups and put a significant burden on health services [(3)]. The prevalence of Diabetic retinopathy Among Saudi population is 31% after a mean duration of diabetes more than 10 years (4). There is strong association between duration of diabetes and the incidence and severity of diabetic retinopathy [(4)]. In addition to diabetes duration, uncontrol glucose, hypertension and dyslipidemia are the main risk factors for development of retinopathy in all groups, presence of nephropathy associated with sever retinopathy in all age groups as a significant complication[(5)].

Serum uric acid is the end product of purine metabolism [(6)]. In the purine metabolic pathway, the adenosine has vasoactive properties which play a role in retinal blood flow. It produces superoxide nitric oxide that affect the retinal circulation by causing capillary occlusion, apoptosis of pericytes and thickening of basement membrane [(7)]. A substrate of xanthine oxidase (Xanthine), promote superoxide production and causing microvascular dysfunction, tissue damage resulting in lipid and protein peroxidation [(6)]. These changes are clearly seen in pathogenesis of retinopathy in diabetic patient.

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Multiple base evidence studies suggest that uric acid has a role in the etiology of type 2 diabetes mellitus [8, 9]. In 1950, Griffiths M [10] reported the role of serum uric acid in diabetes and suggested that high levels are associated with increased risk of developing type 2 diabetic complications. Various other studies have similar findings [11, 12]. Goldberg RB [13], referred proatherogenic properties of serum uric acid to be accountable for the pathogenesis of diabetic retinopathy and other diabetic vascular complications. These include the activation of endothelial cells and platelets and increase in platelet adhesiveness. Navin S *et al*. [6] also concluded that not controlledglycemia in type 2 diabetes was associated with high serum uric acid level and lipid disorder, which might be the initial ongoing biochemical change in the complication of diabetes.

In review of various evidences suggesting the role of uric acid in diabetic complication, our study conducted to see the association between high uric acid and incidence and progression of diabetic retinopathy.

Patients and methods

This is a retrospective cross sectional study is a part of ongoing study. The study was performed on subjects who were participated in a previous study in project titled "Important diagnostic biomarkers in prediction and progression of nephropathy in patients with type 2 diabetes" (Project No: E-10-140), and a follow up study for same group with study titled "Role of serum and urinary biomarkers in the progression of Diabetic Nephropathy in T2 diabetic Saudi Population: A follow up study", (IRB# E-19-3969).

The study was conducted on at the University Diabetes Center, King Abdul-Aziz University Hospital, Riyadh, Saudi Arabia, and the laboratory work was done at Strategic Center for Diabetes Research, King Saud University.

Statistical analysis

Data entry and statistical analysis were performed using the Statistical Package for Social Sciences (SPSS), version 25. Categorical variables were presented in the form of frequency and percentage while continuous variables were presented as median interquartile range (IQR) and mean rank as they were abnormally distributed as evidenced by significant Shapiro-Wilk test. For univariate analysis, chi-square test was applied to test for association between categorical variables whereas Mann-Whitney and Kruskal-Wallis tests were applied to compare two groups and more than two groups, respectively. Multivariate logistic regression analysis was done, including significant variables from univariate analysis, to control for the confounding effects. Statistical significance was determined at $p<0.05$.

RESULTS

The study included 433 type 2 diabetic patients. Table 1 summarizes their personal characteristics. Most of them (78.5%) aged over 50 years. Females represent 56.1% of them. Smoking and practicing recommended exercise were mentioned by 2.5% and 15.9% of the patients whereas following a diabetic diet was reported among 27.9% of them.
Duration of diabetes ranged between 10 and 15 years among more than half of patients (52%). Family history of diabetes and renal diseases were observed among 85.9% and 18.2% of patients, respectively. More than one-third of patients (38.6%) were treated by both oral hypoglycemic and insulin whereas 18% were treated by insulin only. Table 2

The commonest reported complications of diabetes were Nephropathy (57.3%) and neuropathy (49.7%) whereas the prevalence of diabetic retinopathy was 47.3% as illustrated in Figure 1

Hyperlipidemia and hypertension were reported among majority of the participants (82.2% and 70.2%, respectively). Figure 2

Factors associated with diabetic retinopathy
-Categorical variables

Diabetic patients aged 50 years or less were more likely to develop diabetic retinopathy compared to older patients (66.7% versus 48.8%), p=0.002. Patients whose duration of DM ranged between 16 and 20 years were more likely than those with shorter duration to develop DR (57.7% versus 37.8%), p<0.001. Majority of patients treated with only insulin (74.4%) compared to 22.1% of those treated with only oral hypoglycemic medications had DR, p<0.001. Patients who did not follow diabetic diet were more likely than their counterparts to develop DR (51.6% versus 36.4%), p=0.004. Also, patients who did not practice physical recommendations were more likely than their counterparts to develop DR (51.4% versus 26.1%), p<0.001. Hypertension patients were more likely than non-hypertension patients to develop DR (54.3% 32.3%), p<0.001. Also, those with thyroid diseases were more likely than those without to develop DR (58.1% versus 44.7%), p=0.027. Similarly, patients with other similar diseases were at higher risk for having DR than others (59.5% versus 44.6%), p=0.016. Patients with history of nephropathy were more likely to develop DR that others (60.5% versus 29.7%), p<0.001. Similarly, those with history of neuropathy were more likely to develop DR that others (55.8% versus 39%), p<0.001. Table 3
-Continuous parameters

Table 4 shows that levels of systolic blood pressure (p<0.001), uric acid (p=0.014), HbA1c (p=0.017), triglycerides (p=0.005), and creatinine (p<0.001) were significantly higher in patients with diabetic retinopathy. On the other hand, hemoglobin level was significantly lower in patients with DR, p<0.001.

Multivariate logistic regression analysis

Multivariate logistic regression analysis revealed that compared to patients aged 50 years or less, those aged more than 50 years were at 55% less risk to develop DR (Adjusted odds ratio "AOR"=0.45; 95% confidence interval "CI": 0.24-0.83, p=0.010). Compared to patients treated with oral hypoglycemic only, those treated with insulin only or both oral hypoglycemic and insulin were at increased risk for DR (AOR=4.68; 95%CI: 1.89-11.53, p=0.001 and AOR=3.71; 95%CI: 2.09-6.59, p<0.001, respectively). Those with hypertension were at higher risk for DR compared to those without it (AOR=1.69; 95%CI: 1.01-2.92, p=0.049). Patients with other chronic diseases were at higher risk for DR than others (AOR=1.93; 95%CI: 1.04-3.59, p=0.038). Considering patients without diabetic neuropathy or nephropathy as reference categories, those with diabetic neuropathy or nephropathy were at almost double risk of developing DR (AOR=1.85; 95%CI: 1.15-2.97, p=0.010 and AOR=1.78; 95%CI: 1.04-3.04, p=0.035, respectively). Increase in the levels of creatinine or HbA1c% by one unit was significantly

associated with increase in the risk of DR (AOR=1.13; 95%CI: 1.01-1.28, p=0.047 and AOR=1.15; 95%CI: 1.01-1.33, p=0.049, respectively). Systolic blood pressure, uric acid, triglycerides, duration of diabetes, following a diabetic diet, practicing recommended exercise, and thyroid diseases were not significantly associated with DR. Table 5

Table 1 Personal characteristics of type 2 diabetic patients participated in the study

	Frequency	Percentage
Age (years)		
≤50	93	21.5
>50	340	78.5
Gender		
Male	190	43.9
Female	243	56.1
Smoking		
No	422	97.5
Yes	11	2.5
Following a diabetic Diet		
No	312	72.1
Yes	121	27.9
Practicing recommended exercise		
No	364	84.1
Yes	69	15.9

Table 2 Diabetes related characteristics of the participants

	Frequency	Percentage
Duration of diabetes (years)		
10-15	225	52.0
16-20	208	48.0
Family history of diabetes		
No	61	14.1
Yes	372	85.9
Family history of renal diseases		
No	354	81.8
Yes	79	18.2
Medication		
Oral hypoglycemic	140	32.3
Insulin	78	18.0
Both	167	38.6
None	48	11.1

Table 3 Factors associated with diabetic retinopathy among type 2 diabetic patients

	Retinopathy		p-value
	No N=228 N (%)	Yes N=205 N (%)	
Age (Years)			
≤50 (n=93)	31 (33.3)	62 (66.7)	
>50 (n=340)	174 (51.2)	166 (48.8)	0.002
Gender			
Male (n=190)	107 (56.3)	83 (43.7)	
Female (n=243)	121 (49.8)	122 (50.2)	0.177
Duration of diabetes (years)			
10-15 (n=225)	140 (62.2)	85 (37.8)	
16-20 (n=208)	88 (42.3)	120 (57.7)	<0.001
Diabetes medication			
Oral hypoglycemics (n=140)	109 (77.9)	31 (22.1)	
Insulin (n=78)	20 (25.6)	58 (74.4)	
Both (n=167)	80 (47.9)	87 (52.1)	
None (n=48)	19 (39.6)	29 (60.4)	<0.001
Following a diabetic diet			
No (n=312)	151 (48.4)	161 (51.6)	
Yes (n=121)	77 (63.6)	44 (36.4)	0.004
Practicing recommended exercise			
No (n=364)	177 (48.6)	187 (51.4)	
Yes (n=69)	51 (73.9)	18 (26.1)	<0.001
History of smoking			
No (n=422)	223 (52.8)	199 (47.2)	
Yes (n=11)	5 (45.5)	6 (54.5)	0.628
Family history of diabetes			
No (n=60)	31 (51.7)	29 (48.3)	
Yes (n=372)	197 (53.0)	175 (47.0)	0.853
Family history of renal diseases			
No (n=343)	178 (51.9)	165 (48.1)	
Yes (n=79)	43 (54.4)	36 (45.6)	0.684
History of hypertension			
No (n=124)	84 (67.7)	40 (32.3)	
Yes (n=304)	139 (45.7)	165 (54.3)	<0.001
History of hyperlipidemia			
No (n=75)	43 (57.3)	32 (42.7)	
Yes (n=356)	185 (52.0)	171 (48.0)	0.397
History of thyroid diseases			
No (n=333)	184 (55.3)	149 (44.7)	
Yes (n=86)	36 (41.9)	50 (58.1)	0.027
History of other diseases			
No (n=350)	194 (55.4)	156 (44.6)	
Yes (n=79)	32 (40.5)	47 (59.5)	0.016
History of nephropathy			
No (n=185)	130 (70.3)	55 (29.7)	
Yes (n=248)	98 (39.5)	150 (60.5)	<0.001
History of vasculopathy			
No (n=339)	184 (54.3)	155 (45.7)	
Yes (n=81)	35 (43.2)	46 (56.8)	0.073
History of neuropathy			
No (n=218)	133 (61.0)	85 (39.0)	
Yes (n=215)	95 (44.2)	120 (55.8)	<0.001

Table 4 Comparison of different continuous parameters between patients with and those without diabetic retinopathy

	Diabetic retinopathy						p-value*
	No			Yes			
	Median	IQR	Mean rank	Median	IQR	Mean rank	
BMI	31.29	28.06-35.45	216.11	31.60	27.04-35.96	216.94	0.945
Hip circumference	106	100-116	208.69	110	99.25-118	221.13	0.299
Waist circumference	104	95.25-114	207.56	106	98-116	227.50	0.098
Systolic blood pressure	133	120-143	186.04	142	129-160	246.64	<0.001
Diastolic blood pressure	74	67-81	219.04	72	65-81	209.38	0.420
Uric acid	5.1	4.2-6.3	202.93	5.5	4.65-6.7	232.65	0.014
Blood glucose	197.70	139.8-250.84	209.03	208.13	149.02-271.52	219.59	0.377
HbA1c	9.86	8.63-11.14	202.86	10.34	9.27-11.44	231.60	0.017
Cholesterol	178.94	145.49-209.3	212.10	176.64	151.97-215.0	220.38	0.491
LDL	127.33	99.35-161.09	221.29	124.57	193.56-157.63	208.00	0.268
HDL	42.73	36.38-51.54	216.51	43.25	36.43-50.54	212.29	0.724
Triglycerides	155.14	105.42-220.82	200.01	176.89	130.48-237.08	233.63	0.005
Creatinine	1.04	0.85-1.32	187.32	1.24	0.94-5.02	243.37	<0.001
Hemoglobin	13.50	11.72-14.80	228.14	12.60	10.80-13.98	186.46	<0.001

*Mann-Whitney test
BMI: Body mass index
HbA1c: Glycosylated hemoglobin
LDL: Low density lipoprotein
HDL: High density lipoprotein

Table 5 Predictors of diabetic retinopathy: Results of multivariate logistic regression analysis

	B	SE	AOR	95%CI	p-value
Age (Years)					
≤50 (n=93)[a]	-		1.0		
>50 (n=340)	0.800	0.312	0.45	0.24-0.83	0.010
Diabetes medication					
Oral hypoglycemics (n=140)			1.0		
Insulin (n=78)[a]	1.541	0.461	4.68	1.89-11.53	0.001
Both (n=167)	1.311	0.293	3.71	2.09-6.59	<0.001
None (n=48)	0.828	0.500	2.29	0.86-6.10	0.097
History of hypertension					
No (n=124)[a]			1.0		
Yes (n=304)	0.524	0.279	1.69	1.01-2.92	0.049
History of other diseases					
No (n=350)[a]			1.0		
Yes (n=79)	0.658	0.316	1.93	1.04-3.59	0.038

History of neuropathy					
No (n=218)[a]			1.0		
Yes (n=215)	0.616	0.214	1.85	1.15-2.97	0.010
History of nephropathy					
No (n=185)[a]			1.0		
Yes (n=248)	0.576	0.273	1.78	1.04-3.04	0.035
Creatinine	0.121	0.065	1.13	1.01-1.28	0.047
HbA1c	0.137	0.074	1.15	1.01-1.33	0.049

[a]: Reference category B: Slop SE: Standard error
AOR: Adjusted odds ratio CI: Confidence interval

Terms of systolic blood pressure, uric acid, triglycerides, duration of diabetes, following a diabetic diet, practicing recommended exercise, and thyroid diseases were removed from the final regression model.

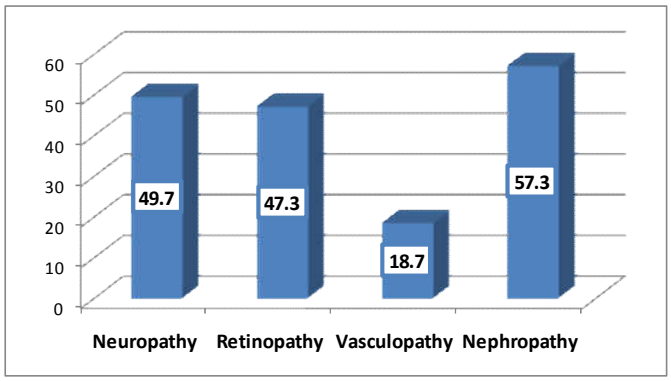

Figure 1 Prevalence of diabetic complications among the participants

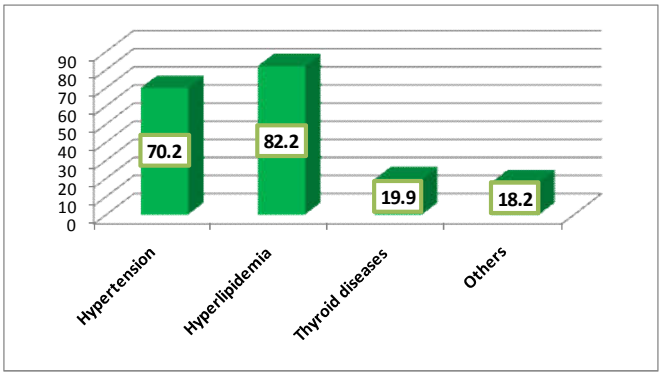

Figure 2 History of other chronic diseases among the participants

DISCUSSION

Diabetic retinopathy (DR) is one of the micro-vascular complications of diabetes a leading cause of blindness, if not discovered and treated early.[8] Exploring the magnitude of the problem and defining its risk factors are necessary in achieving better management of the status at earlier stages, therefore this study was conducted to estimate the prevalence and identify determinants of DR among type II diabetes mellitus patients registered in King Abdul-Aziz University Hospital, Riyadh, Saudi Arabia.

The prevalence of diabetic retinopathy in the current study is relatively high (47.3%). This figure is higher than those reported in other local studies. In Abha (2016),[14] the prevalence was 36.4%. In Jazan (2015), it was 27.8%.[15]In Al-Madinah Al-Munawara (2012), 36.1% of diabetic patients had DR.[16]In Al Hasa Region of Saudi Arabia (2010), the prevalence was 30%.[17]. In Taif (2012), it was 36.8%.[18].

Regarding International studies, the age-adjusted prevalence of DR in China (2017) was 27.9% whereas the gender-adjusted rate was 12.6%.[19]. In Spain (2015), 12.3% of type 2 diabetic patients had DR.[20]. Also lower rates than reported in the present study were observed in studies carried out in UAE (19%),[21] Kuwait (12%),[22] 34.1% in Jordan (34.1%) [23] Egypt (20.5%),[24] Iran (26.6%).[25] However, comparable result was reported in Oman (42.4%).[26]A pooled analysis of data from eight population-based eye surveys done among DM patients in the United States in 2004 revealed a prevalence of 40.3%.[27]On the other hand, higher rate was reported in another Jordanian study (64%)[28]

The variation in the prevalence of DR between various studies could be explained by application of different techniques to diagnose DR as well as difference in the socio-demographic and clinical characteristics of patients in various studies.

In the present study, patients with longer duration of diabetes were at higher risk for DR in univariate analysis. However, after controlling for confounders in multivariate logistic regression analysis, this effect disappeared. This is could be attributed to the fact that in the present study, the duration of diabetes ranged between 10 and 20 years. In most of other studies,[14, 16, 21, 25, 29] patients with longer duration of DM were at higher risk for having DR.

In the current study, patients treated with insulin or a combination of insulin and oral hypoglycemic were at higher risk for developing DR than those treated with oral hypoglycemic only. The same has been documented by others.[14, 30-32]However, in a study carried out in Taif by Alharthi *et al*,[29]DR was more reported among patients treated by oral hypoglycemic drugs only and least among those treated by both insulin and oral hypoglycemic drugs. The mechanism of the link between DR and insulin utilization is not clear till now.

Patients with other diabetic complications, particularly neuropathy and nephropathy were at greater risk for DR in the current study, even after controlling for confounders. Moreover, increase in serum creatinine level was a significant predictor for development of DR in both univariate and multivariate analyses. Other studies observed an association between diabetic neuropathy and nephropathy from one side and DR from the other side.[14, 33] A recent published systematic review revealed an association between DR and all other micro and macro-vascular complications of diabetes.[34]
In accordance with many numerous studies,[14, 16, 29, 34] the current study revealed that patients with uncontrolled diabetes, evidenced by higher level of glycated hemoglobin were at higher risk to develop DR compared to those with controlled disease.

Contrary to what had been reported by others [14], younger patients in the present study were at higher risk for DR compared to older patients. However, in the current study most patients were old as the mean age was almost 55 years. In the present survey and in accordance with others,[14, 28, 29] hypertension was significantly associated with the development of DR.

The present study revealed that increased serum uric acid level was a significant factor for DR in univariate analysis. However, after controlling for confounders in multivariate analysis, its effect became insignificant. In another study carried out in Taiwan,[35] elevated serum uric acid concentration was significantly associated with DR and its severity, even in multivariate analysis.

In India (2019), Manickam S *et al* observed that serum uric acid was significantly higher in patients with micro vascular complications of diabetes than those without such complications.[36] Additionally, Lia L-X *et al* (2015) in china showed a significant decrease in the prevalence of DR in patients across the urine uric acid excretion quartiles after adjustment for age, gender and duration of diabetes and this effect remained in multiple logistic regression analyses. [37] Cai XL, *et al* reported an association between level of serum uric acid and severity of DR.[38]

The mechanism of the association between elevated serum uric acid and microvascular diabetic complications, including DR could be explained by inhibition of endothelial nitric oxide synthetase and activation of the renin-angiotensin system. [39] Also, the direct effect of elevated serum uric acid on endothelial cells and vascular smooth muscle cells could lead to microvascular complications. [40]

The present study has some limitations that should be addressed. First of all, it is a single-center study; therefore its findings cannot be generalized over the entire population of type 2 diabetic patients in Riyadh. However, this center is one of the biggest in Riyadh and many cases of complicated DM were referred to it, which could partially explain the high prevalence of DR observed in this study. Additionally, the cross-sectional design is considered a limitation due to its problems in the cause-effect temporal relationship. Despite of those limitations, the study has an adequate sample size and investigated many risk factors for DR.

CONCLUSION AND RECOMMENDATIONS

Diabetic retinopathy is prevalent among type 2 diabetic patients attending the University Diabetes Center, King Abdul-Aziz University Hospital, Riyadh, Saudi Arabia. Determinants for the development of DR among type 2 diabetic patients were age, treatment with insulin, hypertension and other chronic diseases, diabetic neuropathy and nephropathy, higher levels of creatinine and glycated hemoglobin. Association with serum uric acid is not conclusive.

According to the study`s results, the following are recommended:

1. Screening for DR among all diabetic patients, particularly for those treated with insulin, having neuropathy or nephropathy and those with high HbA1c.
2. Raising awareness of diabetic patients for annual retinal examination and having controlled blood sugar.
3. Further study is needed including patients from other healthcare facilities in Riyadh to have clearer image of the situation.

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