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Original Research Article

GLYCOSYLATED HEMOGLOBIN HBA1C AS A BIOMARKER FOR DIABETIC RETINOPATHY

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Abstract: *Diabetes Mellitus (DM) is a long-term metabolic disorder marked by hyperglycemia. Diabetes may lead to various complications like retinopathy. Diabetic retinopathy is a microvascular disorder that may lead to vision loss. It was a hospital-based study to determine the prevalence of diabetic retinopathy in chronic diabetic patients. Patients who visited DHQ and Al Sheikh Hospital Sialkot with blurry or poor vision were taken as samples. The sample size for this study was 100. The demographic and medical history of patients were taken through a questionnaire. These patients were checked by an experienced ophthalmologist after the pupil dilation. After the proper examination, it was suggested that a patient have an HbA1c test to monitor diabetic control. The HbA1c test is one of the most effective techniques to monitor diabetic control. Out of the 100 patients, 60% were diagnosed with diabetic retinopathy. Out of these, 36% were diagnosed with non-proliferative diabetic retinopathy, and 24% were diagnosed with proliferative retinopathy. The results were quite alarming, as 60 out of 100 were suffering from diabetic retinopathy. This study provided the prevalence of diabetic retinopathy in the district of Sialkot. This study also helps to understand the severity of hyperglycemia that may lead to vision loss due to diabetic retinopathy.*

Keywords: Hyperglycemia, Diabetes Mellitus, Retinopathy, Metabolic Disorders, Microvascular Disorders

Introduction

Diabetes mellitus (DM) is characterized by a high glucose level in the blood (hyperglycemia) resulting from defective mechanisms in insulin secretion, insulin action, or both (Kharroubi & Darwish, 2015). High blood sugar levels caused by the body's inability to produce insulin, tolerance to insulin action or both are characterized by all chronic metabolic illnesses known as diabetes (Sierra, 2009). All chronic metabolic disorders collectively referred to as diabetes are characterized by hyperglycemia brought on by the loss of the ability to manufacture insulin, resistance to its action, or both (Organization, 2019). Raised blood glucose levels are a hallmark of diabetes mellitus (DM), a chronic metabolic condition brought on by either insulin insufficiency or insulin resistance (Tripathy et al., 2019). Diabetes mellitus (DM) is a significant medical disorder that can cause macrovascular complications like ischemic heart disease and peripheral vasculopathy, in addition to microvascular effects like retinopathy, nephropathy, and neuropathy. It also leads to significant morbidity (Sayin et al., 2015). Due to a sharp rise in occurrence over the past several years, diabetes mellitus (DM) is regarded as a significant global public health issue (Nakagami et al., 2017).

Diabetes is a leading cause of morbidity, disability, and premature death. Diabetes poses significant health and socioeconomic challenges for a country already dealing with other health issues, such as infectious diseases. Diabetes impairs vision through cataracts and diabetic retinopathy, a progressive disease of the retinal microvasculature (Vision, 2020). Particularly in low- and middle-income nations, diabetes has emerged as a global health and economic problem (Guariguata et al., 2014). Metabolic complications (hyperglycemia), macrovascular complications (such as cardiovascular and cerebrovascular disease), and microvascular complications (such as nephropathy, neuropathy, and retinopathy) are three categories of diabetes complications that are all associated with an increased risk of premature death (Badedi et al., 2016).

Type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus are the two categories into which diabetes is divided depending on the age of onset and pathology (T2DM). While T2DM, also known as insulin-independent diabetes, develops later in life and has various etiologies, T1DM, also known as insulin-dependent diabetes, develops due to pancreatic beta cell damage and an inability to make insulin (Al Slail et al., 2016). Type I diabetes mellitus is common in younger patients and requires insulin treatment. Type II diabetes is more common in older people. It can usually be treated with diet alone or in combination with antidiabetic drugs (although, in some cases, insulin therapy is required). T1DM has a higher incidence of DR than T2DM (Klein et al., 1984). Diabetic retinopathy (DR) is one of the most common chronic complications of diabetes mellitus (DM). DR is characterized by gradually progressive alterations in the retinal microvasculature, leading to areas of retinal non-perfusion, increased vascular permeability, and pathologic intraocular proliferation of retinal vessels. The complications are associated with macular edema and uncontrolled neovascularization, termed proliferative diabetic retinopathy (PDR), resulting in severe and permanent vision loss if not treated in a timely and appropriate manner. DR is the leading cause of blindness among working-aged adults worldwide. However, with proper medical and ophthalmologic care,

more than 90% of vision loss from PDR can be prevented (Klein et al., 2021).

Methodology

A hospital-based study was conducted in DHQ Sialkot and Al Sheikh Hospital Sialkot between May 2022 and July 2022. The sample size of this study was 100. The people with chronic diabetes who attended the DHQ and Al Sheikh Hospital were examined at ages 45 and 90. The medical and demographic histories were taken through a questionnaire. An experienced ophthalmologist examined the patients after the dilation of the pupil. Tropicamide was used for the dilation of the pupil. An ophthalmologist used a Topcon slit lamp to inspect the subject's anterior segment, an applanation tonometer to assess the intraocular pressure and a 90-dioptre hand-held fundus imaging lens to do dilated fundoscopy. All the patients were suggested to have an HbA1c lab test, and data were collected for a comparative study between Diabetic Retinopathy (DR) and hyperglycemia recorded by HbA1c results. HbA1c is considered one of the bio-markers for Diabetic Retinopathy as it gave results of glycemic control over the past three months.

Visual acuity was measured using Snellen's chart. A slit lamp was used for anterior segment evaluation. Goldman, a planation tonometer, performed IOP measurement. Indirect ophthalmoscopy was performed after complete pupillary dilatation with 1% tropicamide eye drops. Based on the results of the fundus examination of each subject's worst eye, retinopathy was classified. A blood sample was taken for the analysis of HbA1c by fluorescence immunoassay by ichroma^{TM}.

The test uses a sandwich immunodetection method; the detector antibodies in the buffer bind to antigens in the sample, forming antigen-antibody complexes, and migrate onto the nitrocellulose matrix to be captured by the other immobilized antibodies on the test strip. More antigens in the sample will form more antigen-antibody complexes, which lead to stronger fluorescence signals by detector antibodies, which are processed by instrument form chroma ^{TM} tests to show the content of glycated hemoglobin in terms of percent of the total hemoglobin in the blood. The test is performed under the supervision of experts by following procedure.

I remove a cartridge from the pouch and insert it into the chamber (30◦c). After this, I transfer 100µl of hemolysis buffer into the detection buffer tube. After this, I add 5µl of whole blood into the detection buffer tube through the capillary tube. Then, I closed the lid of the detection buffer tube and mixed the sample thoroughly by shaking it about 15 times.

Then I took out half of the cartridge from the i-chamber slot and piped out 75 µl of the sample mixture, loaded it into the sample well of the test cartridge, and waited till the sample mixture flows appeared in the window. Then, insert the cartridge into the i-chamber slot (30◦c) and leave it in the i-chamber for 12 mins before removing it. To scan the sample-loaded cartridge, I inserted it into the cartridge holder of the instrument for chroma tests and pressed the select button to start watching. The immediate result is displayed on the screen.

Statistical Package for the Social Sciences version 21 (SPSS, 21) software was used to analyze the data. In addition to looking at descriptive data, the chi-square test was employed to determine the incidence of diabetic retinopathy (DR) in people with chronic diabetes mellitus (DM) and to find the association between hyperglycemia by HbA1c and Diabetic Retinopathy (DR) Along with other risk factors.

Results

This study involved 100 patients with chronic Diabetes Mellitus (DM) who visited DHQ and Al Sheikh Hospital Sialkot. The primary objective was to determine the prevalence of Diabetic Retinopathy (DR) among Chronic Diabetes Patients in District Sialkot. Figure 1 shows that among these patients, 40 were not diagnosed with Diabetic Retinopathy (DR), while 60 patients were diagnosed with the disease. The prevalence of Non-Proliferative Diabetic Retinopathy (NPDR) was 38%, and the prevalence of Proliferative Diabetic Retinopathy (PDR) was 22%.

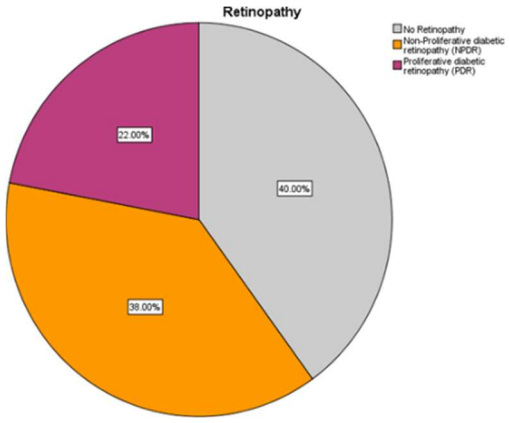

Figure 1 shows the prevalence of Diabetic Retinopathy in Chronic Diabetes Mellitus (DM) patients.

Our objective was to find the association between Hyperglycemia and Diabetic Retinopathy (DR) in Chronic Diabetic patients by HbA1c. Figure 2 elaborates on the glycemic control of patients according to three categories: (a) Excellent Control (<7.0); (b) Good Control (7.0 - 8.0); (c) Poor Control (>8.0). These results were drawn from the patient's HbA1c results. According to this table, 28% of patients had excellent control, 10% had reasonable control, and 62% had Poor Glycemic control.

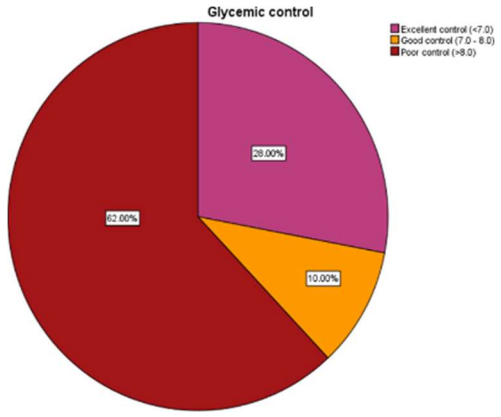

Figure 2: Shows the percentage of glycemic control of Chronic Diabetes Mellitus Patients

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Figure 3 shows the frequency of 'Oral Medication or Insulin patients' taken by patients to control hyperglycemia; 63% were taking oral medications, while 37% were on Insulin

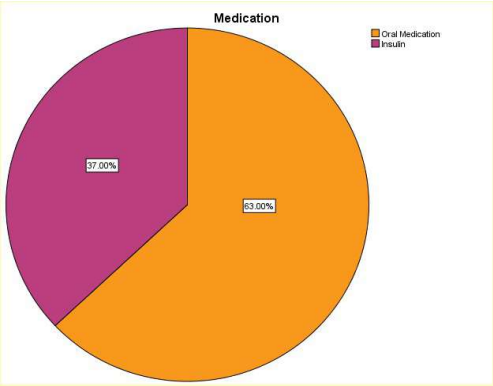

Figure 3 shows that 63% of patients take oral medication, whereas 37% take insulin.

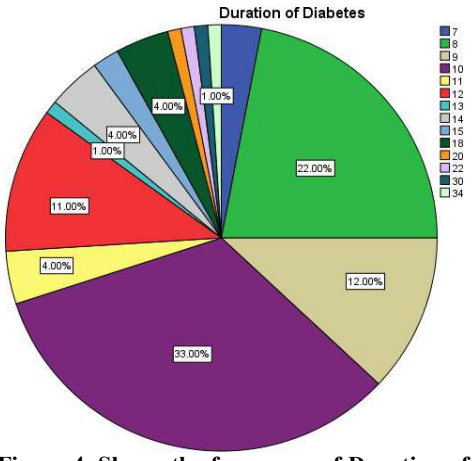

Figure 4. Shows the frequency of Duration of Diabetes Mellitus (DM)

Table 1 explains that among patients diagnosed with Diabetic Retinopathy (DR), the majority have poor glycemic control. While some have reasonable glycemic control, their number is negligible compared to those with poor control. After reviewing Table 1, it can be concluded that there is a significant association between diabetic retinopathy and hyperglycemia. This is because the p-value for chi-square is less than the level of significance (α) of 0.05.

Table 2 shows that out of a total of 40 patients, 12 were male and 28 were female who had "No Retinopathy." Thirty-six patients were diagnosed with "Non-Proliferative Diabetic Retinopathy (NPDR)" - 16 males and 20 females. Additionally, 24 patients were diagnosed with "Proliferative Diabetic Retinopathy (PDR)" - 6 males and 18 females. Therefore, 36 females and 24 males were diagnosed with Diabetic Retinopathy (DR). According to the table, the p-value for chi-square is 0.234, greater than α=0.05. As p-value=0.234>α=0.05, the null hypothesis is not rejected. It can be concluded that there is no association between Diabetic Retinopathy and Gender.

Table 3 reveals that most patients diagnosed with Retinopathy were taking oral medication. Of 39 Non-Proliferative Diabetic Retinopathy Patients, 30 were on oral medication, while only nine were on insulin. Similarly, out of 22 Proliferative Diabetic Retinopathy Patients, 18 took oral medication, and four were on insulin to control Hyperglycemia. According to the output in Table 3, the p-value for chi-square is 0.000, less than α=0.05. This means that the null hypothesis is rejected, and it is concluded that there is an association between diabetic retinopathy and medication.

Based on Table 4, the p-value for chi-square is 0.000, less than the significance level of α=0.05. Since the p-value is 0.00<α=0.05, the null hypothesis is rejected. Therefore, it can be concluded that there is a significant association between the occurrence of diabetic retinopathy and the duration of the disease.

However, Our study did not find any association between Diabetic Retinopathy and Age ($p > 0.05$)

The analysis also indicates that 77% of patients with Diabetes Mellitus (DM) adhere to their medication regimen, while 33% exhibit non-adherence. Only 36% consistently monitor their glycemic levels, with 64% neglecting regular monitoring. Before DM, 40% of patients experienced poor vision, contrasting with 60% who did not. Additionally, 64% of individuals are unaware of DM's potential ocular complications, while 36% recognize this association. These findings underscore interventions needed to improve medication adherence, promote glycemic monitoring, and enhance awareness of DM-related visual risks.

Table 1: Association between the glycemic control and the Diabetic Retinopathy:

Types of retinopathies	Excellent control (HBA1C < 7)	Good control (HBA1C 7-8)	Poor control (HBA1C >7)	*P*-value
No Retinopathy (n)	28	5	7	0.001
Non- Proliferative diabetic retinopathy (n)	0	4	34	
Proliferative diabetic retinopathy (n)	0	1	21	
Total	28	10	62	

Table 2: Association of Gender and Diabetic Retinopathy

Types of retinopathies	Gender		*P*-value
	Male	Female	
No Retinopathy (n)	12	28	0.234
Non- Proliferative diabetic retinopathy (n)	16	20	
Proliferative diabetic retinopathy (n)	6	18	
Total	34	66	

[Citation: Fatima, S., Ashraf, S., Tahir, A., Batool, A., Latif, I., Ameen, I. (2024). Glycosylated hemoglobin hba1c as a biomarker for diabetic retinopathy. *Biol. Clin. Sci. Res. J.,* **2024***: 717*. doi: https://doi.org/10.54112/bcsrj.v2024i1.717]

Table 3: Association between 'Retinopathy and Medication'

Types of retinopathies	Medication		*P*-value
	Oral Medication	Insulin	
No Retinopathy (n)	15	24	<0.001
Non- Proliferative diabetic retinopathy (n)	30	9	
Proliferative diabetic retinopathy (n)	18	4	
Total	63	37	

Table 4: Association between "Retinopathy and Disease duration"

Types of retinopathies	Disease duration			*P*-value
	(7-10) years	(11-14) years	(15-18) years	
No Retinopathy (n)	37	1	0	<0.001
Non- Proliferative diabetic retinopathy (n)	23	10	5	
Proliferative diabetic retinopathy (n)	9	10	5	
Total	69	21	10	

Discussion

This study has been taken in DHQ and Al Sheikh Hospital Sialkot. The study's primary objectives were to determine the prevalence of Diabetic Retinopathy (DR) in Chronic Diabetes patients and to find an association between HbA1c and hyperglycemia. The participants of this study were 100, who were interviewed using a proper demographic questionnaire and a detailed ophthalmic examination. In this study, the association between Diabetic Retinopathy (DR) and different variables like Age, Gender, Medication, and Duration of Disease. The incidence of Diabetic Retinopathy (DR), according to this study, is 60% (38% with NPDR; 22% with PDR) with a sample size of 100.

One of the most prevalent microvascular consequences of diabetes, diabetes-related retinopathy (DR), has a catastrophic effect on quality of life and the potential to result in blindness and severe vision loss. Despite a large body of research highlighting the significance of strict insulin sensitivity and treating risk factors, including hypertension, failure to achieve target HbA1c levels is a significant factor in the emergence and spread of diabetic retinopathy (Corcóstegui et al., 2017). Patients with diabetes who had poor glycemic control had a higher risk of developing diabetic retinopathy than patients with reasonable glycemic control. Research done in Jimma, China, Bangladesh, and India backed this conclusion: High glucose levels affect glucose uptake and enhance oxidative stress in retinal artery endothelial cells, resulting in diabetes complications like diabetic retinopathy (Rogers et al., 2010).

According to this study, 60% of diabetic patients were diagnosed with diabetic retinopathy in the district of Sialkot. This is an alarming situation, and patients with chronic diabetes mellitus need to be aware of this complication. As most people don't know about the consequences, they can face due to uncontrolled diabetes.

According to the current study, 34.10% of diabetic patients experienced DR, which is comparable to other hospital-based studies from Bangladesh (36.10%) and Nigeria (36%). The prevalence figure was lower than that previously recorded from Addis Abeba (50.1%) and Jimma (41.10%) but higher than that reported previously from BahirDar (25.50%), Gondar (17.00%), and Arba Minch (13.00%) in Ethiopia (Alemu et al., 2022). According to the study, high blood pressure, kind of medicine, and time were significant time antecedents to DR, whereas weight, present age, and time were significant antecedents of FBS alterations (Kebede et al., 2022).

Furthermore, diabetes management strongly influences the development of DR. Effective diabetes management can ensure reasonable HbA1c control. Poor diabetes management, on the other hand, may result in unsatisfactory HbA1c levels, increasing the likelihood of developing DR. This study, like previous studies, found a strong link relation between HbA1c and the emergence of diabetic retinopathy (Yau et al., 2012b). Furthermore, diabetes management strongly influences the development of DR. Effective diabetes management can ensure reasonable HbA1c control. Poor diabetes management, on the other hand, may result in unsatisfactory HbA1c levels, increasing the likelihood of developing DR. This study, like previous studies, shows a direct correlation between diabetic retinopathy development and HbA1c (Ibrahim, 2017).

This study shows an association with different risk factors; first of all was poor glycemic control tested with HbA1c test; results show that there was a strong relationship between poor glycemic control. The occurrence of Diabetic Retinopathy as most of the patients had poor glycemic control.

Numerous studies have established the relationship between glycemic management and diabetes retinopathy as well as the value of reducing glycosylated hemoglobin (HbA1c) in the development and progression of DR. Metabolic management is closely related to the risk of diabetes-related complications in people with type 2 diabetes. Any endpoint related to diabetes is reduced by 21% for every 1% decrease in HbA1c (Chaturvedi, 2007).

For effective diabetic management, the American Diabetes Association suggests a HbA1c target of 7%. The UK Prospective Diabetes Study and the DCCT discovered an association between rising HbA1c levels and the onset and development of diabetic retinopathy (I. et al. et al., 2000). Diabetic retinopathy is the most prevalent visual fundus condition in diabetic people. Other risk factors for diabetic retinopathy include age, male sex, hypertension, duration of

diabetes, diabetic neuropathy, diabetic nephropathy, diabetic foot ulcer, foot amputation, FBS, serum total cholesterol, serum triglyceride, and HbA1c (Zheng et al., 2012)

Additionally, the current study supported the associations between DR and risk variables such as systemic hypertension, nephropathy, and the duration of diabetes that had been discovered in other investigations. According to a recent systematic analysis, DR incidence and progression are decreased by strict glycemic control (HbA1c in the expected level) (Varma et al., 2007).

Moreover, this study also shows an association of Diabetic Retinopathy with other variables taken as risk factors like gender, age, medication, and duration of disease. It shows an association between the duration of disease and medication. However, there was no correlation between patient age and gender. This was also an awareness study that let the patients know about the consequences they can face in the future if they do not control their glycemic levels and make them aware of the effects of diabetes on their eyes and the aftereffects of poor glycemic control.

Male gender, macroalbuminuria, HbA1c, T2DM, diabetes duration, and glycemic control were all independent predictor variables for the severity of diabetic retinopathy (Pradeepa et al., 2008). Numerous studies have discovered that an essential indicator of diabetic retinopathy is the length of diabetes. After 20 years, 40% of patients with type 2 diabetes and approximately 60% of those with T1DM have PDR. In line with earlier studies, those with diabetes who had it for a longer duration than those who suffered from it for a shorter time had a higher prevalence of diabetic retinopathy. The results show that the development of diabetic retinopathy is significantly linked to having diabetes mellitus for a more extended period (Din et al., 2006).

Our study also has some limitations as it occurs in an eye care center where all the patients visit because they were facing some difficulties, but they visited there when the disease already had affected their eyes badly as it may be Diabetic Retinopathy or any other eye problem. This study also has a small sample size and a limited period. However, it is undoubtedly a very effective work that will inform the participants of the effects of a disease they have been suffering from for a long time, i.e., Diabetes Mellitus (DM). This study is an initiative that will also motivate and encourage future researchers to conduct their research on public health awareness, as Pakistan is an underdeveloped country suffering from economic crisis and illiteracy. Studies like this will help compensate for public health issues like Diabetic Retinopathy (DR).

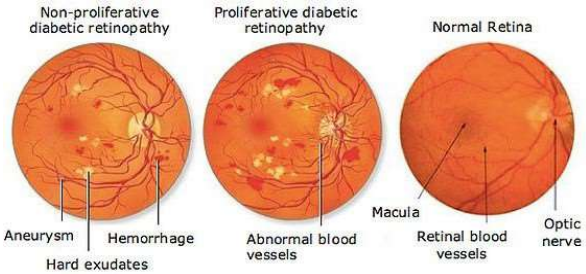

Figure 5: Visual representation of Normal Retina, PDR, and NPDR

Conclusion

Diabetic Retinopathy (DR) is becoming more common every day, and it is associated mainly with hyperglycemia (i.e., Elevated levels of HbA1c). Additional risk factors like Age, Duration of diabetes, and Medication also play an important role. This study provided specific information about the relationship between diabetic retinopathy and ongoing diabetes mellitus. The 100 patients were checked, and a proper medical and demographic history was taken through a questionnaire. 60% were diagnosed with diabetic retinopathy, out of which 36% were diagnosed with non-proliferative diabetic retinopathy (16 Males and 20 Females), and 24% were diagnosed with proliferative (6 Males and 18 Females). This study shows a strong correlation between medication and patient duration. There is no association between gender and age of the person with diabetic retinopathy. All the patients were also guided about the consequences of hyperglycemia, the effect of diabetes on their vision and eyes, taking their medication correctly, and checking their glycemic control regularly. Finally, research conducted at Sialkot health facilities has made it abundantly evident. Diabetic education is crucial to halting the dangerous rise in the prevalence of DR and diabetes mellitus (DM). To maximize available funds and implement methods that will lessen the impact of the Diabetes epidemic in Pakistan, additional research will be needed.

Declarations

Data Availability statement

All data generated or analyzed during the study are included in the manuscript.

Ethics approval and consent to participate

Approved by the department Concerned.

Consent for publication

Approved

Funding

Not applicable

Conflict of interest

The authors declared absence of conflict of interest.

Author Contribution

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Coordination of collaborative efforts.
Study Design, Review of Literature.
Conception of Study, Development of Research Methodology Design, Study Design,, Review of manuscript, final approval of manuscript.

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Conception of Study, Final approval of manuscript.
Manuscript revisions, critical input.

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ADEEBA BATOOL
Conception of Study, Development of Research Methodology Design, Study Design,, Review of manuscript, final approval of manuscript.

IRUM LATIF
Data acquisition, analysis.

Coordination of collaborative efforts.
IQRA AMEEN
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Data entry and Data analysis, drafting article.

References

Al Slail, F. Y., Abid, O., Assiri, A. M., Memish, Z. A., & Ali, M. K. (2016). Cardiovascular risk profiles of adults with type-2 diabetes treated at urban hospitals in Riyadh, Saudi Arabia. Journal of epidemiology and global health, 6(1), 29–36.

Alemu Mersha, G., Alimaw, Y. A., & Woredekal, A. T. (2022). Prevalence of diabetic retinopathy among diabetic patients in Northwest Ethiopia—A cross-sectional hospital-based study. PLoS One, 17(1), e0262664.

Badedi, M., Solan, Y., Darraj, H., Sabai, A., Mahfouz, M., Alamodi, S., & Alsabaani, A. (2016). Factors associated with long-term control of type 2 diabetes mellitus.

Journal of diabetes research, 2016. Chaturvedi, N. (2007). The burden of diabetes and its complications: trends and implications for intervention. Diabetes research and clinical practice, 76(3), S3-S12.

Corcóstegui, B., Durán, S., González-Albarrán, M. O., Hernández, C., Ruiz-Moreno, J. M., Salvador, J., . . . Simó, R. (2017). Update on diagnosis and treatment of diabetic retinopathy: a consensus guideline of the working group of ocular health (Spanish Society of Diabetes and Spanish Vitreous and Retina Society)—Journal of Ophthalmology, 2017.

Din, J.-u., Qureshi, M. B., Khan, A. J., Khan, M. D., & Ahmed, K. (2006). Prevalence of diabetic retinopathy among individuals screened positive for diabetes in five community-based eye camps in northern Karachi, Pakistan. J Ayub Med Coll Abbottabad, 18(3), 40.

Guariguata, L., Whiting, D. R., Hambleton, I., Beagley, J., Linnenkamp, U., & Shaw, J. E. (2014). Global estimates of diabetes prevalence for 2013 and projections for 2035. Diabetes research and clinical practice, 103(2), 137–149.

Ibrahim, M. (2017). Impact of Age, Duration, and Control of Diabetes on Risk of Diabetic Retinopathy among Sudanese Diabetic Patients in Khartoum, Sudan- 2016: Hospital-based Cross-Sectional study. International Journal of Sciences: Basic and Applied Research (IJSBAR), 33(1), 68–75.

Kebede, S. A., Tessema, Z. T., Balcha, S. A., & Ayele, T. A. (2022). Joint modeling of time to diabetic retinopathy and change in fasting blood sugar among type 2 diabetic patients, Northwest Ethiopia. Scientific reports, 12(1), 1-9.

Kharroubi, A., & Darwish, H. (2015). Diabetes mellitus: The epidemic of the century. World J Diabetes 6 (6): 850–867. In.

Klein, R., Klein, B. E., Moss, S. E., Davis, M. D., & DeMets, D. L. (1984). The Wisconsin epidemiologic study of diabetic retinopathy: II. Prevalence and risk of diabetic retinopathy when the age at diagnosis is less than 30 years. Archives of ophthalmology, 102(4), 520-526.

Nakagami, T., Takahashi, K., Suto, C., Oya, J., Tanaka, Y., Kurita, M., . . . Uchigata, Y. (2017). Diabetes diagnostic thresholds of the glycated hemoglobin A1c and fasting plasma glucose levels considering the 5-year incidence of retinopathy. Diabetes research and clinical practice, 124, 20-29.

Organization, W. H. (2011). Use of glycated hemoglobin (HbA1c) in the diagnosis of diabetes mellitus: abbreviated report of a WHO consultation. Retrieved from Organization, W. H. (2019). Classification of diabetes mellitus.

Rogers, S. L., McIntosh, R. L., Lim, L., Mitchell, P., Cheung, N., Kowalski, J. W., . . . Wong, T. Y. (2010). Natural history of branch retinal vein occlusion: an evidence-based systematic review. Ophthalmology, 117(6), 1094–1101. e1095. Sayin, N., Kara, N., & Pekel, G. (2015). Ocular complications of diabetes mellitus.

World journal of diabetes, 6(1), 92. Sierra, G. (2009). The global pandemic of diabetes. African Journal of Diabetes Medicine, 17(11), 4–8.

Stratton, I., Kohner, E., Aldington, S., Turner, R., Holman, R., Manley, S., & Matthews, D. (2001). UKPDS 50: Risk factors for incidence and progression of retinopathy in Type II diabetes over six years from diagnosis. Diabetologia, 44(2), 156-163.

Stratton, I. M., Adler, A. I., Neil, H. A. W., Matthews, D. R., Manley, S. E., Cull, C. A., . . . Holman, R. R. (2000). Association of glycemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): a prospective observational study. Bmj, 321(7258), 405-412.

Tripathy, D., Merovci, A., Basu, R., Abdul-Ghani, M., & DeFronzo, R. A. (2019). Mild physiologic hyperglycemia induces hepatic insulin resistance in healthy, regular glucose-tolerant participants. The Journal of Clinical Endocrinology & Metabolism, 104(7), 2842–2850.

Varma, R., Macias, G. L., Torres, M., Klein, R., Peña, F. Y., Azen, S. P., & Group, L.

A. L. E. S. (2007). Biologic risk factors associated with diabetic retinopathy: the Los Angeles Latino Eye Study. Ophthalmology, 114(7), 1332–1340.

Vision, W. (2020). The Right to Sight, Global Initiative for Eliminating Avoidable Blindness: Action Plan 2006–2011. Geneva: World Health Organization, 207.

Yau, J. W., Rogers, S., Kawasaki, R., Lamoureux, E., Kowalski, J., Bek, T., . . . Grauslund, J. (2012a). 148 Bibliography MS Roy, T. Sharma, J. Shaw, H. Taylor, JM Tielsch, R. Varma, JJ Wang, N. Wang, S. West, L. Xu, M. Yasuda, X. Zhang, P. Mitchell, TY Wong, and for the Meta-Analysis for Eye Disease (META-EYE) Study Group, "Global Prevalence and Major Risk Factors of Diabetic Retinopathy," Diabetes Care, 35(3), 556-564.

Yau, J. W., Rogers, S. L., Kawasaki, R., Lamoureux, E. L., Kowalski, J. W., Bek, T.,Grauslund, J. (2012b). Global prevalence and major risk factors of diabetic retinopathy. Diabetes care, 35(3), 556-564.

Zheng, Y., He, M., & Congdon, N. (2012). The worldwide epidemic of diabetic retinopathy. Indian journal of ophthalmology, 60(5), 428.

Zheng, Y., Lamoureux, E. L., Lavanya, R., Wu, R., Ikram, M. K., Wang, J. J., . . . Saw, S.-M. (2012). Prevalence and risk factors of diabetic retinopathy in migrant Indians in an urbanized society in Asia: the Singapore Indian eye study. Ophthalmology, 119(10), 2119-2124