

Significance of HbA1c levels in diabetic retinopathy extremes in South Africa

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Background. Diabetic retinopathy (DR) is one of the leading causes of blindness in sub-Saharan Africa and globally, placing a huge disease burden on patients and the public health system. DR varies in severity from non-proliferative to proliferative DR (PDR).

Objectives. Using a monitor of medium- to long-term blood glucose control, to determine the association between glycated haemoglobin (HbA1c) levels in patients with PDR and those with no DR.

Methods. A prospective, cross-sectional study was conducted at McCord Provincial Eye Hospital in Durban, South Africa. We studied only patients diagnosed with diabetes mellitus (DM) for >1 year who had either PDR or no DR, and compared their HbA1c levels. Patients with non-proliferative DR were not included.

Results. Patients with PDR had significantly higher HbA1c levels than those with no DR. Patients with type 1 DM had higher HbA1c levels than patients with type 2 DM in both the PDR and no-DR groups. Older patients (>70 years) had lower HbA1c levels than younger patients. Gender, race and duration of diabetes had no influence on HbA1c levels.

Conclusions. PDR was associated with higher HbA1c in type 2 DM in all races and age groups and was independent of duration of disease. The trend was the same for type 1 DM, but significance could not be reached, probably because of small numbers in this subset of patients.

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Diabetic retinopathy (DR) is one of the microvascular complications of diabetes mellitus (DM), and falls into two main classes: non-proliferative DR, which can be mild, moderate or severe, and proliferative DR (PDR), which is the advanced stage of the disease. The present study focuses primarily on PDR. PDR results from significant ischaemia to the retina, causing an increase in vascular endothelial growth factor (VEGF) secretion in an attempt to form new blood vessels. These new but abnormal blood vessels tend to bleed and leak, which often leads to macular oedema and vitreous haemorrhage. At the final stage, fibrous tissue forms. This can cause traction on the retina, which in turn can lead to retinal detachment.^[1,2] DR is one of the leading causes of blindness globally.^[2] It is estimated that 11.9 million adults in the USA aged >40 years have some degree of DM. Of these, 3.3 million have PDR and are at risk of vision loss.^[3] Of particular concern is that the incidence of sight-threatening DR is three times higher in sub-Saharan Africa than in Europe. In a study in Malawi, Burgess *et al.*^[4] found an incidence of sight-threatening DR of 38.6 per 100 000 people and an incidence of PDR ~10 times higher than in a European population. In a cluster randomised trial in the Tshwane district of South Africa (SA), Webb *et al.*^[5] found that the prevalence of DR and PDR was 24.9 % and 5.5%, respectively.

Patients with any DR should have regular eye examinations.^[3] PDR requires several sessions of pan-retinal photocoagulation (PRP) laser treatment and/or intravitreal anti-VEGF injections, while some patients will need specialised vitreoretinal surgery.^[6] DR places a significant burden on patients and the public health system.^[3] In the USA, Lin *et al.*^[7] showed that the cost to the patient ranged from USD102 539 to USD436 902 per quality-adjusted life-year in the first 2 years of treatment. This amount decreased to between USD21 752 and USD338 348 per quality-adjusted life-year beyond 2 years. The

variation in costs was due to differences in treatment modalities.^[7] The burden of disease also leads to loss to follow-up of patients, and ultimately the burden increases because patients do not receive timely intervention to improve their outcomes. It has been reported that between 22.8% and 28% of patients were lost to follow-up, the proportion being higher for patients who require PRP than for those receiving intravitreal anti-VEGF injections.^[8] Patients with a lower gross annual income were also more likely to default on their follow-up appointments.^[8]

The main goal of managing DR is primary prevention, but secondary preventive measures are required in established disease. Strict blood glucose control is therefore essential in managing this disease.^[9] Serum glycated haemoglobin (HbA1c) is an acknowledged method of measuring medium- to long-term blood glucose control and should be a routine part of standard follow-up diabetes clinic visits. It measures average glycaemic control over ~120 days.^[10] HbA1c may even be helpful to inform us of the state of the patient's retina. A study by Ganjifrockwala *et al.*^[11] in Mthatha, Eastern Cape Province, SA, showed increased HbA1c levels in patients with DR. In another study, conducted by Pirie *et al.*^[12] in KwaZulu-Natal Province (KZN), SA, a statistically significant difference was observed in HbA1c levels in patients with and without DR. However, there was no mention of patients with PDR, and whether HbA1c levels were elevated even further in this group.

When fundus photographs of patients with DM were reviewed and compared with HbA1c levels, Samadi Aidenloo *et al.*^[13] found that DR changes were visible primarily at an HbA1c level >6.5%. In Korea, Park *et al.*^[14] found that the chances of developing DR increased significantly after an HbA1c level of 6.2% was reached. A Swedish study by Lind *et al.*^[15] showed that the risk of any retinopathy increased with an HbA1c level between 7.0%

and 7.4%, while a Chinese study by Hua *et al.*^[16] found that an increase in HbA1c levels was a risk factor for developing other eye complications as well, such as diabetic optic neuropathy, anterior ischaemic optic neuropathy, diabetic papillopathy and new vessels at the disc. Diallo *et al.*^[17] showed that HbA1c was a predictive marker for PDR, with the risk increasing significantly with an HbA1c level >8.6%. Khalil^[18] suggested that a target HbA1c level of <7.6% assists in preventing DR, while Nordwall *et al.*^[19] in Sweden found that keeping HbA1c levels <7.6% as a treatment target seemed to prevent PDR for up to 20 years.

Objectives

There is limited literature on the relationship between HbA1c levels and PDR in SA. The primary objective of this study was to determine the association between HbA1c levels in DM patients with PDR and in those with no DR at a public sector eye hospital in Durban. We hoped to inform general practitioners and other primary caregivers about the risk of eye complications and that their measuring the HbA1c could prompt earlier referral to ophthalmology. A secondary objective was to see whether there is an association between known DR risk factors, such as patient age, duration of illness, type of diabetes and treatment modality, and serum HbA1c levels. It was hoped that the study would be a valuable tool for educating diabetic patients about the importance of blood glucose control in the ongoing quest to prevent blindness.

Methods

Design

A prospective, cross-sectional study was conducted at McCord Provincial Eye Hospital (MPEH) in Durban, KZN.

Participants

Patients making their routine clinical visits to MPEH were recruited. The study population included only patients diagnosed with DM for >1 year, with either PDR or no DR. Patients with non-proliferative DR were excluded, as the purpose of the study was to compare serum HbA1c levels of patients with the two extremes of DR. The duration of DM was determined from the patient history. Diagnoses of no DR and PDR were made by ophthalmologists and ophthalmology registrars working in the MPEH eye clinic. The diagnosis was made after dilated funduscopy slit-lamp examination, via either a 90 dioptre or a 78 dioptre lens, using the International Council of Ophthalmology Grading System. One hundred patients were recruited for the study. Fifty patients had PDR and 50 had no DR. Patients were required to be able to provide informed consent.

Procedure

A blood sample was taken from each patient to ascertain their HbA1c level. The results were made available on the National Health Laboratory Service website. A data collection form was used to capture the data, which included demographic details, duration of illness, type of treatment and HbA1c levels, and whether the patient had type 1 or type 2 DM, and PDR or no DR. The groupings for age, duration of illness and ethnicity were based on similar groupings in other DR studies in Ireland, China and Singapore.^[20-22]

Ethical considerations

Ethical approval was received from the Biomedical Research Ethics Committee of the University of KwaZulu-Natal (ref. no. BE445/17). Permission to proceed with the research was given by MPEH and the KZN provincial government. Informed consent forms were signed by every participant in the study.

Data and statistical analysis

In the study, continuous variables such as patient ages were expressed as means (standard deviation (SD)) or medians (interquartile range (IQR)) and were compared using Student's *t*-test. Proportions and categorical variables were compared using Pearson's χ^2 test or Fisher's exact test, as appropriate. An investigation was conducted to determine the association between DR and PDR and numerous risk factors, such as age, sex and duration of diabetes. All analyses were performed using SPSS version 25 (IBM Corp., USA). The level of significance was set at $p < 0.05$.

Results

A total of 100 patients were included in the study (Table 1). The mean (SD) age of the participants was 60 (9.8) years, and the median (IQR) age was 60 (12) years. Of the patients, 64% were female and 36% male, and the majority were either black Africans (43%) or Indians (53%). The mean (SD) duration of DM was 13.76 (10) years, with a median (IQR) of 10.5 (15) years. There was no statistically significant difference in HbA1c levels between the different ethnic groups ($p = 0.892$).

There were 50 patients with PDR and 50 patients with no DR in the study sample (Table 2). The mean (SD) HbA1c level for the entire sample of patients was 9.01% (1.75%). The mean HbA1c levels for the PDR and no-DR groups were 9.78% and 8.25%, respectively, which was statistically significant ($p = 0.001$). This significance persisted when adjusted for duration of illness. Each group was further subdivided based on their treatment: insulin or oral hypoglycaemic medication (OHM). In both groups, the mean HbA1c level was higher in patients on insulin than in those on OHM.

Table 3 shows HbA1c levels based on type of DM. Patients with type 1 DM had a mean (SD) HbA1c level of 10.2% (1.5%), while those with type 2 DM had a mean level of 8.7% (1.7%). This difference was statistically significant ($p = 0.001$). There were 8 patients with no DR and type 1 DM, and 42 patients with no DR and type 2 DM. The mean (SD) HbA1c level for the no-DR type 1 group was 9.45% (1.4%), while that for the no-DR type 2 group was 8.0% (1.3%). This difference was statistically significant ($p = 0.008$). When these figures were adjusted for duration of DM using linear regression analysis, the HbA1c levels in the type 1 group were still statistically significantly higher.

The PDR group was also separated into type 1 and type 2 DM. The type 1 group had a mean (SD) HbA1c level of 10.5% (1.4%) and the type 2 group a level of 9.4% (1.8%). This difference was statistically significant ($p = 0.034$). Using linear regression analysis to adjust for the duration of illness, the *p*-value remained statistically significant. Among the type 1 DM patients, those with PDR had a mean (SD) HbA1c level of 10.5% (1.4%), while those with no DR had a level of 9.4% (1.4%) ($p = 0.08$, and $p = 0.071$ when adjusted for duration of illness). When the type 2 DM patients were similarly divided into PDR and no-DR groups, the PDR group had a mean (SD) HbA1c level of 9.4% (1.8%) and the no-DR group a level of 8.0% (1.3%) ($p = 0.0002$).

Discussion

Our DM patients with PDR had significantly higher HbA1c levels than those with no DR. These findings suggest that in our population, patients with poorer control of DM are more likely to develop PDR. A Malaysian study^[23] as well as the study by Diallo *et al.*^[17] had similar findings, showing that HbA1c levels can be used as a predictive marker for PDR. Without mentioning PDR in their study, Pirie *et al.*^[12] found a significant difference between HbA1c levels of patients with no DR and those with DR. Hou *et al.*^[21] reported that DR rates

Table I. Demographic and clinical profile of patients

Variables	n (%)	HbA1c (%), mean (SD)	p-value (ANOVA)
Age groups (years)			0.01*
18 - 49 (group 1)	13 (13)	9.74 (1.79)	
50 - 69 (group 2)	73 (73)	9.12 (1.75)	
≥70 (group 3)	14 (14)	7.81 (1.16)	
Total	100		
Gender			0.053
Male	36 (36)	8.56 (1.76)	
Female	64 (64)	9.27 (1.76)	
Total	100		
Race			0.892
Black	43 (43)	9.05 (1.75)	
Indian	53 (53)	8.96 (1.78)	
Mixed race	1 (1)	8.6 (0.00)	
Caucasian	3 (3)	9.73 (1.78)	
Total	100		
Duration of diabetes (years)			0.14
<5	22 (22)	8.43 (1.75)	
5 - 10	28 (28)	8.96 (1.81)	
>10	50 (50)	9.31 (1.69)	
Total	100		

HbA1c = glycated haemoglobin; SD = standard deviation; ANOVA = analysis of variance.
 *Using the Tukey post hoc test, there was a statistically significant difference in mean HbA1c levels between age groups 1 and 3, as well as between age groups 2 and 3 ($p=0.01$ and $p=0.026$, respectively). There was no statistically significant difference in HbA1c levels between age groups 1 and 2 ($p=0.44$).

Table 2. Clinical groups with average HbA1c levels

Clinical groups	n (%)	HbA1c (%), mean (SD)	p-value (ANOVA)	Adjusted for duration of illness, HbA1c (%), mean (SD)	Adjusted for duration of illness, p-value
No DR	50 (50)	8.25 (1.39)	<0.001	8.28 (0.23)	<0.001
PDR	50 (50)	9.78 (1.75)		9.75 (0.23)	
No DR (insulin)	19 (19)	9.02 (1.28)	0.027		
No DR (OHM)	31 (31)	7.78 (1.26)			
PDR (insulin)	30 (30)	10.20 (1.69)	0.078		
PDR (OHM)	20 (20)	9.16 (1.70)			

HbA1c = glycated haemoglobin; SD = standard deviation; ANOVA = analysis of variance; No DR = no diabetic retinopathy; PDR = proliferative diabetic retinopathy; No DR (insulin) = no diabetic retinopathy on insulin; No DR (OHM) = no diabetic retinopathy on oral hypoglycaemic medication; PDR (insulin) = proliferative diabetic retinopathy on insulin; PDR (OHM) = proliferative diabetic retinopathy on oral hypoglycaemic medication.

started to rise markedly at HbA1c levels >6.5%, while the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR)^[24] showed that there was a three-fold higher risk of retinopathy if the patient had an HbA1c level of ≥12%. Hsu *et al.*^[9] also demonstrated that good and sustained glycaemic control as measured by HbA1c levels is important in preventing the onset of DR. It would seem that the literature supports the notion that an elevated HbA1c level is associated with an elevated risk of DR, and indeed PDR.

Correlation of the findings with type 1 DM could not be ascertained adequately in this study because of the relatively small number of type 1 patients in the sample. We were able to conclude that in type 2 DM patients, the PDR group had significantly higher HbA1c levels than the no-DR group. This finding suggests that in type 2 DM, good

glycaemic control prevents the onset of PDR, and is in line with the UK Prospective Diabetes Study Group findings^[25] that after 12 years of follow-up, tight glycaemic control was associated with a 21% reduction in retinopathy progression and a 29% reduction in the need for laser therapy in patients with type 2 DM. However, we cannot compare these findings with those in our type 1 diabetics owing to the small number in the sample.

The duration of DM is probably one of the strongest predictors for the development and progression of DR.^[24] In the WESDR, the prevalence of any retinopathy was 8% at 3 years' duration, 25% at 5 years, 60% at 10 years and 80% at 15 years.^[24] Mohd Ali *et al.*^[23] showed that longer duration of DM was associated with PDR, and that longer duration of DM was a predictive marker for PDR. In

Table 3. HbA1c according to type of diabetes and adjusted for duration of illness

Type of DM	n	HbA1c (%)		Adjusted for duration of illness	
		Mean (SD)	p-value	Mean (SD)	p-value
Overall					
Type 1 DM	24	10.2 (1.5)	<0.001	10.13 (0.36)	0.001
Type 2 DM	76	8.7 (1.7)		8.66 (0.19)	
Total	100	9.0 (1.8)			
No DR					
Type 1 DM	8	9.4 (1.4)	0.008	9.32 (0.50)	0.024
Type 2 DM	42	8.0 (1.3)		8.04 (0.21)	
Total	50	8.25 (1.39)			
PDR					
Type 1 DM	16	10.5 (1.4)	0.034	10.71 (0.45)	0.017
Type 2 DM	34	9.4 (1.8)		9.35 (0.3)	
Total	50	9.78 (1.75)			
Type 1 DM					
PDR	16	10.5 (1.4)	0.08	10.56 (0.36)	0.071
No DR	8	9.4 (1.4)		9.37 (0.51)	
Type 2 DM					
PDR	34	9.43 (1.8)	0.0002	9.44 (0.27)	<0.01
No DR	42	8.03 (1.29)		8.01 (0.24)	

HbA1c = glycated haemoglobin; SD = standard deviation; DM = diabetes mellitus; No DR = no diabetic retinopathy; PDR = proliferative diabetic retinopathy.

contrast, our study did not show that patients with a longer duration of DM had significantly higher mean HbA1c levels than those with a shorter duration (Table 1).

Young patients and the elderly with DM are at increased risk of developing DR. Those who are diagnosed with DM at a young age are at the highest risk, as they have the disease for many years. Tracey *et al.*^[20] showed that younger people have a higher incidence of visual impairment due to DR than other age groups. The results from the present study showed that age made no difference to HbA1c levels or rates of PDR, except for the group aged >70 years (Table 1). We postulate that diabetics with better glycaemic control should generally have better life expectancy, and suspect that many poorly controlled patients had died.

Insulin is an important therapeutic measure in the treatment of DM. A study by Jongsareejit *et al.*^[26] showed higher prevalences of NPDR and PDR in insulin-taking than in non-insulin-taking groups. Our study showed that mean HbA1c levels were higher in patients on insulin than in those on OHM (Table 2). This finding applied to patients with no DR and those with PDR. HbA1c levels being higher in patients on insulin compared with OHM cannot in itself be taken as an independent variable for the development of PDR, since the variable is confounded by the fact that a more severe degree of diabetes often necessitates the use of more aggressive treatment such as insulin. The higher incidence of PDR among insulin users probably simply reinforces the fact that worse diabetic disease results in worse DR.

The exact impact of ethnicity and HbA1c levels in the present study could not be determined owing to the low number of white and mixed-race individuals in the sample group. When comparing black African and Indian patients, who formed the majority of the participants in our study, we found that ethnicity had no effect on the HbA1c level. This is in line with the study by Pirie *et al.*^[12] but is at odds with what was found in a study by Thomas *et al.*^[27] in Johannesburg, SA. They showed that in type 1 DM patients, Asian Indians were at an increased risk of DR compared with white patients, while black African patients had an increased risk of referable diabetic retinopathy, which includes preproliferative, proliferative and exudative maculopathy. In addition, they found that

in type 2 DM, non-Caucasian patients had an increased risk of DR. In a study in Singapore, Tan *et al.*^[22] showed that Indian Singaporeans had a higher prevalence of DR than Chinese and Malaysian patients in the same area. In other parts of the world, DR therefore has a higher prevalence in certain ethnic groups.

Our study showed that the mean HbA1c level for patients with no DR was 8.25%. This figure is above the global average of 6.5 - 7.6%^[13,14,18,22] where DR changes start to become evident on fundoscopy, and indicates that medium-term blood glucose control is generally poor in our population. In time it is likely that these patients will develop DR.

Study limitations

A limitation of the present study is that its cross-sectional nature makes it difficult to establish an exclusively causal link between HbA1c and PDR. A further limitation is that there was a small sample size for patients with type 1 DM ($n=24$), making it difficult to determine a meaningful correlation between type 1 DM and PDR. The small number of type 1 DM patients compared with type 2 also means that we could not confidently compare the findings between the two groups.

A potential further research point would be to have the same number of type 1 and type 2 DM patients, so that a correlation between the two groups could be made. Further research could also be done to determine the HbA1c level at which PDR starts to appear, so that we can have a target level to prevent PDR in an SA context.

Conclusions

Patients with higher HbA1c levels have an increased association with PDR compared with patients with no DR. Serum HbA1c levels can therefore be used as a tool to assess the risk of PDR in DM. Strict blood glucose control is always essential in preventing debilitating PDR and blindness, and in SA we should consider having HbA1c levels tested in DM patients of all races and ages to assess their risk of PDR.

Patients with DM need to be educated about the importance of blood glucose control to prevent the microvascular and

macrovascular complications of the disease, including visual impairment and blindness. Primary healthcare workers have a vital role in ensuring that these patients are managed adequately to prevent the complications associated with DM. Collaborations with primary healthcare workers and ophthalmic specialists need to be encouraged and reinforced to manage and decrease the incidence of both macro- and microvascular complications of DM.

Declaration. The research for this study was done in partial fulfilment of the requirements for MM's MMed (Ophthalmology) degree at the University of KwaZulu-Natal.

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- Stitt AW, Curtis TM, Chen M, Medina RJ, McKay GJ, Jenkins A. The progress in understanding and treatment of diabetic retinopathy. *Prog Retin Eye Res* 2016;51:156-186. <https://doi.org/10.1016/j.preteyeres.2015.08.001>
- Flaxman SR, Bourne RRA, Resnikoff S, Ackland P, Braithwaite T, Cicinelli MV. Global causes of blindness and distance vision impairment 1990 - 2020: A systematic review and meta-analysis. *Lancet Glob Health* 2017;5(12):e1221-e1234. [https://doi.org/10.1016/S2214-109X\(17\)30393-5](https://doi.org/10.1016/S2214-109X(17)30393-5)
- Candrilli SD, Davis KL, Kan HJ, Lucero MA, Rousculp MD. Prevalence and the associated burden of illness of symptoms of diabetic peripheral neuropathy and diabetic retinopathy. *J Diabetes Complications* 2007;21(5):306-314. <https://doi.org/10.1016/j.jdiacomp.2006.08.002>
- Burgess PJ, Harding SP, Garcia-Finana M, Beare NAV, Msukwa G, Allain TJ. First prospective cohort study of diabetic retinopathy from sub-Saharan Africa: High incidence and progression of retinopathy and relationship to human immunodeficiency virus infection. *Ophthalmology* 2016;123(9):1919-1925. <https://doi.org/10.1016/j.ophtha.2016.05.042>
- Webb EM, Rheeder P, Roux P. Screening in primary care for diabetic retinopathy, maculopathy and visual loss in South Africa. *Ophthalmologica* 2016;235(3):141-149. <https://doi.org/10.1159/000443972>
- Avery RL, Pearlman J, Pieramici DJ, et al. Intravitreal bevacizumab (avastin) in the treatment of proliferative diabetic retinopathy. *Ophthalmology* 2006;113(10):1695-1705.E6. <https://doi.org/10.1016/j.ophtha.2006.05.064>
- Lin J, Chang JS, Yannuzzi NA, Smiddy WE. Cost evaluation of early vitrectomy versus panretinal photocoagulation and intravitreal ranibizumab for proliferative diabetic retinopathy. *Ophthalmology* 2018;125(9):1393-1400. <https://doi.org/10.1016/j.ophtha.2018.02.038>
- Obeid A, Gao X, Ali FS, Talcott KE, Aderman CM, Hyman L. Loss to follow-up in patients with proliferative diabetic retinopathy after panretinal photocoagulation or intravitreal anti-VEGF injections. *Ophthalmology* 2018;125(9):1386-1392. <https://doi.org/10.1016/j.ophtha.2018.02.034>
- Hsu C-R, Chen Y-T, Sheu WHH. Glycemic variability and diabetes retinopathy: A missing link. *J Diabetes Complications* 2015;29(2):302-306. <https://doi.org/10.1016/j.jdiacomp.2014.11.013>
- Gan T, Liu X, Xu G. Glycated albumin versus HbA1c in the evaluation of glycemic control in patients with diabetes and CKD. *Kidney Int Rep* 2018;3(3):542-554. <https://doi.org/10.1016/j.ekir.2017.11.009>
- Ganjifrockwala FA, Joseph JT, George G. Evaluation of kidney function and risk factors of retinopathy in type 2 diabetes mellitus people in South Africa. *Diabetes Res Clin Pract* 2017;127:218-123. <https://doi.org/10.1016/j.diabres.2017.03.022>
- Pirie FJ, Maharaj S, Esterhuizen TM, Paruk IM, Motala AA. Retinopathy in subjects with type 2 diabetes at a tertiary diabetes clinic in Durban, South Africa: Clinical, biochemical and genetic factors. *J Clin Translat Endocrinol* 2014;1(1):e9-e12. <https://doi.org/10.1016/j.jcte.2013.12.002>
- Samadi Aidenloo N, Mehdizadeh A, Valizadeh N, Abbaszadeh M, Qarequran S, Khalkhali H. Optimal glycemic and hemoglobin A1c thresholds for diagnosing diabetes based on prevalence of retinopathy in an Iranian population. *Iran Red Crescent Med J* 2016;18(8):e31254. <https://doi.org/10.5812/ircmj.31254>
- Park Y-M, Ko S-H, Lee J-M, Kim D-J, Kim D-J, Han K. Glycaemic and haemoglobin A1c thresholds for detecting diabetic retinopathy: The fifth Korea National Health and Nutrition Examination Survey (2011). *Diabetes Res Clin Pract* 2014;104(3):435-442. <https://doi.org/10.1016/j.diabres.2014.04.003>
- Lind M, Pivodic A, Svensson AM, Olafsdottir AF, Wedel H, Ludvigsson J. HbA1c level as a risk factor for retinopathy and nephropathy in children and adults with type 1 diabetes: Swedish population based cohort study. *BMJ* 2019;366:4894. <https://doi.org/10.1136/bmj.4894>
- Hua R, Qu L, Ma B, Yang P, Sun H, Liu L. Diabetic optic neuropathy and its risk factors in Chinese patients with diabetic retinopathy. *Invest Ophthalmol Vis Sci* 2019;60(10):3514-3519. <https://doi.org/10.1167/iovs.19-26825>
- Diallo AM, Novella J-L, Lukas C, Souchon P-E, Dramé M, François M. Early predictors of diabetic retinopathy in type 1 diabetes: The Retinopathy Champagne Ardenne Diabète (ReCAD) study. *J Diabetes Complications* 2018;32(8):753-758. <https://doi.org/10.1016/j.jdiacomp.2018.05.011>
- Khalil H. Diabetes microvascular complications – a clinical update. *Diabetes Metab Syndr* 2017;11:S133-S139. <https://doi.org/10.1016/j.dsx.2016.12.022>
- Nordwall M, Abrahamsson M, Dhir M, Fredriksson M, Ludvigsson J, Arnqvist HJ. Impact of HbA1c, followed from onset of type 1 diabetes, on the development of severe retinopathy and nephropathy: The VISS Study (Vascular Diabetic Complications in Southeast Sweden). *Diabetes Care* 2015;38(2):308-315. <https://doi.org/10.2337/dc14-1203>
- Tracey ML, McHugh SM, Fitzgerald AP, Buckley CM, Canavan RJ, Kearney PM. Trends in blindness due to diabetic retinopathy among adults aged 18 - 69 years over a decade in Ireland. *Diabetes Res Clin Pract* 2016;121:1-8. <https://doi.org/10.1016/j.diabres.2016.08.016>
- Hou J-N, Bi Y-F, Xu M, Huang Y, Li X-Y, Wang W-Q. The change points of HbA1C for detection of retinopathy in Chinese type 2 diabetic patients. *Diabetes Res Clin Pract* 2011;91(3):401-405. <https://doi.org/10.1016/j.diabres.2010.11.029>
- Tan GS, Gan A, Sabanayagam C, Tham YC, Neelam K, Mitchell P. Ethnic differences in the prevalence and risk factors of diabetic retinopathy: The Singapore Epidemiology of Eye Diseases Study. *Ophthalmology* 2018;125(4):529-536. <https://doi.org/10.1016/j.ophtha.2017.10.026>
- Mohd Ali MH, Draman N, Mohamed WMIW, Yaakub A, Embong Z. Predictors of proliferative diabetic retinopathy among patients with type 2 diabetes mellitus in Malaysia as detected by fundus photography. *J Taibah University Med Sci* 2016;11(4):353-358. <https://doi.org/10.1016/j.jtumed.2016.03.002>
- Klein R, Klein BE, Moss SE, Davis MD, DeMets DL. The Wisconsin Epidemiologic Study of Diabetic Retinopathy: III. Prevalence and risk of diabetic retinopathy when age at diagnosis is 30 or more years. *Arch Ophthalmol* 1984;102(4):527-532. <https://doi.org/10.1001/archophth.1984.01040030405011>
- UK Prospective Diabetes Study Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* 1998;352(9131):837-853.
- Jongsareejit A, Potisat S, Krairitichai U, Sattaputh C, Arunratnachote W. The Thai DMS Diabetes Complications (DD.Comp.) project: Prevalence and risk factors of diabetic retinopathy in Thai patients with type 2 diabetes mellitus. *J Med Assoc Thai* 2013;96(11):1476-1482.
- Thomas RL, Distiller L, Luzio SD, Chowdhury SR, Melville VJ, Kramer B. Ethnic differences in the prevalence of diabetic retinopathy in persons with diabetes when first presenting at a diabetes clinic in South Africa. *Diabetes Care* 2013;36(2):336-341. <https://doi.org/10.2337/dc12-0683>

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