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Risk factors Association with Diabetic Retinopathy and Maculopathy in Egyptian type 2 Diabetics

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Abstract: The aim of this work is to evaluate association of retinopathy and maculopathy with nutritional and biochemical factors. 149 type 2 diabetic patients were classified into three groups according to their body mass index; group 1(BMI ≤ 25; n=33), group 2 (BMI ≤ 29.9; n=64) and group 3 (BMI ≥ 30; n =52). The signs and grading of diabetic retinopathy (DR) and maculopathy were ascertained from retinal digital photographs. Different parameters were analyzed including: age, gender, diabetes duration and body mass index (BMI). Calculation of daily consumption pattern and nutrient intake were estimated including total calories and its sources, proteins, carbohydrate, fats and fibers. Biochemical analysis included blood glucose level and lipids profile. 72 patients (48.3%) exhibited mild diabetic retinopathy, 8 cases (5.4%) with moderate NPDR, 6 cases (4%) with severe NPDR and 14 cases (9.4%) with proliferative DR (PDR). Cases with mild retinopathy were significantly more in group 2 and group 3 (P=0.0001). Cases with severe PDR were more in group 3. There was significant higher incidence of maculopathy among patients of group 2 and group 3 (42 cases, 65.6%), 40 cases (76.9%) respectively) (P=0.0001). In group 3, there was a significant increase in low density lipoproteins and cholesterol. In groups 2 and 3 the intake of energy exceeded the mean of ideal physiological requirement, while the intake of protein and fat was satisfactory. Patients with higher intake of saturated fat and plant origin protein showed higher incidence of retinopathy and maculopathy. A positive correlation between obesity, increased saturated fat intake, glycemic control and severity of retinopathy was found. These results support the role of obesity, quality of glycemic control and saturated fat as factors involved in diabetic retinopathy among Egyptian diabetic patients.

Key words: diabetic retinopathy-diabetic maculopathy-obesity-body mass index-lipids, proteins.

INTRODUCTION

Diabetic eye complications and, in particular, diabetic retinopathy are leading causes of blindness with higher prevalence of diabetic retinopathy in type I diabetics (young onset and insulin dependent) than in type II diabetics (old onset and insulin independent) Klein *et al.,* (1984). Retinopathy is a multifactorial microvascular complication, which apart from hyperglycemia, is associated with high blood pressure, increased lipid concentrations and high body mass index(BMI) Kohner *et al.,* (1989). There is a grounding evidence that retinopathy is not only related to hyperglycemia and diabetes duration. It was found that elevated serum lipids levels promote retinopathy and especially hard exudates Klein *et al.,* (1991). Type 2 diabetes mellitus was mentioned to be one of numerous consequences of obesity. Obesity was established as a risk factor for many systemic diseases including coronary heart disease, hypertension, stroke, dyslipidemia, osteoarthritis, and sleep apnea. Cataract Foster *et al.,* (2033), age related maculopathy Clemons *et al.,* (2005), diabetic retinopathy Van Leiden *et al.,*(2002), and glaucoma Gasser *et al.,* (1999) were mentioned to be associated with obesity. Knowledge about risk factors of diabetic retinopathy is of importance for identifying subgroups at risk, for prevention of complications, and for the planning of public health policies. In Egypt, how obesity, influences diabetic retinopathy is not well documented. Therefore, the purpose of the present study was to investigate and correlate between the contributing role of obesity as detected by BMI, lipids, lipid intake, protein intake to retinopathy severity in cross sectional study of patients with type 2 diabetes.

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MATERIALS AND METHODS

This study was done on 149 subjects with type 2diabetes who attended the outpatient clinic in both research institute of ophthalmology and memorial institute of ophthalmology looking for medical care. Cases were divided into three groups according to their body mass index(BMI) ;group 1 BMI ≤ 25 ,group 2 BMI ≥25.1 and ≤ 29.9, group 3 (BMI ≥ 30)

Definitions:

- Diabetes type 1: diabetes developing in patients aged 30 or less.
- Diabetes type 2: diabetes developing in patients over 30.
- The world health organization (WHO) defines obesity as a body mass index, (BMI; which is defined as weight in kg/height squared in m^2) of 30 kg/m^2 or greater and overweight as individuals whose BMI falls between 25 kg/m^2 and 29.9 kg/m^2 (WHO) 2004.
- Clinical significant macular edema (CSME) was defined according to the early treatment diabetic retinopathy study (ETDRS) Early (1987), as any of the following clinical situations: Solid exudates associated to adjacent retinal thickening in the centre of the macula or at 500 microns, or Retinal thickening at 500 microns or less from the center of the macula, or retinal thickening equal to or greater than one disc diameter with any part of it within one disc diameter of the centre of the macula Early (1987).

Baseline and Ophthalmic Evaluation:

The study was non-interventional and cross-sectional, and was carried out on patients with diabetes mellitus type 2. Patients with corneal opacity, cataract or severe vitreous hemorrhage, retinal detachment or other diseases which may affect the quality of digital photography and patients with severe mental diseases were excluded. After informed consent, participants underwent a detailed examination of each eye including best corrected visual acuity (BCVA), applanation tonometry, and anterior segment slit-lamp examination. Dilated fundoscopy was performed with a 90 diopter hand held lens used at a slit lamp (Topcon). Indirect ophthalmoscopy was done to reveal peripheral abnormalities. Colored fundus photographs and fluorescein angiography were then taken with a fundus camera (Topcon, USA). Two 50 degree fields of the fundus were photographed in each eye; one centered on the optic disc and the other centered on the fovea. Photographs were evaluated for the presence or absence of any diabetic retinopathy (DR), proliferative retinopathy, clinically significant macular edema and previous retinal laser treatment. Overall retinopathy and maculopathy levels were assessed based on the International Clinical Diabetic Retinopathy and Diabetic Macula Edema Disease Severity Scale Knudsen *et al.,* (2007) for each patient based on the grading score of the worse eye, as follows: grade 0: no abnormalities, grade 1(mild non proliferative diabetic retinopathy(NPDR): microaneurysms only, grade 2(moderate NPDR): more than just microaneurysms but less severe than grade 3- that is, microaneurysms and 20 hemorrhages in at least one quadrant or venous beading in one quadrant, grade 3(severe NPDR): any of the following: 20 or more intraretinal hemorrhages in each of the four quadrants; definite venous beading exceeding two quadrants; prominent intraretinal microvascular abnormalities (IRMA) in more than one quadrant, grade 4:proliferative diabetic retinopathy(PDR) with one or more of the following: neovascularisation, vitreous or preretinal hemorrhages, previous panretinal laser treatment. In addition, the presence and severity of maculopathy was identified and recorded. Both eyes of the 149 patients (298 eyes) enrolled in the study were examined and the eye with worst vision was used for statistical analysis.

Relationships between VA, retinopathy and maculopathy and nonocular characteristics included in the baseline assessment were examined. These characteristics included age, sex, body mass index (BMI), duration of diabetes .Also association with nutritional and biochemical factors mentioned below was estimated.

Nutritional assessment:

The 24 hours recall method which seems to be the most suitable was used. The recall was done for all cases to get most possible accurate information. It was repeated within two days for the same patient and the mean of the sum was considered for analysis. Daily consumption of nutrients relevant to research design were estimated including total calories and its sources, proteins, carbohydrate, fats, fibers. Nutrient intake was calculated using a nutritional computer program (Food and Nutrient intake program, 1997) based on Egyptian recipies, the amount of food consumed were analysed and their nutrients contents evaluated as percentage from total calories.

An ideal diet was calculated for each patient. A diet containing the ideal amounts of calories, carbohydrates, protein, fat and fibers was calculated for each individual according to age, height, weight and his activity. Also, consumption of each nutrient for each individual was compared with the ideal amount. Ideal diet calculation for diabetic patients was estimated according to Myers, (1997). The ideal total daily caloric requirement was determined by multiplying the ideal body weight (Kg) by suitable calorie according to their activity level.

The ideal daily caloric need which varied with the patients' activity was calculated taking into consideration that most of patients exerted moderate physical activity.

Table (1) showed the daily caloric requirement for patients according to their physical activity level. The distribution of calories among different nutrients was done as follows 12-20 % of the total calories as protein (4 Kcal/gm), 50-60% as carbohydrate (4 Kcal/gm)and the remaining 20-30 % as fat (9 Kcal/gm) Myers, (1997).

Biochemical analysis:

For each patient, after fasting for at least 12 hours, 10 ml blood samples were taken, placed into two clean dry Wassermann tube, allowed to clot at room temperature. The serum was separated and kept frozen at -20^{o}C until used. The analysis included lipid profile; triglycerides (Fossati and Precipe), total cholesterol Finely M.K. (1978), high density lipoprotein Lopes-Virella *et al.,* (1977) and low density lipoprotein Friedewalde *et al.,* (1973).

The Students *t*-test was used to analyze continuous variables such as age, duration of diabetes, severity of vision loss, nutritional and biochemical values. The Mann- Whitney non parametric test was used to analyze categorical variables such as sex, grades of retinopathy and maculopathy. Pearson correlation test was done to evaluate the association of diabetic retinopathy to the studied risk factors: age, gender, diabetes type, diabetes duration, cholesterol, triglycerides, HDL, hyperlipidemia and BMI. Multivariate logistic regression tests were used to estimate the effect of each risk factor on DR and maculopathy. A *P*-value less than 0.05 was considered statistically significant .For these estimations, SPSS software package version 9.0 was used.

RESULTS AND DISCUSSION

Patient's mean age was 56.80±9.95.years, ranged between 30 and 80 years. 49% were women and 51% were men. The mean of diabetes duration was 11.798±6.282, ranged between one and 30 years. The mean of visual acuity of the worst eye was 0.37±0.30 (6/18 snellen equivalent), with significant deterioration in group 3 as compared with group 1 and group 2 (P=0.0001, *t* test). 49 cases (32.9%) did not have retinopathy against, meanwhile 100 cases (67.1%) had, in varying degrees. Out of these, 72 patients (48.3%) exhibited mild diabetic retinopathy, 8 cases (5.4%) had moderate NPDR, 6 cases (4%) had severe NPDR and 14 cases (9.4%) showed PDR. Cases with mild retinopathy were significantly more in group 2 (35 cases ; 54.7%) and group3 (32 cases; 61.5%) as compared to group 1(P=0.0001, Mann-Whitney test).Cases with severe and proliferative retinopathy were more in group 3 as compared to group 1 and group 2 (Table 2). As for maculopathy, there was significant higher incidence of maculopathy among patients of group 2 and group 3 (42 cases; 65.6%) and (40 cases; 76.9%), respectively) (P=0.0001, Mann-Whitney test, Table 2).

Increased body mass index was significantly associated with decreased visual acuity and increased severity of diabetic retinopathy (p=0.0001) (Table 2) .There was significant negative correlation between retinopathy grade and severity of vision loss (P =0.0001).

There was significant positive correlation between retinopathy and BMI (P=0.04, Pearson correlation), duration of diabetes (P=0.001), high energy diet (P=0.005), increased carbohydrate intake (P=0.001), increased plant protein (P=0.001), total proteins (P=0.0001), unsaturated fat (P=0.016), total fat (P=0.037), (Table 3) High blood cholesterol level was significantly associated with increase in BMI (P=0.0001), older age (P=0.045), increased blood glucose (P=0.0001), high energy diet (P=0.0001), increased carbohydrate intake (P=0.0001), increased animal protein (P=0.001), total fat (P=0.0001), unsaturated fat (P=0.0001), (Table 4).

Multivariate tests showed significant association of retinopathy (P=0.025) and maculopathy (P=0.008) with duration of diabetes. Although, there was significant association of maculopathy with increased BMI and hyperglycemia, no significant association with other nutritional factors was detected. In group 3, there was a significant increase in low density lipoproteins and cholesterol with higher incidence of diabetic retinopathy (P=0.0001). In groups 2 and 3 the intake of energy exceeded the mean of ideal physiological requirement, while the intake of protein and fat was satisfactory. However, it was evidenced that patients with higher intake of saturated fat and plant origin protein showed higher incidence of retinopathy and maculopathy

Table 1: daily caloric requirement for patients according to their physical activity level

Body built BMI	Sedentary low activity (Kcal/Kg)	Moderate activity (Kcal/Kg)	Very active (Kcal/Kg)
Obese	20-25	30	35
Normal	30	35	40
Under weight	32	40	45-50

Table 2: Ocular findings and comparison between the three groups.

Parameters	Group 1 n=33	Group 2 n=64	Group 3 n=52	Total n=149	P 1	P2	P3
Vision(mean(SD) worst eye	0.49(0.38)	0.42(0.3)	0.24(0.19)	0.37(0.30)	0.36	0.0001*	0.001*
Retinopathy((%)) No	26(78.8)	13(20.3)	10(19.2)	49(32.9)	0.0001†	0.75	0.0001†
Mild NPDR	5(15.2)	35(54.7)	32(61.5)	72(48.3)			
Moderate NPDR	-	5(7.8)	3(5.8)	8(5.4)			
Severe NPDR	-	6 (9.4)	-	6(4.0)			
PDR	2(6.1)	5(7.8)	7(13.5)	14(9.4)			
Maculopathy (n%)							
No maculopathy	27(81.8)	22(34.4)	12(23.1)		0.0001†	0.19	0.0001†
With maculopathy	6(18.2)	42(65.6)	40(76.9)				

*Significant P<0.05, t test. † Significant P<0.05, Mann-Whitney test. P1 =group1 versus group 2, P2 =group 2 versus group 3, P3 =group 1 versus group 3.

Table 3: P values for correlations (Pearson Correlation).

Parameters	Age	Diabetes duration	BMI	Glucose	Energy	Carbohydrate
Age	1	0.605	0.002*	0.061	0.0001*	0.001*
Duration	0.605	1.0	0.494	0.951	0.639	0.489
BMI	0.002*	0.494	1.0	0.0001*	0.0001*	0.0001*
Glucose	0.061	0.951	0.0001*	1.0	0.0001*	0.0001*
Energy	0.000*	0.639	0.0001*	0.0001*	1.0	0.0001*
Carbohydrate	0.001*	0.489	0.0001*	0.0001*	0.0001*	1.0
Animal protein	0.137	0.029*	0.0001*	0.008*	0.0001*	0.0001*
Plant protein	0.001*	0.593	0.432	0.003*	0.0001*	0.0001*
Total protein	0.006*	0.625	0.0001*	0.0001*	0.0001*	0.0001*
Sat. fat	0.001*	0.865	0.0001*	0.0001*	0.0001*	0.0001*
Unsat.fat	0.039*	0.603	0.0001*	0.0001*	0.0001*	0.0001*
Total fat	0.037*	0.640	0.0001*	0.0001*	0.0001*	0.0001*
Cholesterol	0.045*	0.136	0.0001*	0.0001*	0.0001*	0.0001*
Fiber	0.414	0.192	0.0001*	0.0001*	0.0001*	0.0001*

Table 3: Continue

Animal protein	Plant protein	Total protein	Sat fat	Unsat. fat	Total fat	Cholesterol	Fiber
0.137	0.001*	0.006*	0.001*	0.039*	0.037*	0.045*	0.414
0.029*	0.593	0.625	0.865	0.603	0.640	0.136	0.192
0.0001*	0.432	0.0001*	0.0001*	0.0001*	0.0001*	0.0001*	0.0001*
0.008*	0.003*	0.0001*	0.0001*	0.0001*	0.0001*	0.0001*	0.0001*
0.0001*	0.0001*	0.0001*	0.0001*	0.0001*	0.0001*	0.0001*	0.0001*
0.0001*	0.0001*	0.0001*	0.0001*	0.0001*	0.0001*	0.0001*	0.0001*
1.0	0.901	0.010*	0.0001*	0.334	0.0001*	0.001*	0.0001*
0.901	1.0	0.0001*	0.002*	0.0001*	0.008*	0.637	0.114
0.010*	0.0001*	1.0	0.0001*	0.0001*	0.0001*	0.0001*	0.004*
0.0001*	0.002*	0.0001*	1.0	0.0001*	0.0001*	0.0001*	0.0001*
0.334	0.0001*	0.0001*	0.0001*	1.0	0.0001*	0.042*	0.553
0.0001*	0.008*	0.0001*	0.0001*	0.0001*	1.0	0.0001*	0.0001*
0.001*	0.637	0.0001*	0.0001*	0.042*	0.0001*	1.0	0.0001*
0.0001*	0.114	0.004*	0.0001*	0.553	0.0001*	0.0001*	0.0.0001*

Table 4: Nutritional and biochemical variables among the three groups.

Variable Mean (SD)	Group1	Group2	Group3	P1	P2	P3
Blood gluocose	185.85(53.25)	248.7(76.4)	295(76.53)	0.0001*	0.002*	0.0001*
Energy intake	1670.6(13.71)	1874.95(32.43)	1972.37(33.24)	0.0001*	0.0001*	0.0001*
Carbohydrate intake	253.28(8.27)	285.8(3.1)	300.88(16.82)	0.0001*	0.0001*	0.0001*
Animalprotien intake	20.36(0.84)	20.28(2.60)	23.12(1.7)	0.86	0.0001*	0.0001*
Plantprotien intake	39.55(1.11)	45.1(1.39)	42.99(1.8)	0.0001*	0.0001*	0.0001*
Total protein intake	60.3(1.3)	65.32(0.74)	65.84(1.01)	0.0001*	0.002*	0.0001*
Sat fat intake	18.43(0.66)	22.06(1.12)	27.18(1.55)	0.0001*	0.0001*	0.0001*
Unsat fat intake	25.9(2.13)	31.47(2.6)	30.6(1.88)	0.0001*	0.046*	0.0001*
Total fat intake	44.7(2.03)	51.03(6.2)	59.87(1.42)	0.0001*	0.0001*	0.0001*
Blood cholesterol	150.39(4.97)	157.36(8.42)	206.19(49.56)	0.0001*	0.0001*	0.0001*
Fibre intake	24.93(2.01)	24.43(2.03)	28.96(2.01)	0.25	0.0001*	0.0001*

*Significant P<0.05, t test. P1 group1 versus group 2, P2 group 2 versus group 3, P3 group 1 versus group 3.

Discussion:

In this study, the prevalence of DR in Egyptians of type 2 diabetes was 67.1%, which was higher than the prevalence found in other population based studies. In the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR) study, DR prevalence rates were 71% in type 1 diabetes and 39% in type 2 diabetes Klein, (1989). The Blue Mountain Eye Study (BMES) Mitchell *et al.,* (1989) found a DR prevalence of 32% among 253 people with diabetes aged 49 or older in western Sydney. In Robert et al study, the prevalence was 29% McKay *et al.,* (2000). The cause for this variation may be attributed to various techniques of fundus photography or it may indicate that Egyptians showed higher prevalence of diabetic retinopathy due to poor diabetes control, racial or socioeconomic factors with malnutrition.

Relationship of retinopathy with various nutritional components suggested that nutritional control should be applied to diabetic patients in order to reduce diabetic retinopathy and maculopathy. This study confirmed the impact of increased BMI and nutritional factors such as high energy diet with increased carbohydrate, plant protein, total proteins, unsaturated fat and total fat on diabetic retinopathy with consequent deterioration of visual acuity. Higher BMI was mentioned to be associated with diabetic retinopathy in various studies (Ballard *et al.,* 1986; Ozmen and Boyvada, 2003). However, associations between serum lipids and hard exudates were found in persons with type 1 but not type 2 diabetics Klein *et al.,* (1991). Contradictory work of Raman et al found no association of obesity with severity of diabetic retinopathy Raman *et al,* (2009). Looker et al found that lower BMI was associated with increased retinopathy prevalence. This was attributed to the tendency towards weight loss after the diagnosis of diabetes Looker *et al.,* (2001).

In this study, the presence of macular edema was associated with longer duration of diabetes, higher levels of blood glucose and increased BMI. These findings were consistent with previous studies Van Leiden *et al.,* (2002). Also, maculopathy was not associated with the studied nutritional factors, which was in agreement to work done by Wong *et al.* (2006). Significant associations of maculopathy with increased lipid levels in type 2 diabetic patients was mentioned in previous studies Zander *et al.,* (2002).

The obtained data emphasized the association between longer duration of diabetes and increased prevalence of retinopathy. Other large epidemiological studies have also supported such association (Mitchell *et al.,* 1998; Orchard *et al.,* 1990). In this Study, presence of diabetic retinopathy was independent of gender. This was in contrast to studies on other populations in which a male preponderance had been reported, such as in the United Kingdom Prospective Diabetes Study (UKPDS) Kohner *et al.,* (1998) and the recent Los Angeles Latino Eye Study Varma *et al.,* (2007). The reason for the discrepancy is not yet clear.

Recently, Serum angiogenic factors, such as the vascular endothelial growth factor (VEGF) was observed to be elevated in obese human Silha *et al.,* (2005). Moreover, oxidative stress was suggested to induce over-expression of VEGF with increased retinal neovascularization and macular edema Caldwell *et al.,* (2005). These findings provided a potential link between obesity and proliferative diabetic retinopathy. Obesity may increase oxidative stress because of its associated hyperleptinemia. High levels of plasma leptin have been found to relate to both hypertensive and diabetic retinopathy Uckaya *et al.,* (2000). In conclusion, the present study results suggested that additional improved regulation of the nutritional habits may have little additional benefit on diabetic retinopathy, and somewhat may affect maculopathy. The identification of additional risk factors should have a high priority in future studies.

REFERENCES

Ballard, D.J., L.J. Melton, M.S. Dwyer, J.C. Trautmann, C.P. Chu, W.M.O. Fallon *et al*. 1986. Risk factors for diabetic retinopathy: a population-based study in Rochester, Minnesota. Diabetes Care, 9: 334-342.

Caldwell, R.B., M. Bartoli, M.A. Behzadian, A.E. El-Remessy, M. Al-Shabrawey, D.H. Platt, *et al*. 2005. Vascular endothelial growth factor and diabetic retinopathy: role of oxidative stress. Curr Drug Targets, 6: 511-524.

Clemons, T.E., R.C. Milton, R. Klein, J.M. Seddon, F.L. Ferris, 2005. Risk factors for the incidence of Advanced Age-Related Macular Degeneration in the Age-Related Eye Disease Study (AREDS) AREDS report no. 19. Ophthalmology, 112: 533-539.

Early Treatment Diabetic retinopathy Study Research Group, 1987. Treatment technique and clinical guidelines for photocoagulation of diabetic macular edema: Early Treatment Diabetic Retinopathy Study report no 2. Ophthalmology, 94: 761-774.

Finely, M.K., 1978. Enzymatic calorimetric determination of serum total cholesterol. Clin. Chem., 24: 391.

Fossati, P., L. Precipe. The determination of triglycerides using enzymatic method. Clin. Chem., 28: 2077.

Foster, P.J., T.Y. Wong, D. Machin, G.J. Johnson, S.K.L. Seah, 2003. Risk factors for nuclear, cortical and posterior subcapsular cataracts in the Chinese population of Singapore: the Tanjong Pagar Survey. Br J Ophthalmol., 87: 1112-1120.

Friedewalde, W.T., R.I. Levy, D.S. Fredrickson, 1973. Estimation of the concentration of LDL cholesterol in plasma without use of preparative ultracentrifuge. Clin. Chem., 18: 499.

Klein, R., B.E.K. Klein, S.E. Moss, M.D. Davis, D.L. DeMets, 1984. The Wisconsin Epidemiologic Study of Diabetic Retinopathy. II Prevalence and risk of diabetic retinopathy when age at diagnosis is less than 30 years. Arch. Ophthalmol., 102: 520-526.

Kohner, E.M., S.J. Aldington, I.M. Stratton, S.E. Manley, R.R. Holman, D.R. Matthews *et al*. 1998. United Kingdom prospective diabetes study, Diabetic retinopathy at diagnosis of non insulin dependent diabetes mellitus and associated risk factors. Arch Ophthalmol., 116: 297-303.

Klein, B.E., S.E. Moss, R. Klein, T.S. Surawicz, 1991. The Wisconsin Epidemiologic Study of Diabetic Retinopathy XII. Relationship of serum cholesterol to retinopathy and hard exudates. Ophthalmology, 98: 1261-1265.

Klein, R., B.E.K. Klein, S.E. Moss, 1989. The Wisconsin Epidemiologic Study of Diabetic Retinopathy: a review. Diab. Met. Rev., 5: 559-570.

Knudsen, L.L., H.H. Lervang, S. Lundbye-Christensen, A. Gorst-Rasmussen, 2007. The North Jutland County Diabetic Retinopathy Study (NCDRS) 2. Non-ophthalmic parameters and clinically significant macular oedema. Br. J. Ophthalmol., 91: 1593-1595.

Looker, H.C., W.C. Knowler, R.C. Hanson, 2001. Changes in BMI and weight before and after the development of type 2 diabetes. Diabetes Care, 24: 1917-1922.

Lopes-Virella, M.F., S. Stone, S. Ellis and J.A. Collwell, 1977. Cholesterol determination in high density lipoprotein separated by three different methods. Clin. Chem., 23(5): 882.

Mitchell, P., W. Smith, J.J. Wang, K. Attebo, 1998. Prevalence of diabetic retinopathy in an older community: the Blue Mountain Eye Study. Ophthalmology, 105: 406-411.

McKay, R, Catherine A McCart, R.T. Hugh, 2000. Diabetic retinopathy in Victoria,Australia: the Visual Impairment Project. Br J Ophthalmol., 84: 865-870.

Myers, A-R., Medicine 3rd edition, 1982. Mass Publishing CO William & Walkins published by special arrangement with Waverly International Poltimore, Mayrland 1997.

Orchard, T.J., J.S. Dorman, R.E. Maser, D.J. Becker, A.L. Drash, D. Ellis *et al*. 1990. Prevalence of complications in IDDM by sex and duration. Pittsburgh Epidemiology of Diabetes Complications Study II. Diabetes, 39: 1116–1124.

Ozmen, B., S. Boyvada, 2003. The relationship between self-monitoring of blood glucose control and glycosylated haemoglobin in patients with type 2 diabetes with and without diabetic retinopathy. J. Diabetes Complications, 17(3): 128–134.

Raman, R., P.K. Rani, P. Gnanamoorthy, R.R. Sudhir, G. Kumaramanikavel, T. Sharma, 2009. Association of obesity with diabetic retinopathy: Sankara Nethralaya diabetic retinopathy epidemiology and molecular genetics study (SN-DREAMS Report no. 8). Acta Diabetologica © Springer-Verlag, 10.1007/s00592-009-0113-8.

Silha, J.V., M. Krsek, P. Sucharda, L.J. Murphy, 2005. Angiogenic factors are elevated in overweight and obese individuals. Int J Obes (Lond), 29: 1308-1314.

Uckaya, G., M. Ozata, Z. Bayraktar, V. Erten, N. Bingol, I.C. Ozdemir, 2000. Is leptin associated with diabetic retinopathy? Diabetes Care, 23: 371-376.

Van Leiden, H.A., J.M. Dekker, A.C. Moll, G. Nijpels, R.J. Heine, L.M. Bouter, *et al.* 2002. Blood pressure, lipids, and obesity are associated with retinopathy: the Hoorn study. Diabetes Care, 25: 1320-1325. Gasser P, Stümpfig D, Schützau A, Ackermann-Liebrich U, Flammer J. 1999. Body mass index in glaucoma. J Glaucoma, 8: 8-11.

Varma, R., G.L. Macias, M. Torres, R. Klein, F.Y. Pena, S.P. Azen, 2007. Los Angeles Latino Eye Study Group; Biologic risk factors associated with diabetic retinopathy: the Los Angeles Latino Eye Study. Ophthalmology; 114: 1332-1340.

World Health Organization (WHO), 2004. Expert Consultation Appropriate body mass index for Asian populations and its implications for policy and intervention strategies. Lancet, 363: 157-163.

Wong, T.Y., R. Klein, F.M.A. Islam, M.F. Cotch, A.R. Folsom, B.E.K. Klein, 2006. Diabetic Retinopathy in a Multi-ethnic Cohort in the United States. Am J Ophthalmol, 141: 446-455.

Zander, E., S. Herfurth, B. Bohl, P. Heinke, U. Herrmann, K. Kohnert, *et al.* 2000. Maculopathy in patients with diabetes mellitus type 1 and type 2: associations with risk factors Br. J. Ophthalmol., 84: 871-876.