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Original Article

The Association of Serum Leptin Level and Anthropometric Measures With the Severity of Diabetic Retinopathy in Type 2 Diabetes Mellitus

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ABSTRACT

This study was performed to determine the association amongst serum leptin level and anthropometric measures with the severity of Diabetic Retinopathy (DR) in subjects with type 2 Diabetes Mellitus (DM). This case-controlled study was conducted within a one-year period, during year 2016, at outpatient retina ophthalmology clinics of Shiraz, southern Iran. Eighty-three patients with type 2 DM, referring for ophthalmoscopy evaluation, were included. Anthropometric measures, serum leptin level, and baseline laboratory assessment was performed for all subjects. Patients were categorized as group 1, consisting of patients with severe Non-Proliferative Diabetic Retinopathy (severe NPDR) and Proliferative Diabetic Retinopathy (PDR) (n = 44), and group 2, consisting of patients without Diabetic Retinopathy (no DR) or mild/moderate NPDR (n = 39). The serum leptin level and anthropometric measures were compared between the two study groups. The correlation between these variables was also assessed. The mean age of the participants was 59.3 ± 6.9 years old. The two study groups were comparable regarding baseline characteristics. Cases of group 1 had significantly higher Erythrocyte Sedimentation Rate (ESR) (P = 0.049) and Systolic Blood Pressure (P = 0.025) when compared with those of group 2. The serum level of leptin was found to be significantly higher in cases of group 1 when compared to those of group 2 (P = 0.003). However, anthropometric measures, including Body Mass Index (BMI) (P = 0.167), Body Adiposity Index (BAI) (P = 0.061), and Waist to Hip Ratio (WHR) (P = 0.220) were comparable between the two study groups. Serum leptin level was positively correlated with BMI (r = 0.819; P < 0.001) and BAI (r = 0.630; P < 0.001) in group 1. Increased serum levels of leptin were associated with advanced stages of DR in subjects with type 2 DM. Serum leptin level might be a better indicator of the effects of obesity on DR, compared to anthropometric measures (BAI or BMI).

KEY WORDS

Diabetic Retinopathy; Leptin; Body Mass Index; Body Adiposity Index; Waist to Hip Ratio

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INTRODUCTION

Diabetic retinopathy (DR) is considered an important and devastating microvascular complication of Diabetes Mellitus (DM). Proliferative diabetic retinopathy (PDR) is associated with decreased visual acuity, retinal

detachment, hemorrhage, and complete loss of vision [1-3]. The prevalence of DRwas reported as 37% in patients with type 2 DM, from whom 27.3% had Non-Proliferative (NPDR) and 9.6% had PDR. The prevalence of Clinically Significant Macular Edema (CSME) and sight threatening retinopathy was reported as 5.8% and 14.0%, respectively [4, 5]. Hypertension, anemia, renal failure, serum level of Hemoglobin A1C (HbA_1C), age, type of DM, renal disease, physical inactivity, and inflammatory biomarkers were determined as risk factors for DR in patients with DM [6, 7]. Obesity is a morbid state, affecting many organs and many of the risk factors of DR. Metabolic syndrome is characterized by obesity, insulin resistance, hyperinsulinemia, hypertension, hyperlipidemia, and inflammation, which result in endothelial dysfunction and pathogenesis of DR [8]. It has been well-demonstrated that DR is associated with obesity, determined by Body Mass Index (BMI), Visceral Fat Accumulation (VFA), and Body Adiposity Index (BAI) [9-11]. Several lines of evidence have demonstrated that adipocytokines have pathophysiologic roles in complications related to obesity. Leptin is an adipocytokine that acts directly on the hypothalamus. It regulates energy expenditure and food intake [12]. Serum levels of leptin have been associated with obesity and obesity-associated microvascular complications [13, 14]. Evidence has also suggested the role of leptin in the pathogenesis of DR. It has been demonstrated that serum levels of leptin are associated with proliferative retinopathy, when compared with non-proliferative retinopathy [15-17]. In addition, vitreous levels of leptin are higher in those with PDR or retinal detachment [18, 19]. However, controversy still exists in this regard, while some studies have failed to demonstrate any association between serum leptin levels and DR [20]. Thus, the search for the role of leptin in pathogenesis of DR is still underway. The aim of the current study was to determine the association amongst serum leptin levels and anthropometric measures (BMI, BAI, and Waist to Hip Ratio) with the severity of DRin subjects with type 2 DM.

MATERIALS AND METHODS

This case-controlled study was conducted at Poostchi outpatient ophthalmology clinic, affiliated to Shiraz University of Medical Sciences, Shiraz, Southern Iran, during a one-year period, form February, 2016 to February, 2017. The study protocol was approved by the Institutional Review Board (IRB) and the medical ethics committee of Shiraz University of Medical Sciences and all patients provided informed written consents before being included in the study. This study included adult (>18 years) patients with type 2 DM, referring to the clinic of study during the study period for screening of DR. The diagnosis of DM was based on standard criteria by two endocrinologists. This study excluded those with type 1 DM, renal impairment with an estimated Glomerular Filtration Rate (eGFR) of <30 mL/min/1.73 m^2, secondary hypertension (renal vascular hypertension, primary aldosteronism, pheochromocytoma, and hyperthyroidism), liver dysfunction, chronic pulmonary disease, arteriosclerotic obliterans, severe anemia, sleep apnea syndrome, and symptomatic cerebrovascular disease. Those taking thiazolidinediones and corticosteroids, pregnant subjects, those with malignancies or immunodeficiency, were also excluded. All patients were evaluated initially and medical history and physical examination findings were recorded. The demographic data, weight, height, hip diameter, waist circumference, drug history, and DM duration were also recorded. The BMI was calculated as the weight in kilograms divided by the square of the height in meters. Waist to Hip Ratio (WHR) was also used as an index of obesity. Furthermore, BAI was calculated by a formula suggested by Bergman et al. [21].

All patients underwent complete ophthalmoscopic examination, including air puff applanation tonometry, slit lamp biomicroscopy, binocular indirect slit lamp fundoscopy, and fundus photography, after mydriasis was performed. Color fundus photographs of two fields, which included macular field and disc/nasal field of both eyes, were taken using a 45° fundus camera (DRS: Digital Retinography System). The physical examination as well as the two-field 45° fundus photography and standard photographs were used to grade retinal lesions, according to international clinical disease severity scale based on the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR) and Early Treatment Diabetic Retinopathy Study (ETDRS) [22]. The more seriously affected eye was the basis of evaluation of the grade of the disease. Diagnosis of DR was made by vitreo-retinal fellowships, according to the presence of one or more of the following clinical characteristics in the fundus: Venous beading, hard or soft exudates, hemorrhages, intra-retinal microvascular abnormalities, pre-retinal new vessels, cotton wool spots, fibrous proliferation, and scars of panretinal photocoagulation. Based on the ophthalmologic examination, the participants were divided to the following two groups: patients with severe severe NPDR and PDR (group 1); and patients without DR or mild/moderate NPDR (group 2). Patients with vitreous hemorrhage or tractional retinal detachment were placed in the first study group. A 10-cc sample of venous

blood was withdrawn from each subject, from the cubital vein for laboratory assessment. Fasting Blood Sugar (FBS), HbA1c, Complete Blood Count (CBC), lipid profile containing High Density Lipoprotein (HDL), Low Density Lipoprotein (LDL), total cholesterol, triglycerides, renal function tests, Erythrocyte Sedimentation Rate (ESR), and C Reactive Protein (CRP) were measured, according to a standard protocol. The serum level of leptin was assessed by the Enzyme Linked Immunosorbent Assay (ELISA) kit of Labor Diagnostika Nord Gmbh & Co (LDN). Coefficient of Variation (CV) for intra-assay and inter-assay precision were reported to be 3.7% to 5.0% and 5.9% to 6.8%, respectively. All measurements of leptin were done during one session and at the same time, according to the manufacturer's instructions. All the data are presented as mean ± Standard Deviation (SD) and proportions, as appropriate. The parametric variables with normal distribution were compared using independent t-test while those without normal distribution were compared using the Mann-Whitney U-test. Proportions were compared using the chi-squared test. The linear correlation between the serum level of leptin and the anthropometric measures was determined by Pearson's correlation analysis. A multivariate logistic regression model was used to measure the influence of independent variables (leptin, GFR, Creatinine, TG, total cholesterol, Gender, LDL, CRP, and ESR) on the dependent variable (retinopathy groups). A two-sided p-value of less than 0.05 was considered statistically significant. This study also reported the correlation coefficients for the correlation analysis.

RESULTS

Overall, the current research screened 84 patients for eligibility, of whom one was not included. Thus, a total of 83 patients were included.

Table 1: The Baseline Characteristics of Patients with Type 2 Diabetes Mellitus included in the Current Study, in Two Study Groups

	Group 1 (n = 44) mean ± SD	Group 2 (n = 39) mean ± SD	P-Value *
Age (years)	59.3 ± 6.33	58.7 ± 7.69	0.125
Gender			0.101
Male (%)	28 (63.4%)	18 (46.2%)	
Female (%)	16 (36.6%)	21 (53.8%)	
Glycemic control			0.701
Oral medication (%)	22 (54.6%)	22 (56.5%)	
Insulin (%)	20 (45.4%)	17 (43.5%)	
Disease duration			0.133
≥ 10 years (%)	23 (52.3%)	14 (35.9%)	
< 10 years (%)	19 (47.7%)	25 (64.1%)	
Hb (g/dL)	13.6 ± 1.88	13.83 ± 1.56	0.553
FBS (mg/dL)	153.93 ± 77.9	159.21 ± 61.8	0.327
GFR (mL/min/1.73 m^2)	68.95 ± 24.17	75.24 ± 15.30	0.162
TG (g/dL)	138.02 ± 63.2	143.63 ± 68.5	0.704
Cholesterol (mg/dL)	164.21 ± 44.7	153.50 ± 40.36	0.262
HDL (mg/dL)	45.53 ± 12.7	49.58 ± 47.67	0.351
LDL (mg/dL)	86.86 ± 32.72	89.89 ± 39.79	0.711
HbA1c (%)	7.67 ± 2.18	7.26 ± 1.57	0.325
ESR (mm/hr)	19.98 ± 21.49	10.24 ± 7.91	**0.049**
CRP (mg/L)	5.86 ± 16.63	1.42 ± 2.93	0.497
SBP (mmHg)	139.53 ± 17.34	131.71 ± 15.34	**0.025**
DBP (mmHg)	89.30 ± 11.12	85.92 ± 8.37	0.691

n: Number; SD: Standard Deviation; %: Percentage; FBS: Fasting Blood Sugar; CRP: C-reactive Protein; DBP: Diastolic Blood Pressure; ESR: Erythrocyte Sedimentation Rate; GFR: Glomerular filtration rate; Hb: Hemoglobin; HDL: High-density lipoprotein; LDL: Low-density Lipoprotein; SBP: Systolic blood pressure; TG: Triglyceride ;g/dl : Grams per Deciliter ; mg/dl : Milligrams per Deciliter ; mg/l: Milligrams per Litre; kg/m2: Kilogram per Square Meter; mmHg: Millimeter of Mercury; mm/hr: millimeter per hour; mL/min/1.73 m^2: milliliter per minute per 1.73 square meters.

*** P-Value less than 0.05 are in Bold**

Table 2 The Baseline Characteristics of Patients with Type 2 Diabetes Mellitus included in the Current Study in Two Study Groups

	Group 1 (n = 44) mean ± SD	Group 2 (n = 39) mean ± SD	P-Value *
Serum leptin (ng/mL)	40.39 ± 33.15	19.29 ± 14.37	**0.003**
BMI (kg/m^2)	29.58 ± 5.33	27.88 ± 4.46	0.167
BAI (%)	0.343 ± 0.081	0.311 ± 0.047	0.061
WHR	0.934 ± 0.028	0.943 ± 0.021	0.220

n: Number ;ng/dl : Nano grams per Deciliter ; kg/m2: Kilogram per Square Meter ; %: Percentage; SD: Standard Deviation; BMI: Body Mass Index; BAI: Body Adiposity Index; WHR: Waist-to-Hip Ratio

*** P-Value less than 0.05 are in Bold**

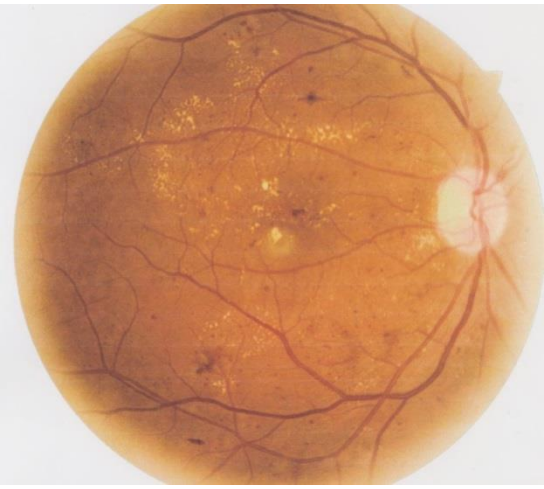

Figure 1: A 65-year-old male with corrected distance visual acuity of 40/200 in both eyes with severe non-proliferative diabetic retinopathy and CSME categorized in group 1.

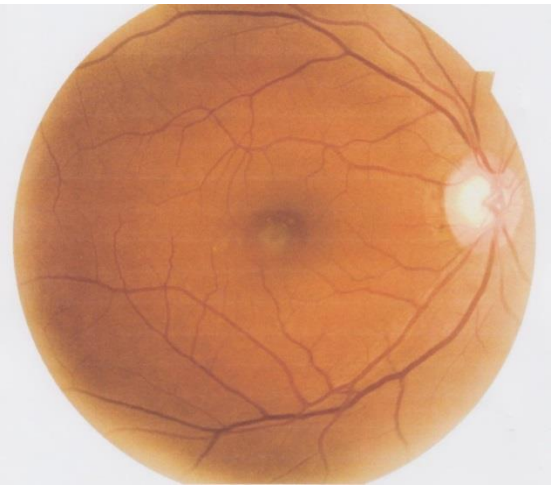

Figure 3: A 53-year-old female with no diabetic retinopathy categorized in group 2.

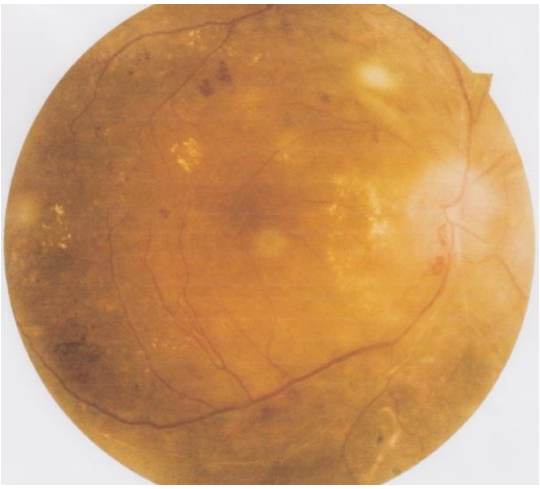

Figure 2: A 68-year-old male with active proliferative diabetic retinopathy and history of previous pan-retinal photo coagulation categorized in group 1.

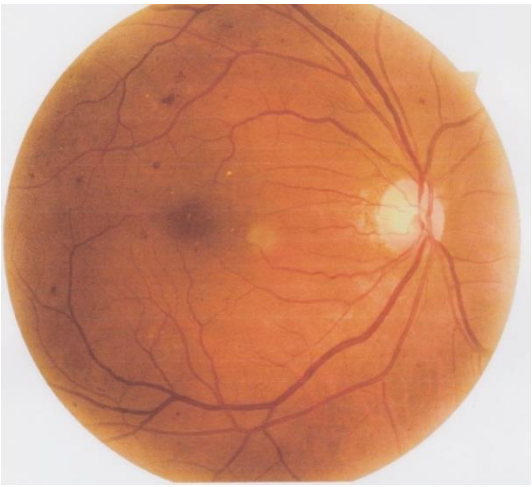

Figure 4: A 60-year-old male with non-proliferative diabetic retinopathy and diabetic macular edema categorized in group 2.

The mean age of the participants was 59.3 ± 6.9 (ranging from 42 to 78) years. In total, there were 46 (55.4%) males and 37 (44.6%) females. Based on the ophthalmoscopic examination, 44 (53%) cases were included in the PDR group, while 39 (47%) were included in the NPDR group. The two study groups were comparable regarding baseline characteristics, such as age and gender. The baseline characteristics of the two study groups are summarized in Table 1.

As demonstrated, those in group 1 had significantly higher ESR (P = 0.049) and systolic blood pressure (P = 0.025) when compared to those in group 2. The comparison between the two study groups, regarding the anthropometric measures and the serum leptin level, is demonstrated in Table 2.

The serum level of leptin was found to be significantly higher in group 1 when compared to that of group 2 (P = 0.003). However, the anthropometric measures, including BMI (P = 0.167), BAI (P = 0.061), and WHR (P = 0.220) were comparable between the two study groups. The serum level of leptin remained significantly higher in group 1 when compared to that of group 2, after adjusting for GFR, age, HbA1C, SBP, TG, HDL, LDL, and ESR (P = 0.001), though the multivariate logistic regression model. Serum leptin level was positively correlated with BMI (r = 0.819; P < 0.001) and BAI (r = 0.630; P < 0.001) in group 1. In group 2, serum leptin level had a linear positive correlation with BMI (r = 0.521; P = 0.042) and BAI (r = 0.568; P = 0.008). In those with PDR, the serum leptin level was also associated with ESR (r = 0.423; P = 0.032). Sample color fundus photographs of both study groups illustrated in figure 1 to 4.

DISCUSSION

In the current study, the researchers compared the serum levels of leptin among patients with type 2 DM, having various degrees of DR. Higher serum leptin levels were found in patients with severe DR (severe NPDR or PDR) compared to those with mild to moderate NPDR. However, the anthropometric measures, such as BMI and BAI, were not found to be associated with severity of DR. These results are in line with previous studies that found serum and vitreous levels of leptin as an indicator of extension of DR in patients with type 2 DM [9, 18, 19]. According to the results of the current study, it could be suggested that serum leptin level is a more valuable marker of DR extension in subjects with type 2 DM and is superior to anthropometric measures of obesity. Measurement of serum level of leptin is accessible, feasible, and inexpensive, and could be available even at secondary healthcare centers. Thus, its addition to screening programs of patients with type 2 DM could be beneficial. Several studies have indicated that leptin has the ability to influence CRP expression, both by affecting other pro-inflammatory modulators, such as IL6, and by promoting its hepatic and vascular production [23, 24]. In turn, CRP causes leptin resistance, by changing its bioavailability and co-precipitating with this molecule [24, 25]. This study measured ESR and CRP, as markers of the inflammatory state. The two study groups were comparable regarding serum CRP levels. The ESR level was significantly higher in patients with more severe DR. The current research found a positive correlation between ESR and leptin level in patients with PDR. This indicates that inflammation plays a role in the pathophysiology of DR, separately, or as part of the effects of leptin. This might be due to the complex endocrine and pro-inflammatory nature of leptin [26]. This theory was suggested regarding the increase in the strength of correlation between leptin and DR after omitting ESR from the equation. Therefore, ESR may be considered as an adjunctive factor to leptin rather than a confounding one in the pathophysiology of diabetic retinopathy. To prove this assumption, further investigations are required. Elevated vitreous levels of leptin in patients with PDR have been observed in some studies [18, 19], yet intraocular production, as a cause of this elevation, has been rejected by some others [20]. It is not clear whether the increase in vitreous levels of leptin is paracrine or is the result of active permissive mechanisms [18]. Simultaneous measurement of plasma and vitreous leptin is needed for further clarification.

The measured leptin level was compatible with previously measured leptin levels in patients with diabetes [13]. Increase in leptin level was associated with increased risk of development of DR [9, 13]. In fact, one-unit increase in leptin increased the chance of having more severe stages of retinopathy by 5.4%, which is in concordance with previous studies [15]. Multiple studies have investigated the correlation of indices, such as BMI, WHR, and BAI, as indices of obesity with DR [27-29]. Previous studies have shown different results regarding BMI. Increased BMI has been protective for DR in some instances [29, 30] and predictive of DR in others [31]. This research did not find any statistically significant differences in BMI, BAI or WHR between the two study groups. This may be due to the fact that factors, such as calorie intake, physical activity, and lifestyle modifications were not taken in account by the current study. Although increase in BMI and BAI is associated with increase in leptin level, it is not correlated with development of retinopathy. This may indicate the effect of leptin in DR, as an endocrine hormone.

Measurements, such as BMI and BAI, indicate the total body fat amount without being able to measure its activity as a functional unit. This research found no correlation between these measurements and presence of more severe stages of DR, which means that total body fat was not a risk factor for development of DR in the current research. Instead, if one considers fat tissue as a functional organ and measures its hormonal activity, leptin may be a better indicator. It could be suggested that leptin, if not a replacement of BMI and BAI, is a good adjunctive measure to these tests for evaluation of fat tissue and its effect on retina in diabetes. With the increased role of anti-VEGF agents in the treatment of diabetic macular edema, certain groups of patients showed a less optimal response to these agents [32, 33]. This mandates a search for alternative treatment pathways. Targeting leptin in this group of patients may provide other means of treatment in the future. There were a number of limitations in the current study. First, the research included a limited number of patients; as a case-controlled study, it would be difficult to match the patients and the controls, thus, this research applied a rigorous inclusion and exclusion criteria to eliminate the confounders. A multivariate logistic regression model was also employed for this purpose while the power of the study was 80%. Further studies with larger study populations and prospective nature are required. The other limitation was that the researchers did not include a control group with normal and non-diabetic patients. Finally, the current research did not take daily energy expenditure and activity into account, which may have influenced the leptin level [13]. Also, there were no means of measuring endogenous insulin. Finally, liver function was not assessed. These pitfalls should be addressed in further studies.

CONCLUSION

Increased serum level of leptin was associated with advanced stages of DR in subjects with type 2 DM. Thus, the serum leptin level might be a better indicator of the effects of obesity on DR compared to anthropometric measures (BAI or BMI).

DISCLOSURE

Ethical issues have been completely observed by the authors. All named authors met the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this manuscript, take responsibility for the integrity of the work as a whole, and have given final approval for the version to be published. No conflict of interest has been presented.

REFERENCES

1. Thomas RL, Dunstan FD, Luzio SD, Chowdhury SR, North RV, Hale SL, et al. Prevalence of diabetic retinopathy within a national diabetic retinopathy screening service. Br J Ophthalmol. 2015;99(1):64-8. doi: 10.1136/bjophthalmol-2013-304017 pmid: 25091950
2. Song SJ, Han K, Choi KS, Ko SH, Rhee EJ, Park CY, et al. Trends in diabetic retinopathy and related medical practices among type 2 diabetes patients: Results from the National Insurance Service Survey 2006-2013. J Diabetes Investig. 2018;9(1):173-8. doi: 10.1111/jdi.12655 pmid: 28294558
3. Ting DS, Cheung GC, Wong TY. Diabetic retinopathy: global prevalence, major risk factors, screening practices and public health challenges: a review. Clin Exp Ophthalmol. 2016;44(4):260-77. doi: 10.1111/ceo.12696 pmid: 26716602
4. Javadi MA, Katibeh M, Rafati N, Dehghan MH, Zayeri F, Yaseri M, et al. Prevalence of diabetic retinopathy in Tehran province: a population-based study. BMC Ophthalmol. 2009;9:12. doi: 10.1186/1471-2415-9-12 pmid: 19835608
5. Kyari F, Tafida A, Sivasubramaniam S, Murthy GV, Peto T, Gilbert CE, et al. Prevalence and risk factors for diabetes and diabetic retinopathy: results from the Nigeria national blindness and visual impairment survey. BMC Public Health. 2014;14:1299. doi: 10.1186/1471-2458-14-1299 pmid: 25523434
6. Sabanayagam C, Yip W, Ting DS, Tan G, Wong TY. Ten Emerging Trends in the Epidemiology of Diabetic Retinopathy. Ophthalmic Epidemiol. 2016;23(4):209-22. doi: 10.1080/09286586.2016.1193618 pmid: 27355693
7. Yau JW, Rogers SL, Kawasaki R, Lamoureux EL, Kowalski JW, Bek T, et al. Global prevalence and major risk factors of diabetic retinopathy. Diabetes Care. 2012;35(3):556-64. doi: 10.2337/dc11-1909 pmid: 22301125
8. Tomic M, Ljubic S, Kastelan S, Gverovic Antunica A, Jazbec A, Poljicanin T. Inflammation, haemostatic disturbance, and obesity: possible link to pathogenesis of diabetic retinopathy in type 2 diabetes. Mediators Inflamm. 2013;2013:818671. doi: 10.1155/2013/818671 pmid: 24363502
9. Anan F, Masaki T, Ito Y, Eto T, Umeno Y, Eshima N, et al. Diabetic retinopathy is associated with visceral fat accumulation in Japanese type 2 diabetes mellitus patients. Metabolism. 2010;59(3):314-9. doi: 10.1016/j.metabol.2009.06.001 pmid: 20004426
10. Rooney D, Lye WK, Tan G, Lamoureux EL, Ikram MK, Cheng CY, et al. Body mass index and retinopathy in Asian populations with diabetes mellitus. Acta Diabetol. 2015;52(1):73-80. doi: 10.1007/s00592-014-0602-2 pmid: 24880522
11. Thivel D, O'Malley G, Pereira B, Duche P, Aucouturier J. Comparison of total body and abdominal adiposity indexes to dual x-ray absorptiometry scan in obese adolescents. Am J Hum Biol. 2015;27(3):334-8. doi: 10.1002/ajhb.22643 pmid: 25327573
12. Borer KT. Counterregulation of insulin by leptin as key component of autonomic regulation of body weight. World

J Diabetes. 2014;5(5):606-29. doi: 10.4239/wjd.v5.i5.606 pmid: 25317239
13. Considine RV, Sinha MK, Heiman ML, Kriauciunas A, Stephens TW, Nyce MR, et al. Serum immunoreactive-leptin concentrations in normal-weight and obese humans. N Engl J Med. 1996;334(5):292-5. doi: 10.1056/NEJM199602013340503 pmid: 8532024
14. Pradeepa R, Surendar J, Indulekha K, Chella S, Anjana RM, Mohan V. Association of serum adiponectin with diabetic microvascular complications among south Indian type 2 diabetic subjects - (CURES-133). Clin Biochem. 2015;48(1-2):33-8. doi: 10.1016/j.clinbiochem.2014.10.009 pmid: 25445230
15. Suganami E, Takagi H, Ohashi H, Suzuma K, Suzuma I, Oh H, et al. Leptin stimulates ischemia-induced retinal neovascularization: possible role of vascular endothelial growth factor expressed in retinal endothelial cells. Diabetes. 2004;53(9):2443-8. pmid: 15331557
16. Uckaya G, Ozata M, Bayraktar Z, Erten V, Bingol N, Ozdemir IC. Is leptin associated with diabetic retinopathy? Diabetes Care. 2000;23(3):371-6. pmid: 10868868
17. Er H, Doganay S, Ozerol E, Yurekli M. Adrenomedullin and leptin levels in diabetic retinopathy and retinal diseases. Ophthalmologica. 2005;219(2):107-11. doi: 10.1159/000083270 pmid: 15802936
18. Maberley D, Cui JZ, Matsubara JA. Vitreous leptin levels in retinal disease. Eye (Lond). 2006;20(7):801-4. doi: 10.1038/sj.eye.6702011 pmid: 16052255
19. Gariano RF, Nath AK, D'Amico DJ, Lee T, Sierra-Honigmann MR. Elevation of vitreous leptin in diabetic retinopathy and retinal detachment. Invest Ophthalmol Vis Sci. 2000;41(11):3576-81. pmid: 11006255
20. Dossarps D, Petit JM, Guiu B, Cercueil JP, Duvillard L, Bron AM, et al. Body fat distribution and adipokine secretion are not associated with diabetic retinopathy in patients with type 2 diabetes mellitus. Ophthalmic Res. 2014;51(1):42-5. doi: 10.1159/000355323 pmid: 24217637
21. Bergman RN, Stefanovski D, Buchanan TA, Sumner AE, Reynolds JC, Sebring NG, et al. A better index of body adiposity. Obesity (Silver Spring). 2011;19(5):1083-9. doi: 10.1038/oby.2011.38 pmid: 21372804
22. Klein R, Knudtson MD, Lee KE, Gangnon R, Klein BE. The Wisconsin Epidemiologic Study of Diabetic Retinopathy: XXII the twenty-five-year progression of retinopathy in persons with type 1 diabetes. Ophthalmology. 2008;115(11):1859-68. doi: 10.1016/j.ophtha.2008.08.023 pmid: 19068374
23. Chiu FH, Chuang CH, Li WC, Weng YM, Fann WC, Lo HY, et al. The association of leptin and C-reactive protein with the cardiovascular risk factors and metabolic syndrome score in Taiwanese adults. Cardiovasc Diabetol. 2012;11:40. doi: 10.1186/1475-2840-11-40 pmid: 22533665
24. Hribal ML, Fiorentino TV, Sesti G. Role of C reactive protein (CRP) in leptin resistance. Curr Pharm Des. 2014;20(4):609-15. pmid: 23688010
25. Procopio C, Andreozzi F, Laratta E, Cassese A, Beguinot F, Arturi F, et al. Leptin-stimulated endothelial nitric-oxide synthase via an adenosine 5'-monophosphate-activated protein kinase/Akt signaling pathway is attenuated by interaction with C-reactive protein. Endocrinology. 2009;150(8):3584-93. doi: 10.1210/en.2008-0921 pmid: 19359389
26. Chen K, Li F, Li J, Cai H, Strom S, Bisello A, et al. Induction of leptin resistance through direct interaction of C-reactive protein with leptin. Nat Med. 2006;12(4):425-32. doi: 10.1038/nm1372 pmid: 16582918
27. Dirani M, Xie J, Fenwick E, Benarous R, Rees G, Wong TY, et al. Are obesity and anthropometry risk factors for diabetic retinopathy? The diabetes management project. Invest Ophthalmol Vis Sci. 2011;52(7):4416-21. doi: 10.1167/iovs.11-7208 pmid: 21482643
28. Kastelan S, Salopek Rabatic J, Tomic M, Gverovic Antunica A, Ljubic S, Kastelan H, et al. Body mass index and retinopathy in type 1 diabetic patients. Int J Endocrinol. 2014;2014:387919. doi: 10.1155/2014/387919 pmid: 24696683
29. Raman R, Rani PK, Gnanamoorthy P, Sudhir RR, Kumaramanikavel G, Sharma T. Association of obesity with diabetic retinopathy: Sankara Nethralaya Diabetic Retinopathy Epidemiology and Molecular Genetics Study (SN-DREAMS Report no. 8). Acta Diabetol. 2010;47(3):209-15. doi: 10.1007/s00592-009-0113-8 pmid: 19326040
30. Lu J, Hou X, Zhang L, Jiang F, Hu C, Bao Y, et al. Association between body mass index and diabetic retinopathy in Chinese patients with type 2 diabetes. Acta Diabetol. 2015;52(4):701-8. doi: 10.1007/s00592-014-0711-y pmid: 25604042
31. Kastelan S, Tomic M, Gverovic Antunica A, Ljubic S, Salopek Rabatic J, Karabatic M. Body mass index: a risk factor for retinopathy in type 2 diabetic patients. Mediators Inflamm. 2013;2013:436329. doi: 10.1155/2013/436329 pmid: 24347825
32. Khan AA, Rahmani AH, Aldebasi YH. Diabetic Retinopathy: Recent Updates on Different Biomarkers and Some Therapeutic Agents. Curr Diabetes Rev. 2017. doi: 10.2174/1573399813666170915133253 pmid: 28914194
33. Castillo J, Aleman I, Rush SW, Rush RB. Preoperative Bevacizumab Administration in Proliferative Diabetic Retinopathy Patients Undergoing Vitrectomy: A Randomized and Controlled Trial Comparing Interval Variation. Am J Ophthalmol. 2017;183:1-10. doi: 10.1016/j.ajo.2017.08.013 pmid: 28860046