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ROLE OF SOLUBLE LR11 AND APOLIPOPROTEINS A1&B IN THE PROGRESSION OF DIABETIC RETINOPATHY

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Abstract:-To evaluate the serum and vitreous fluid levels of soluble lipoprotein receptor LR11 (sLR11), a novel circulating marker for proliferative diabetic retinopathy (PDR), in patients with PDR and non-PDR (NPDR) in comparison to those in patients with non-diabetic ocular diseases. Also, we evaluate serum levels of apo A1 and B in all studied groups. Fifteen NPDR and 20 PDR cases were included in this study. Ten subjects with macular hole were served as a control group. The sLR11 and apo A1 & B levels were determined by sandwich enzyme-linked immune-sorbent assay. The serumsLR11 levels in the PDR and NPDR groups were significantly higher than those in the control subjects. The vitreous fluid levels of sLR11 were significantly elevated in the PDR while in the NPDR group; it was higher than in the control group, but not statistically significant. Serum apolipoprotein A1 is significantly decreased in PDR compared to NPDR patients, while serum apolipoprotein B were significantly elevated in PDR patients compared to NPDR.sLR11 may be a novel predictor for the early development of PDR patients prior to the increase in the circulating levels in diabetics. Serum apoAI, apoB levels, and the apoB-to-apoAI ratio were consistently associated with the presence of diabetic retinopathy and severity of diabetic retinopathy.

Keywords: Diabetic retinopathy, soluble LR11, apolipoproteins A1&B.

I.INTRODUCTION:

Diabetic retinopathy and other microvascular complications are major causes of morbidity in patients with diabetes. It is caused primarily by diffuse endothelial damage at the micro vascular level and is closely associated with increased cardiovascular mortality (Rajala *et al.*, 2000).

LR11 (also called SorLA or SORL1), a low-density lipoprotein receptor family member, is a molecule expressed in intimal smooth muscle cells associated with development of atherosclerosis and endothelial cells in dyslipidemia (Bujo & Saino, 2006).

The released soluble form of LR11 (sLR11) promotes pathological infiltration of macrophages into the damaged vessels (Ting et al., 2007). The circulating sLR11 levels were reported to increase in patients with coronary artery disease and in subjects with carotid atherosclerosis (Jiang *et al.,* 2008). A multivariate analysis in these independent studies in patients with atherosclerosis indicated that the sLR11 level was correlated with the glycemic level among the classic risk factors for atherosclerosis (Takahashi *et al.*, 2010). Shiba et al. (2013) have recently investigated the relevance of circulating sLR11 to proliferative diabetic retinopathy (PDR) in patients with type 2 diabetes mellitus, and found that the serum sLR11 levels were higherin patients with PDR than in patients with non-PDR (NPDR).

Serum apolipoprotein (apo) A and -B have been shown to be associated with diabetic retinopathy, but the underlying mechanisms are unclear. Recently, it was reported that serum apolipoprotein (apo)AI and apoB levels were strongly associated with the presence and severity of diabetic retinopathy (Cheung&Wong, 2009) and these

associations were more prominent than those of traditional lipids (e.g., total cholesterol). However, the underlying mechanisms in which apos influence diabetic retinopathy remain unclear (Cheung *et al*., 2010). There is limited evidence that lower apoAI or higher apoB levels are correlated with signs of microvascular dysfunction (Hirsch and Brwonlee, 2010), one of the key events in the pathogenesis of diabetic retinopathy (Lyons *et al*., 2004). We therefore hypothesize that impaired microvascular function may be an underlying mechanism for the association between apoAI and apoB with diabetic retinopathy.

In this study, the vitreous fluid levels as well as the serum sLR11 in patients with PDR and NPDR in comparison to those with non-diabetic ocular diseases were evaluated. Also, we aimed to investigate the association of serum apoAI, apoB, and traditional lipid levels in patients with and without diabetic retinopathy with systemic and retinal microvascular function.

MATERIALS AND METHODS

A total of 35 patients with type 2 diabetes (15 consecutive NPDR cases and 20 consecutive PDR cases), were included in this study. PDR was defined according to the international clinical classification of diabetic retinopathy as the neovascularization in the retina All patients with NPDR underwent vitreous surgery for diabetic macular edema; patients with PDR underwent vitreous surgery for vitreous hemorrhage and tractional retinal detachment. Vitreous fluid samples also were obtained from 10 subjects with a macular hole without diabetic mellitus who served as a control group.

FUNDUS FINDINGS

All patients were evaluated by biomicroscopy using a fundus contact lens and gonioscopy with a slit-lamp. The severity of diabetic retinopathy was graded according to the international clinical classification of diabetic retinopathy.

SAMPLE COLLECTION

Samples of vitreous fluid were carefully obtained to prevent the contamination of obvious hemorrhage mass, and no vitreous hemorrhages developed at the time of vitreous surgery. The samples of vitreous fluid were rapidly frozen at - 80°C. Fasting blood samples were collected from the patients with NPDRand PDR. Blood was centrifuged immediately at 4,000 g for 10 minutes, and the supernatant was frozen immediately in polypropylene tubes and stored at - 80°C until use. The sLR11 level and apo A1&B were determined by ELISA technique. Lipid profile and FBS were measured using standard laboratory techniques.

STATISTICAL ANALYSIS

The results of the present study are shown ± standard deviation. The statistical analyses are performed using SPSS statistical Package for windows software program version 18. Comparisons between groups performed using student T. test. The data were subjected to Mann-Whitney U (non-parametric two independent sample tests, one way analysis of variance ANOVA and Tukey's post hoc test. A Pearson correlation coefficient analysis is used to assess the associations between measured parameters. The sensitivity and specificity with respect to presence of PDR are analyzed using a conventional receiver operating characteristic (ROC) cure P value less than 0.05 it considered to be statistically significant.

RESULTS

This study included the age matched and gender matched NPDR and PDR groups included 15 and 20 patients, respectively 8 male and 7 female in NPDR patients and 15 male and 5 female in PDR patients, P>0.05, the mean age 66.9 ± 7.4 in NPDP while in PDR the mean years age 64.9 ± 6.1 years. P> 0.05. Laboratory investigation of non-proliferative diabetic retinopathy NPDR and PDR patients are shown in Table (1).

Table 1: Serum fasting blood glucose levels and lipid profile in NPDR and PDR patients.

Parameters	NPDR Mean ± SD	PDR Mean ± SD	P value
Total cholesterol mg/dl	240.5±13.3	287.8±32.9	<0.05
LDL cholesterol mg/dl	152.9±29.1	149.7±31.7	N.S
HDL cholesterol mg/dl	41.6±6.2	49.3±8.3	N.S
Fasting blood glucose mg/dl	151.3±69.5	197.5±64.5	<0.05

P<0.05 significant

- ❖ The mean fasting blood glucose levels is significantly higher in PDR patients compared to NPDR patients P<0.05.
- ❖ Also, the mean total cholesterol levels is significantly higher in PDR patients compared to NPDR patients P<0.05.
- ❖ While, the LDL cholesterol and HDL cholesterol are not shown statistically significant difference in either NPDR or PDR patients Table (1).
- ❖ Glycosylated Hb1c% are insignificantly different in NPDR & PDR patients by use of Mann-Whitney U (nonparametric two independent sample tests. (Table2)
- ❖ The mean serum levels of sLR II mg/dl are significantly higher in PDR patients compared to NPDR P<0.001 , while the vitreous levels of sLRII mg/dl were higher in PDR patients groups compared to NPDR patients but the difference did not reach significance p=0.005, Table (2).
- ❖ Serum apolipoprotein A (mg/dl) are significantly elevated in NPDR compared to PDR patients p<0.001.
- ❖ While serum apolipoprotein B mg/dl were significantly decreased in NPDR patients P<0.001, Table (2).
- ❖ Table (3) shows that the use of one way ANOVA and Tukey's post hoc test. The mean vitreous sLR11 (ng/dl) are higher in both PDR and NPDR patients compared to controls p<0.001, PDR patients are elevated significantly compared to controls P2<0.001, while the NPDR patients groups sLR11 are higher compared to controls, but the difference did not reach significance P1=0.002, Table (3).
- ❖ The median levels and ranges of vitreous sLR11 ng/dl are illustrated in Table (3) and Fig. (1).
- ❖ To clarify the correction between the serum levels of sLR11 and various laboratory parameters in the PDR patients, Pearson's correlation coefficient of dependent variable is performed. The glycosylated HbA1c% are significantly positive correlated with serum levels of sLR11 r=0.55, P<0001.0 significant positive correlation of vitreous sLR11 with serum sLR11 levels.
- ❖ R=0.95, P<0.001, significant negative correlation of serum apolipoprotein A with serum levels of sLR11, r=-0.797, P<0.001.
- ❖ On the other hand significant positive correlation of serum apolipoprotein B with serum sLR11 r=0.817, P<0.001.

Table 2: Glycosylated hemoglobin A1c (%), serum and vitreous s LR11 serum apolipoprotein A and apolipoprotein B in NPDR and PDR patients.

Test variables	NPDR (mean ±SD)	PDR (mean ±SD)	P-value
1- Glycosylated Hb Ac%	6.7 ± 0.17	6.9 ± 0.29	0.009*
2- Serum of sLRII (ng/dl)	13.4 ± 2.02	20.4 ± 4.46	<0.001*
3- Vitreous of sLRII (ng/dl)	19.2 ± 1.17	25.0 ± 6.03	0.005*
4- Serum Apolipoprotein A (mg/dl)	141.5 ± 4.75	122.6 ± 3.56	<0.001*
5- Serum Apolipoprotein B (mg/dl)	90.7 ± 8.79	118.7 ± 5.83	<0.001*

P<0.05 significant

Table 3: Soluble LR11 levels in vitreous fluid in NPDR and PDR compared to controls.

Test variables	Controls	NPDR (mean ± SD)	PDR (mean±SD)	P-value
Vitreous of sLRII (ng/dl)	11.7 ± 1.48	19.2 ± 1.17	25.0 ± 6.03	<0.001
• Median • Range	11.5 9.3 – 15.1	19.0 16.8 – 21.2	23.5 16.8 - 33.9	

By using one way ANOVA and Tukey's post hoc test:
NPDR compared to the control group (P1= 0.002); PDR compared to the control group (P2 <0.001).

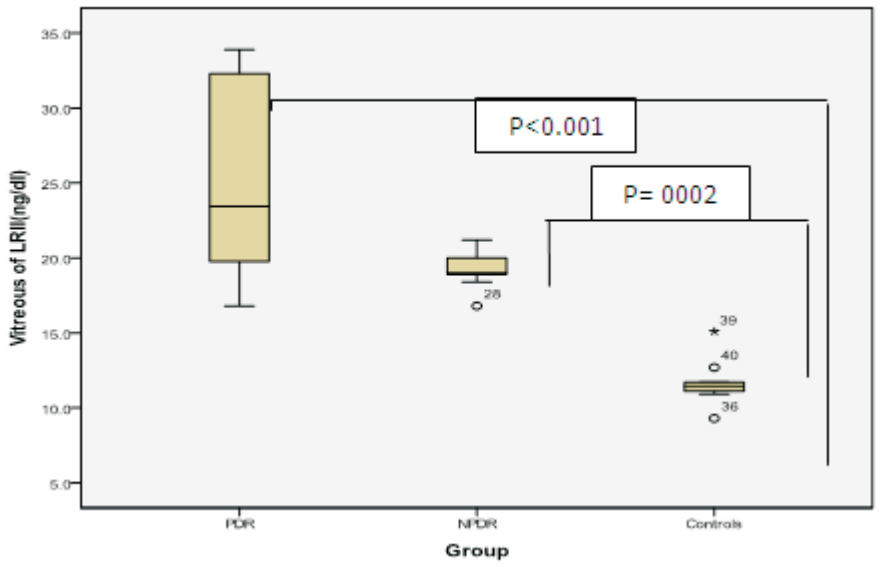

Fig. 1: The vitreous fluid levels of sLR11 in NPDR & PDR groups and macular hole as control group by using the one way ANOVA test and TuKey's post hoc test.

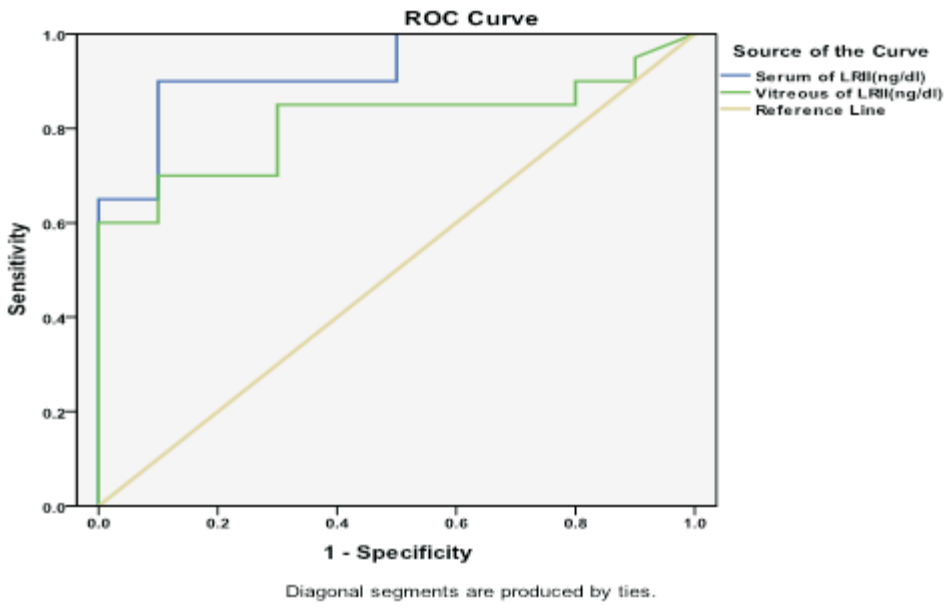

Fig. 2: Receiver operating characteristic curve for discriminating the probability of type 2 diabetes mellitus patients developing PDR from patients without PDR based on the serum & vitreous levels of soluble form Lr11.

The curve shows the fraction of true positive result sensitivity and false positive – result s (specifying for various cutoff levels).

Table 4: Area under the curve analysis receiver operating characteristic investigating cut of P values for PDR.

Test Result Variable(s)	Area	Std. Error [a]	P-value [b]	Asymptotic 95% Confidence Interval	
				Lower Bound	Upper Bound
Serum of LRII (ng/dl)	0.925	0.048	0.000	0.000	1.000
Vitreous of LRII (ng/dl)	0.812	0.079	0.006	0.658	0.967

The test result variable(s): Vitreous of LRII (ng/dl) has at least one tie between the positive actual state group and the negative actual state group. Statistics may be biased. a. Under the nonparametric assumption; b. Null hypothesis: true area = 0.5.

Serum level of LRII (cut off point 16.4 ng/dl) is positive (detecting PDR) with 90 % sensitivity and 90 % specificity. While, vitreous level of LRII (cut off point 19.35 ng/dl) is positive at with 85 % sensitivity and 70% specificity.

RECEIVER OPERATING CHARACTERISTIC (ROC) CURVE

The diagnostic performance or the ability of serum and vitreous sLR11 to be used as a diagnostic tool to predict the development and progression of diabetic retinopathy is evaluated using a receiver operating characteristic (ROC) curve. Roc curve was generated by plotting sensitivity versus specificity of serum and vitreous sLR11 and by selecting cut offs that provide the best combination of sensitivity and specificity. ROC curve determines the threshold value serum and vitreous studied in the groups to get the optimal sensitivity, specificity and the best cut off value that maximizes the sensitivity and specificity.

In this study, (ROC) curve is used to determine the diagnostic performance of serum and vitreous sLR11 in both NPDR and PDR groups to evaluate its performance to predict the progression of retinopathy. Serum levels of sLR11 (cut off point 16.4 ng/dl is true positive results delectating PDR with 90% sensitivity and 90% specificity false positive results. While, vitreous level of sLR11 (cutoff point 19.35 ng/dl is positive at with 85% sensitivity and 70% specificity. Table (4) the area under the curve (Fig. 2).

DISCUSSION

Based on the above background, the purpose of the current study was to investigate the vitreous fluid levels of sLR11, considering the corresponding serum sLR11 levels in patients with or without PDR. The diabetic patients with retinopathy have clearly increased concentrations of serum sLR11 in comparison with healthy normal subjects. Also, the sLR11 levels in the PDR group were increased compared with the NPDR group this agreed with the results of Shiba et al. (2013).

The key cytokines underlying the pathogenesis and development of PDR are similar to those leading to atherosclerosis. The barrier dysfunction of micro-vessels and retinal ischemia provokes an increase in the ocular levels of inflammatory cytokines and growth factors, including vascular endothelial growth factor, platelet-derived growth factor BB (PDGF-BB), and angiotensin II (Imai *et al*., 2010) with increased expression of adhesion molecules, all promoting retinal neovascularization. PDGF-BB and angiotensin II trigger the increased expression of LR11 on vascular smooth muscle cells (Offe *et a*l., 2007).

The LR11 expression in endothelial cells is induced under conditions of dyslipidemia, possibly through the activations of combination of cytokines and adhesion molecules (Mida *et al*., 2007).Thus, considering that endothelial dysfunction is the first sign of microvascular injury at the organ level and that the progression of diabetic microvascular complications is modulated by the severity of hyperglycemia through the gradual damages of the endothelium (Scherezer *et al.*, 2004). A high sLR11 concentration in the serum of diabetic patients with PDR may reflect the pathophysiologic endothelial dysfunction associated with diabetes, although the mechanism responsible for the release of sLR11 in circulation remains unresolved (Ikeuchi et al., 2010).

Also, the analyses of sLR11 concentrations in the vitreous fluid showed that the levels of sLR11 in the PDR group, and surprisingly also in NPDR group, were significantly higher than that in the control group. Future study for vitreous sLR11 levels of patients with diabetic macular edema, which is known to show endothelial dysfunction, is expected to elucidate the pathological role of sLR11 in early diabetic changes of endothelial cells (Takahashi *et al*., 2012).

A significant positive correlation of sLR11 levels were found between the vitreous fluid and serum. The higher levels of sLR11 in vitreous fluid than those in serum suggested that sLR11 in vitreous fluid is not derived from systemic circulation, and possibly reflect the local expression in the eye. In this study, (ROC) curve is used to

determine the diagnostic performance of serum and vitreous sLR11 in both NPDR and PDR groups to evaluate its performance to predict the progression of retinopathy. Serum levels of sLR11 (cut off point 16.4 ng/dl is true positive results delectating PDR with 90% sensitivity and 90% specificity false positive results. While, vitreous level of sLR11 (cutoff point 19.35 ng/dl is positive at with 85% sensitivity and 70% specificity (Takahashi *et al*., 2012).

Thus Considering the lack of sufficient data regarding the role of LR11 in the basic mechanism of diabetic retinopathy, further pathophysiological studies are needed to determine if sLR11 is a systemic or ocular marker or a trigger. Thus, one limitation of the current investigation was the lack of information about sLR11 in the retina and fibro-vascular proliferation in patients with PDR. Second, the current study did not evaluate the relationship between the vitreous fluid levels of sLR11, inflammatory cytokines, and growth factors, including vascular endothelial growth factor, platelet-derived growth factor-BB, and angiotensin II.

Furthermore, the influence of hemorrhage or diabetic macular edema for the vitreous sLR11 levels is not able to be completely excluded, although the current study clarified that the levels of serum LR11 are lower than those in vitreous fluids (Kilpatrrick *et al.*, 2009). Finally, the obtained results were obtained using relatively small sample sets. Clearly, further careful validation studies with larger sample sets to evaluate the effects of sLR11 on micro vascular outcomes as primary end points will be required.

Serum lipids have long been proposed to be risk factors for diabetic retinopathy (Wong *et al.,* 2006), although the relationship of lipids to diabetic retinopathy has been relatively understudied compared with diabetes duration, A1C, and blood pressure. Our study demonstrated that of the traditional lipid measures, only high cholesterol was dependently associated with diabetic retinopathy. However, serum apoAI, apoB, and the apoB-to-apoAI ratio were consistently associated with the presence of diabetic retinopathy and severity of diabetic retinopathy, independent of age, sex, and known diabetic retinopathy risk factors. These findings support previous evidence that traditional serum lipids are not strongly or consistently associated with diabetic retinopathy (Simo *et al.*, 2009 and Sasongko *et al.*, 2012).

ApoAI, the main HDL structural protein that is produced by the liver and intestine, is essential for reverse transport of cholesterol from peripheral tissue to the liver. It also has antioxidant and anti-inflammatory effects (Barter *et al*., 2004). On the contrary, apoB is a major structural protein for VLDL, IDL, and LDL and is responsible for delivering lipids from the liver and intestine to peripheral tissue. Total apoB levels may reflect atherogenic potential (Marcovina and Packard, 2006). There are a few studies showing the presence of apoAI and apoB in intraocular specimens (Wu *et al*., 2011).

Higher apoAI levels in vitreous fluid and retinal pigment epithelium among individuals with diabetes than in those without diabetes suggest protective mechanisms within the retina via apoAI against lipid deposition and inflammation-induced lipotoxicity leading to diabetic retinopathy (Simo *et al*., 2009). Because apoAI has anti-inflammatory and anti-oxidant effects and is also key to intraretinal lipid transport (Tserentsoodol *et al*., 2006), it is conceivable that a low level of this protective agent may promote diabetic retinopathy. Furthermore, evidence showing increased levels of retinal apoB associated with greater severity of diabetic retinopathy suggests that higher apoB levels, which may reflect higher lipoprotein-related toxins, are destructive to the arterial and retinal vascular cells (Wu *et al*., 2011).

In summary, this study presented a novel and potentially clinically relevant new correlation of sLR11 with PDR, thus potentially providing a serum test to indicate patients at greater risk of developing PDR. It was showed that circulating cl sLR11 is predictive of PDR independent of other risk factors. Also, we report new associations among serum apolipoproteins (apoAI, apoB and the apoB-to-apoAI ratio) and the presence and severity of diabetic retinopathy in people with diabetes Although more studies are needed to confirm these findings and to elucidate the mechanisms for these associations, our findings support the fact that these clinically available and feasible apolipoprotein measures may be better biomarkers of diabetic retinopathy than traditional lipid measures.

REFERENCES

1.Barter, P.J., Nicholls S., Rye K.A., Anantharamaiah G.M., Navab M., Fogelman A.M. 2004. Anti-inflammatory properties of HDL. Circ. Res., 95: 764–772.
2.Bujo, H. and Saito Y. 2006. Modulation of smooth muscle cell migration by members of the low-density lipoprotein receptor family. Arterioscler Thromb Vasc Biol., 26: 1246–1252.
3.Cheung, N., Mitchell P., Wong T.Y. 2010. Diabetic retinopathy. Lancet, 376: 124–136.
4.Cheung, N., Wong T.Y. 2009. Diabetic retinopathy and systemic complications. In Diabetic Retinopathy. Duh EJ, Ed. Totowa, NJ, Humana Press, , p. 465–482
5.Hirsch, I.B. and Brownlee M. 2010. Beyond hemoglobin A1c-need for additional markers of risk for diabetic micro-vascular complications. JAMA; 303: 2291–2292.
6.Ikeuchi, T., Hirayama S., Miida T., Fukamachi I., Tokutake T., Ebinuma H., Takubo K., Kaneko H., Kasuga K., Kakita A., Takahashi H., Bujo H., Saito Y., and Nishizawa M. 2010. Increasedlevels of soluble LR11 in cerebrospinal fluid of patients with Alzheimer disease. Dement. Geriatr. Cogn. Disord., 30: 28–32.
7.Imai, E., Horio M., Nitta K., Yamagata K., Iseki K., Hara S., Ura N., Kiyohara Y., Hirakata H., Watanabe T.,

Moriyama T., Ando Y., Inaguma D., Narita I., Iso H., Wakai K., Yasuda Y., Tsukamoto Y., Ito S., Makino H., Hishida A. and Matsuo S. 2007. Estimation of glomerular filtration rate by the MDRD study equation modified for Japanese patients with chronic kidney disease. Clin. Exp. Nephrol., 11: 41–50.
8.Jiang, M., Bujo H., Ohwaki K., Unoki H., Yamazaki H., Kanaki T., Shibasaki M., Azuma K., Harigaya K., Schneider W.J. and Saito Y. 2008. AngII-stimulated migration of vascular SMC is dependent on LR11. J. Clin. Invest., 118: 2733–2746
9.Kilpatrick, E.S., Rigby A.S. and Atkin S.L. 2009. Effect of glucose variability on the long-term risk of microvascular complications in type 1 diabetes. Diabetes Care 32:1901–1903.
10.Lyons, T.J., Jenkins A.J., Zheng D. et al. 2004. Diabetic retinopathy and serum lipoprotein subclasses in the DCCT/EDIC cohort. Invest. Ophthalmol. Vis Sci., 45: 910–918.
11.Marcovina, S. and Packard C.J. 2006. Measurement and meaning of apolipoprotein AI and apolipoprotein B plasma levels. J Intern. Med., 259: 437–446.
12.Mida, T., Takahashi A. and Ikeuchi T. 2007. Prevention of stroke and dementia by statin therapy: experimental and clinical evidence of their pleiotropic effects. Pharmacol. Ther., 113: 378–393.
13.Offe, K., Dodson S.E., Shoemaker J.T., Fritz J.J., Gearing M., Levey A.I. and Lah J.J. 2006. The lipoprotein receptor LR11 regulates amyloidbeta production and amyloid precursor protein traffic in endosomal compartments. J Neurosci 26: 1596–1603
14.Rajala, U., Koskela P., Pajumppaa H. and Keinanen-Kiukaannieemi S. 2000. High cardiovascular disease mortality in subjects with visual impairment caused by diabetic retinopathy. Diabetes Care, 23: 957–961
15.Sasongka, M.B., Wong T.Y., Nguyen T.T. and Kawasaki R. 2012. Serum apo-lipoproteins are associated with retinal microvascular function in people with diabetes Diabetes, 61: 1785- 1792.
16.Scherzer, C.R., Offe K., Gearing M., Rees H.D., Fang G., Heilman C.J., Schaller C., Bujo H., Levey A.I. and Lah J.J. 2004. Loss of apolipoproteinE receptor LR11 in Alzheimer disease. Arch Neurol., 61: 1200–1205.
17.Shiba, T., Bujo H., Takahashi M. and Sato Y. 2013. Vitreous and circulating levels of soluble LR11,a novel, marker for progression of diabetic retinopathy. Graefes Arch. Clin. Exp. Ophthalmol., 2373-9.
18.Simo, R., Garcia-Ramirez M., Higuera M. and Hernandez C. 2009. Apo-lipoprotein A1 is over-expressed in the retina of diabetic patients. Am. J. Ophthalmol., 147: 319–325 e311
19.Takahashi, M., Bujo H., Jiang M., Noike H., Saito Y.and Shirai K. 2010. Enhanced circulating soluble LR11 in patients with coronary organic stenosis. Atherosclerosis, 210: 581–584.
20.Takahashi, M., Bujo H. and Shiba T. 2012. Enhanced circulating soluble LR11 in patients with diabetic retinopathy. Am. J. Ophthalmol., 154: 187-192.
21.Takahashi, M., Bujo H., Shiba T., Jiang M., Maeno T. and Shirai K. 2012. Enhanced circulating soluble lr11 in patients with diabetic retinopathy. Am. J. Ophthalmol., 154: 187–192.
22.Ting, H.J., Stice J.P., Schaff U.Y., Hui D.Y., Rutledge J.C., Knowlton A.A., Passerini A.G. and Simon S.I. 2007. Triglyceride-rich lipoproteins prime aortic endothelium for an enhanced inflammatory response to tumor necrosis factor-alpha. Circ. Res., 100: 381–390.
23.Tserentsoodol, N., Gordiyenko N.V., Pascual I., Lee J.W., Fliesler S.J. and Rodriguez I.R. 2006. Intraretinal lipid transport is dependent on high density lipoprotein-like particles and class B scavenger receptors. Mol. Vis., 12: 1319–1333.
24.Wong, T.Y., Klein R., Islam F.M., et al. 2006. Diabetic retinopathy in a multi-ethniccohort in the United States. Am J Ophthalmol; 141:446–455.
25.Wu, M., Chen Y., Wilson K. et al. 2008. Intra-retinal leakage and oxidation of LDL in diabetic retinopathy. Invest. Ophthalmol. Vis. Sci., 49: 2679–2685.