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Association of Carotid Arterial Resistive Indices and Intima Media Thickness (IMT) With Glycemic Status in Type 2 Diabetic Patients

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Abstract:

Background: *Chronic hyperglycemia causes oxidative stress, impairs endothelial function, facilitates monocyte adhesion to endothelial cells and thickens intima media contributing to development of atherosclerosis. The resistive index and intima-media thickness (IMT) of the carotid artery are sonographic parameters that depend on the degree of atherosclerosis.*

Aim: *The aim of this study was to evaluate the association of carotid arterial resistive index, IMT with glycemic status in type 2 diabetic patients.*

Materials and methods: *Thirty five type 2 diabetic patients with more than 5 year diabetic duration in the age group of 35 to 60 years were selected for this study, 20 age matched healthy individuals were selected as control group. Common carotid artery resistive index, IMT and glycated hemoglobin (HbA1C) were analyzed by conventional standardized methods.*

Results: *The mean levels of Carotid arterial resistive index, IMT are significantly increased in diabetic patients. Common carotid artery resistive index and intima media thickness positively correlated with HbA1c.*

Conclusion: *Evaluation of Carotid arterial resistive index and IMT could be potentially useful diagnostic markers for the assessment of atherosclerotic changes and endothelial dysfunction as a consequence of chronic hyperglycemia in diabetic patients.*

Keywords: *Common carotid artery resistive index (CCARI), Common carotid artery intima media thickness (CCA-IMT), Insulin resistance (IR*)

I. Introduction

Diabetes mellitus (DM) is the leading cause of morbidity and mortality worldwide. The severe metabolic dysregulation associated with diabetes mellitus is known to precede the dysfunctional changes in the endothelium. Individuals with poor glycemic control manifest micro vascular and macro vascular diseases. The majority of complications of DM are related to cardiovascular disease (CVD) and it is therefore, important to assess a noninvasive clinical markers which have a great importance in reducing the rate of CVD. The ultrasound measurement of the resistive index (RI) and intima-media thickness of the common carotid artery (CCA-IMT) has been recognized as a powerful method for identifying subclinical atherosclerosis [1-3]. Thickening of the intima-media complex not only reflects local alterations, but also corresponds to generalized atherosclerosis and CCA distensability which diminishes with increasing severity of atherosclerosis [4-5]. The mean IMT of the common carotid artery is a more reproducible measure than the intima media thickness of the internal carotid artery and is believed to be better suited for cardiovascular risk assessment and intervention studies [6, 7]. In contrast, the resistive index (RI) is a hemodynamic parameter that is easily determined by Doppler sonography and basically reflects vascular resistance according to Pourcelot [8, 9]. Age, vascular risk factors and clinically demonstrated vascular diseases are associated with an increase in RI [10, 11]. The objective of this study was to correlate common carotid artery resistive index (RI) and IMT (CCARI and IMT) with glycemic status in type2 diabetic patients.

II. Materials And Methods

A total of 35 type 2 diabetic patients of both sexes with more than 5 yr diabetic duration aged between 35-60 years on oral hypoglycemic drugs, attending diabetic out-patient department of Rajah Muthiah Medical College and Hospital, Annamalai University, Annamalainagar, Tamil Nadu, India, were selected for our study after approval of Institutional Human ethics committee. We excluded the patients based on the following

criteria: Patients on insulin, Smokers, Alcoholics, Tobacco chewers, abnormal urinary sediment, urinary tract infection, history of other renal disease and active or chronic persistent infection or inflammatory disorders, neoplastic disorders, uncontrolled thyroid disorders, severe liver dysfunction, history of acute myocardial infarction, stroke, and occlusive peripheral vascular disease. Twenty healthy individual age, sex matched subjects were selected as control.

Biochemical analysis:

A random spot urine and fasting blood samples were obtained from the subjects immediately after enrolment. Blood samples were centrifuged at 2000×g for 10 min. Samples were analyzed for fasting blood glucose, lipid profile by using auto analyzer. HbA1C estimated by ion exchange resin method and fasting insulin assessed by ELISA. Urine samples were analyzed for microalbumin, creatinine by using auto analyzer.

Measurement of carotid artery Resistive index, Intima media thickness:

The patient in supine position with pillow kept between the shoulder blades to achieve extension of the neck. Neck exposure was enhanced by tilting and rotating the head away from the side being examined. Carotid arteries were imaged by using a high-resolution B-mode ultrasonography system having an electric linear transducer midfrequency of 7.5 MHz.

Statistical analysis:

Statistical analyses were carried out with SPSS 20.0. Values were expressed as mean ± standard deviation, p value < 0.05 was considered statistically significant. Normally distributed data were analyzed by using one-way ANOVA. The Pearson correlation test was used for correlation analysis.

III. Results

Table 1: Baseline characteristics of control &study subjects

Parameters	Control (n=20) Mean& Std. Deviation	Study (n=35) Mean& Std.deviation	p-value
Age	46.9±4.1	49.7±7.0	0.110
Body mass index	25.2±1.3	26.4±2.7	0.079
Waist/Hip ratio	0.90±0.04	0.92±0.06	0.210
Systolic BP(mmHg)	114.4±6.9	126.4±17.1	0.004
Diastolic BP(mm Hg)	73.5±3.2	77.8±8.9	0.045
Urine Albumin Creatinine ratio (mg/gm. of creatinine)	18.8±2.6	49.3±25.1	0.001
FBS(mg/dl)	81.6±6.1	137.5±53.7	0.001
PPBS(mg/dl)	107.4±10.3	211.8±82.1	0.001
HbA1C	5.4±0.5	7.4±1.1	0.001
Serum cholesterol (mg/dl)	168.4±8.6	170±29.0	0.802
Serum Triglycerides (mg/dl)	96.7±7.6	135.8±45.4	0.001
HDL cholesterol (mg/dl)	43.1±2.2	41.4±3.7	0.073
LDL cholesterol (mg/dl)	105.9±8.7	102.4±27.0	0.573
Bilirubin(mg/dl)	0.76±0.06	0.77±0.07	0.482
Direct Bilirubin(mg/dl)	0.17±0.04	0.17±0.04	0.913
Insulin (µIU/mL)	6.6±0.69	11.4±5.0	0.001
HOMA-IR	1.34±0.17	3.69±2.15	0.001

Data are expressed as mean±SD, p<0.05 was considered statistically significant.

Table 2: Comparison of common carotid artery, internal carotid artery resistive index and intima media thickness control and study subjects.

Parameters	Control (n=20) Mean& Std. Deviation	Study (n=35) Mean& Std.deviation	p-value
Right CCA RI	0.57±0.02	0.70±0.07	0.001
Left CCA RI	0.53±0.03	0.69±0.07	0.001
Right ICA RI	0.55±0.03	0.56±0.06	0.958
Left ICA RI	0.58±0.05	0.62±0.11	0.221
Right CCA IMT(mm)	0.58±0.02	0.79±0.10	0.001
Left CCAIMT(mm)	0.59±0.05	0.82±0.08	0.001

Data are expressed as mean±SD, p<0.05 was considered statistically significant.

Table 3: Correlation between HbA1C&measured parameters

Parameters	Correlation Coefficient(r)	p value
Right CCA RI	0.566**	0.001
Left CCA RI	0.735**	0.001
Right ICA RI	0.134	0.328
Left ICA RI	0.235	0.084
Right CCA IMT(mm)	0.658**	0.001
Left CCAIMT(mm)	0.763**	0.001

**Correlation is significant at the 0.01 level (2-tailed).

Table4: Correlation between HOMA IR &measured parameters

Parameters	Correlation Coefficient(r)	p value
Right CCA RI	0.490**	0.001
Left CCA RI	0.618**	0.001
Right ICA RI	0.103	0.456
Left ICA RI	0.069	0.614
Right CCA IMT(mm)	0.597**	0.001
Left CCAIMT(mm)	0.550**	0.001

*Correlation is significant at the 0.05 level (2-tailed).
**Correlation is significant at the 0.01 level (2-tailed).

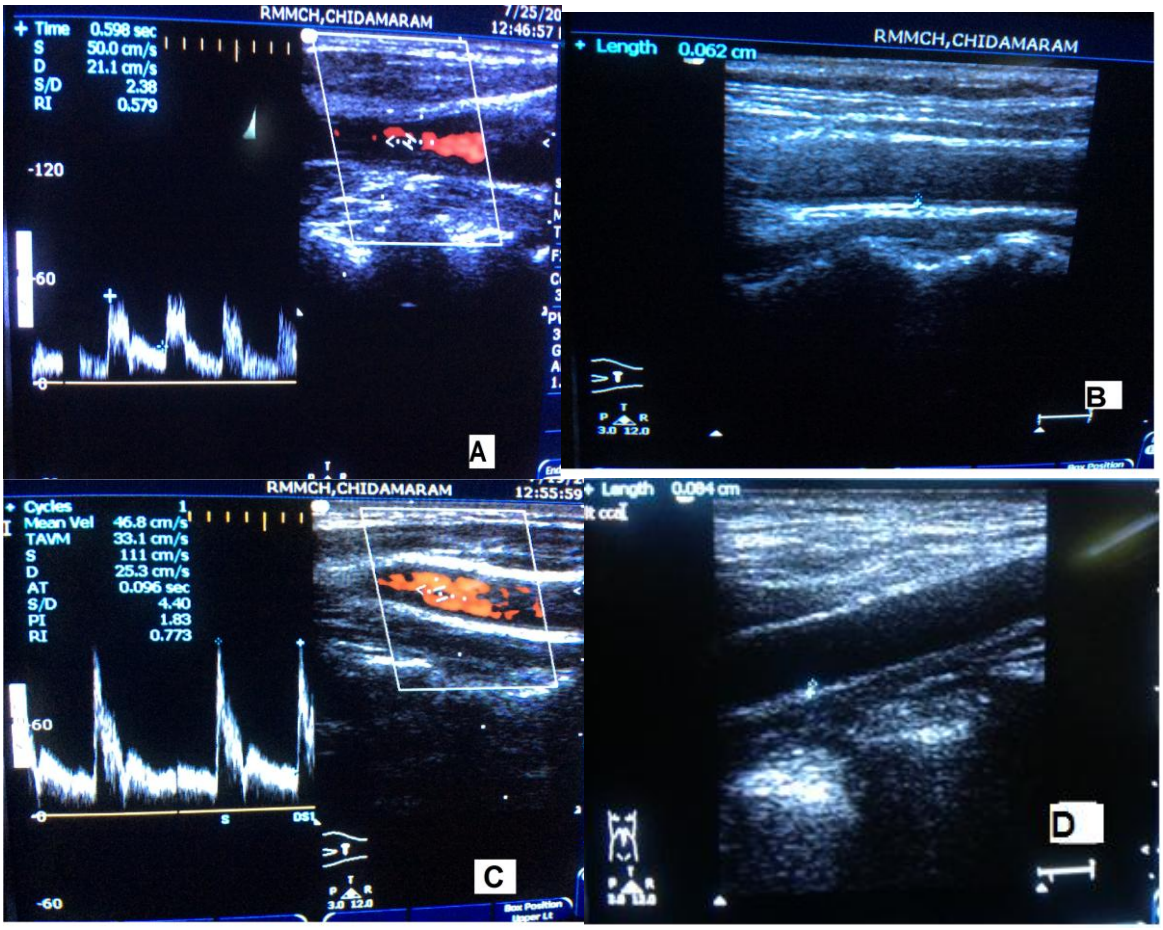

Figure 1 .Examples of A) RI in controls B) Intima media thickness in controls C) RI in study group D) Intima media thickness in study group

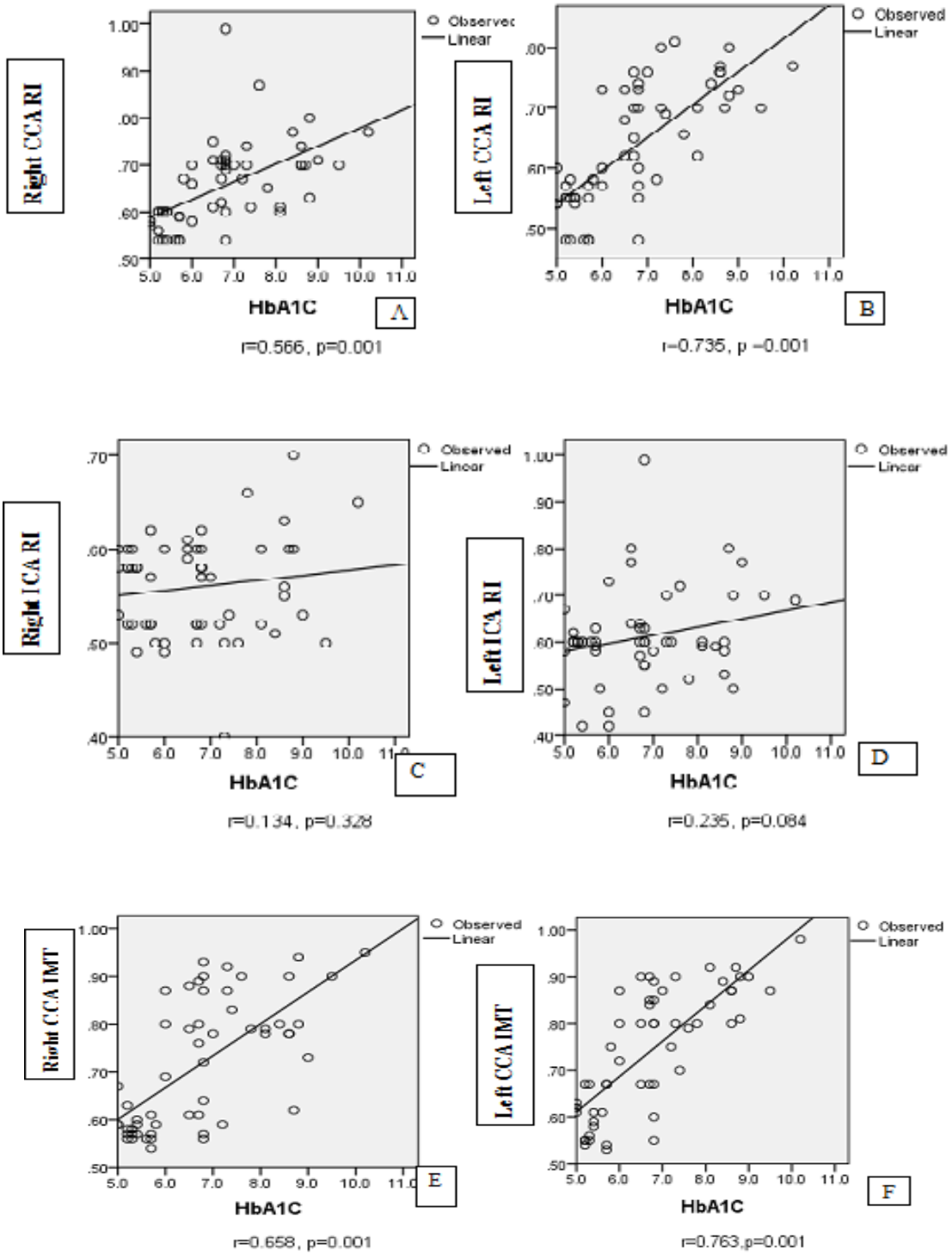

Figure 2: Simple linear regression between HbA1C and A) Right CCA RI B) Left CCA RI C) Right ICA RI D) Left ICA RI E) Right CCA IMT F) Left CCA IMT

IV. Discussion

At present B-mode ultrasonography is extensively used to detect early structural changes in carotid arteries because the thickening process in these areas is considered to be a prognostic marker for the development of atherosclerosis and appears to correlate with coronary lesions [12, 13]. In the present study, we tested the possible existence of a relationship between early structural changes in carotid arteries and endothelial dysfunction in type 2 diabetic patients. We found that RI, and CCA-IMT were higher in diabetic subjects. There

is positive correlation between CCA-IMT and HbA1C & HOMA IR. We also observed significant association between CCA-IMT and HbA1C by simple linear regression analysis. There are several mechanisms by which the examined risk factors may be associated with atherosclerosis. Theories of atherosclerosis suggest that two crucial steps are endothelial injury and LDL uptake by sub endothelial macrophages to form foam cells and eventually atherosclerotic plaques. Greater body mass, waist-hip ratio, physical inactivity and fasting insulin, all tend to be associated with higher blood pressure, which may injure endothelium. They are also associated with high plasma triglycerides, LDL, and low HDL [14-16]. Several studies explain relationship between insulin resistance and IMT [17, 18]. Salonen R & Salonen JT has reported that ambulatory pulse pressure, cigarette smoking, serum LDL cholesterol, history of coronary heart disease, systolic blood pressure, and diabetes were the strongest risk factors for maximal intimal-medial thickening [19].

In our study, RI of RCCA and LCCA was significantly higher in diabetic patients. The increased RI of Right and left CCA in diabetics could be due to enhanced oxidative stress. The metabolic abnormalities of diabetes such as hyperglycemia, dyslipidemia and insulin resistance, provoke increased oxidative stress, protein kinase C (PKC) activation, and advanced glycation end products (AGEs). Hyperglycemia directly produces a reactive oxygen species (such as superoxide anion) via increased production from the mitochondrial electron transport chain and glucose autoxidation [20, 21]. The activation of PKC and the activation of the receptor for AGEs also contribute to superoxide generation [22- 24]. We also observed a significant increase of ACR ratio in diabetic patients. Microalbuminuria is a marker of extensive endothelial dysfunction or generalized vasculopathy [25]. We also observed significant increase of Insulin resistance (HOMA-IR) in diabetic patients. Reduced insulin sensitivity is considered a primary pathophysiologic mechanism linking together metabolic and hemodynamic abnormalities that may result in accelerated atherosclerotic changes [26, 27].

We observed a positive correlation of HOMA-IR with CCA-RI & IMT. Chronic hyperglycemia and insulin resistance induce oxidative stress, apoptosis, and an inflammatory response and arterial stiffness. As a consequence, systolic blood pressure is augmented by early wave reflection due to the fast travel of the pulse wave, resulting in an increase in circumferential wall tension. Stiffer arteries due to atherosclerotic changes have also been shown to be associated with reduced blood flow velocity in diastole, which is reflected by an increase in the RI. The frictional force that blood flow exerts at the endothelial surface of the vessel wall, has been described as the most important local factor causing endothelial damage [28-31].

In conclusion, our results indicate that evaluation of Carotid arterial resistive index, intima media thickness could be potentially useful diagnostic markers for the assessment of atherosclerotic changes and endothelial dysfunction as a consequence of chronic hyperglycemia in diabetic patients and it also reflects the long term glycemic status.

References

[1]. O'Leary DH, Polak JF, Kronmal RA, Manolio TA, Burke GL, Wolfson SK Jr: Carotid-artery intima and media thickness as a risk factor for myocardial infarction and stroke in older adults. Cardiovascular Health Study Collaborative Research Group. N Engl J Med 1999; 340(1):14-22.

[2]. Lorenz MW, Markus HS, Bots ML, Rosvall M, Sitzer M: Prediction of clinical cardiovascular events with carotid intima-media thickness: a systematic review and meta-analysis. Circulation 2007;115(4):459-467.

[3]. Nomura K, Hamamoto Y, Takahara S, Kikuchi O, Honjo S, Ikeda H, Wada Y, Nabe K, Okumra R, Koshiyama H: Relationship between carotid intima media thickness and silent cerebral infarction in Japanese subjects with type 2 diabetes. Diabetes Care 2010, 33(1):168-170.

[4]. Hirai T, Sasayama S, Kawasaki T, Yagi S. Stiffness of systemic arteries in patients with myocardial infarction; a non-invasive method to predict severity of coronary atherosclerosis. Circulation. 1989; 80:78–86.

[5]. Alva F, Samaniego V, Gonzales V, Moguel R, Meaney E. Structural and dynamic changes in the elastic arteries due to arterial hypertension and hypercholesterolemia. Clin Cardiol. 1993; 16:614–618.

[6]. Stein JH, Korcarz CE, Hurst RT, et al. Use of carotid ultrasound to identify subclinical vascular disease and evaluate cardiovascular disease risk: a consensus statement from the American Society of Echocardiography Carotid Intima-Media Thickness Task Force: endorsed by the Society for Vascular Medicine. J Am Soc Echocardiogr. 2008; 21:93-111

[7]. Touboul PJ, Hennerici MG, Meairs S, et al. Mannheim intima-media thickness consensus. Cerebrovasc Dis. 2004; 18:346–349

[8]. Pourcelot L. Applications cliniques de l′examen Doppler transcutan. In: Peronneau P, ed. Velocimetrie Ultrasonore Doppler. Paris, France: INSERM; 1975:213-240.

[9]. Frauchiger B, Bock A, Eichlisberger R, Landmann J, Thiel G, Mihatsch MJ, Jager K. The value of different resistance parameters in distinguishing biopsy-proved dysfunction of renal allografts. Nephrol Dial Transplant. 1995; 10:527-532.

[10]. Pontremoli R, Viazzi F, Martinoli C, Ravera M, Nicolella C, Berruti V, Leoncini G, Ruello N, Zagami P, Bezante GP, Derchi LE, Deferrari G. Increased renal resistive index in patients with essential hypertension: a marker of target organ damage. Nephrol Dial Transplant. 1999; 14:360-365.

[11]. Ishimura E, Nishizawa Y, Kawagishi T, Okuno Y, Kogawa K, Fukumoto S, Maekawa K, Hosoi M, Inaba M, Emoto M, Morii H. Intrarenal hemodynamic abnormalities in diabetic nephropathy measured by duplex Doppler sonography. Kidney Int. 1997; 51:1920-1927.

[12]. Poli A, Tremoli E, Colombo A. Ultrasonographic measurement of the common carotid artery wall thickness in hypercholesterolemic patients: a new model for the quantification and follow up of preclinical atherosclerosis in living human subjects. Atherosclerosis.
1988; 70:253-261.

[13]. Salonen JT, Salonen R. Ultrasonographically assessed carotid morphology and the risk of coronary heart disease. Arterioscler Thromb. 1991; 11:1245-1249.

[14]. Folsom AR, Burke GL, Byers CL, Hutchinson RG, Heiss G, Jacobs DR, Flack JM, Caan B. Implications of obesity for cardiovascular disease in blacks: the CARDIA and ARIC studies.Am J Clin Nutr. 1991; 53:1604-1611
[15]. Howard BV. Lipoprotein metabolism in diabetes mellitus. J Lipid Res. 1987; 28:613-628.
[16]. A R Folsom, J H Eckfeldt, S Weitzman, J Ma, L E Chambless, R W Barnes, K B Cram and R G Hutchinson. Relation of carotid artery wall thickness to diabetes mellitus, fasting glucose and insulin, body size, and physical activity. Atherosclerosis Risk in Communities (ARIC) Study Investigators. Stroke. 1994; 25:66-73.
[17]. Angela Sciacqua, Maria Adelaide Marini, Marta Letizia Hribal, Francesco Perticone. Giorgio Sesti. Association of Insulin Resistance Indexes to Carotid Intima–Media Thickness. PLoS ONE 2013; 8(1):1-7.
[18]. Rutter MK, Meigs JB, Sullivan LM, D'Agostino RB Sr, Wilson PW. Insulin resistance, the metabolic syndrome, and incident cardiovascular events in the Framingham Offspring Study. Diabetes2005; 54: 3252-3257
[19]. Salonen R, Salonen JT. Determinants of carotid intima-media thickness: a population-based ultrasonography study in Eastern Finnish men. / Intern Med. 1991; 229:225-231
[20]. Nishikawa T, Edelstein D, Du XL, Yamagishi S, Matsumura T, Kaneda Y, Yorek MA, Beebe D, Oates PJ, Hammes HP, Giardino I, Brownlee M: Normalizing mitochondrial superoxide production blocks three pathways of hyperglycaemic damage. Nature2000; 404:787-790
[21]. Wolff SP, Dean RT: Glucose autoxidation and protein modification: the potential role of 'autoxidative glycosylation' in diabetes. Biochem J 1987; 245:243 -250
[22]. Creager MA, Luscher TF, Cosentino F, and Beckman JA: Diabetes and vascular disease: pathophysiology, clinical consequences, and medical therapy: part I. Circulation 2003; 108:1527 -1532.
[23]. Hink U, Li H, Mollnau H, Oelze M, Matheis E, Hartmann M, Skatchkov M, Thaiss F, Stahl RA, Warnholtz A, Meinertz T, Griendling
K, Harrison DG, Forstermann U, Munzel T: Mechanisms underlying endothelial dysfunction in diabetes mellitus. Circ Res 2001; 88:E14 -E22
[24]. Wautier MP, Chappey O, Corda S, Stern DM, Schmidt AM, Wautier JL: Activation of NADPH oxidase by AGE links oxidant stress to altered gene expression via RAGE. Am J Physiol Endocrinol Metab 2001; 280:E685 -E694
[25]. D.P. Naidoo, The link between microalbuminuria, endothelial dysfunction and cardiovascular disease in diabetes. Cardiovascular Journal of South Africa 2002; 13: 4:194-199
[26]. Bonfeld KE, Tabas I. Insulin resistance, hyperglycemia and atherosclerosis. Cell Metabolism. 2011; 14:575-585.
[27]. DeFronzo RA. Insulin resistance, lipotoxicity, type 2 diabetes and atherosclerosis: the missing links. The Claude Bernard Lecture 2009. Diabetologia. 2010;53:1270-1287.
[28]. Chien S, Li S, Shyy JY. Effects of mechanical forces on signal transduction and gene expression in endothelial cells. Hypertension 1998; 31:162-169.
[29]. Stéphanie L, Tedgui A. Signal transduction of mechanical stresses in the vascular wall. Hypertension 1998; 32:338-345.
[30]. Irace C, Carallo C, Crescenzo A, et al. NIDDM is associated with lower wall shear stress of the common carotid artery. Diabetes 1999; 48:193-197
[31]. Gnasso A, Carallo C, Irace C, et al. Association between intima-media thickness and wall shear stress in common carotid arteries in
[32]. healthy male subjects. Circulation 1996; 94:3257-3262.