Differences between several atherogenic parameters in patients with Controlled and Uncontrolled Type 2 Diabetes Mellitus

by Ilhamjaya Patellongi

Differences between several atherogenic parameters in patients with Controlled and Uncontrolled Type 2 Diabetes Mellitus

Ellis Susanti,[1,2] Marsetio Donosepoetro,[3] Ilhamjaya Patellongi,[4] Mansyur Arif [4]

[1]Postgraduate Program in Biomedical Science-Clinical Chemistry, Faculty of Medicine, Hasanuddin University, Makassar, Indonesia
[2]Prodia Clinical Laboratory, Jakarta, Indonesia
[3]Faculty of Medicine, University of Airlangga, Surabaya, Indonesia
[4]Faculty of Medicine, Hasanuddin University, Makassar, Indonesia

Abstrak

Tujuan *Untuk mengetahui perbedaan nilai antara Index Aterogenik Plasma (AIP), rasio Low Density Lipoprotein teroksidasi (Ox-LDL)/High Density Lipoprotein (HDL) dan rasio Lipoprotein-associated Phospholipase A2 (Lp-PLA2)/HDL yang dapat memperkirakan besarnya risiko penyakit jantung koroner (PJK) pada penderita DM tipe 2 terkontrol dan tidak terkontrol.*

Metode *Penelitian ini menggunakan disain potong lintang pada 40 penderita DM tipe 2 terkontrol dan 40 penderita DM tipe 2 tidak terkontrol. Metode pengambilan sampel yang digunakan adalah secara consecutive sampling, yaitu setiap penderita yang berkunjung selama kurun waktu penelitian di Laboratorium Klinik Prodia Jakarta yang memenuhi syarat inklusi dan ekslusi. Parameter yang diperiksa adalah trigliserida, HDL, Ox-LDL dan Lp-PLA2. AIP didefinisikan sebagai log (TG/HDL-C).*

Hasil *AIP dan rasio (Ox-LDL/HDL) lebih tinggi secara signifikan pada subjek DM tipe 2 tidak terkontrol dibanding DM terkontrol (0,72 ± 0,13 vs 0,47 ± 0,22 , p < 0,001) dan (1738,8 ± 625,5 vs 1418 ± 535,3, p = 0,02), sedangkan rasio (Lp-PLA2/HDL) tidak berbeda secara bermakna (5,09 ± 2,17 vs 5,95 ± 3,11, p = 0,16).*

Kesimpulan *Nilai AIP dan rasio (Ox-LDL/HDL) lebih tinggi secara bermakna pada DM tipe 2 tidak terkontrol dibandingkan dengan DM tipe 2 terkontrol. Parameter ini dapat dimanfaatkan dalam memprediksi risiko aterosklerosis pada penderita diabetes.* ***(Med J Indones 2010; 19: 103-8)***

Abstract

Aim *to assess the differences between Atherogenic Index of Plasma (AIP), ratio of oxidized-Low Density Lipoprotein (Ox-LDL)/High Density Lipoprotein (HDL) and ratio of Lipoprotein-associated Phospholipase A2 (Lp-PLA2)/HDL in predicting the risk of coronary heart disease (CHD) in patients with controlled and uncontrolled type 2 Diabetes Mellitus (T2DM).*

Methods The study was done observationally with cross sectional design. A total of 80 patients, consisted of 40 controlled and 40 uncontrolled T2DM. The serum triglyceride (TG), HDL-C, Ox-LDL, Lp-PLA2 were examined in their relationship with T2DM risk. AIP is a ratio calculated as log (TG/HDL-C).

Results AIP and ratio of Ox-LDL/HDL were significantly higher in uncontrolled than controlled T2DM (0.72 + 0.13 vs 0.47 ± 0.22 , p < 0.001) and (1738.8 ± 625.5 vs 1418 ± 535.3, p = 0.02), but no significant difference was found in ratio of Lp-PLA2/HDL (5.09 ± 2.17 vs 5.95 ± 3.11, p = 0.16).

Conclusion AIP and ratio of Ox-LDL/HDL value were significantly higher in uncontrolled than in controlled T2DM. These parameters may be beneficial in predicting the risk of atherosclerosis in diabetic patients. ***(Med J Indones 2010; 19:103-8)***

Key words: *AIP, atherosclerosis, Diabetes mellitus, HDL, Lp-PLA2, Ox-LDL.*

Diabetes Mellitus (DM) is continuing to become a health problem since the prevalence of DM has increased dramatically over the past two decades.[1] The patients diagnosed with DM are proven to be prone to atherosclerosis and coronary heart diseases (CHD), especially type 2 Diabetes Mellitus (T2DM). These patients have higher risk of mortality and morbidity for cardiovascular diseases.

The occurrence of Diabetes Mellitus (DM) is due to chronic hyperglycemia and disorder in carbohydrate, fat and protein metabolism, which is related to the progression of micro- and macro vascular complication such as cardiovascular diseases, retinopathies, neuropathies and nephropathies. This disease is caused by the existence of absolute and relative insulin deficiency. The monitoring of Diabetes Mellitus can be done using the Hemoglobin A1C (A1C). Non-enzymatic glycosidation of n-terminal valine of HbA that resulted in A1C, takes place in erythrocyte and is depending on the level of glucose for 120 day, which corresponds to erythrocyte life-span. Inspection of A1C will reflect the long-range DM controll over a two or three months period. [2]

Correspondence email to: ellis_susanti@yahoo.com

Atherogenic index of plasma (AIP) is the new marker of atherogenicity, since the AIP is related directly to the atherosclerosis risk. AIP is the ratio calculated as log (TG/HDL-C).[3] Existence of hypertriglyceridemia will increase the activity of hepatic lipase (HL) which results in the increase of HDL catabolism (degradation of HDL). Each degradation of 1 mg HDL will correlate with 2% increase in the risk coronary heart disease (CHD).[4-6]

Some researchers have proven that Ox-LDL plays a vital, important role in the progression of atherosclerosis. Moreover, high level of Ox-LDL in circulation is proven to be related to plaque instability of ateroma.[7]

Lipoprotein-associated Phospholipase A2 (Lp-PLA2) is pro-inflammatory, due to the formation of lyso-phosphatydilcholine and oxidized free fatty acid (FFA) which have pro-inflammatory characteristics. Activity of Lp-PLA2 is particularly related to small dense LDL particle, which is atherogenic and is proven to independently predict endothelial dysfunction.[8]

Diabetic dyslipidemia in T2DM, also called atherosclerotic diabetic dislipidemia, is generally marked by an increase of plasma triglyceride (TG), small dense LDL concentration and apo lipoprotein B, as well as the decrease in HDL cholesterol concentration.[9] It is reported that AIP has higher predictive value for atherosclerosis.[3] Some ratio of pro atherogenic markers when divided by cholesterol HDL, will increase the odds ratio value which means higher predictive value towards atherosclerosis, as compared to pro atherogenic markers alone.[10]

Besides, ratio of AIP, Ox-LDL and Lp-PLA2 over HDL can also be calculated . This study will examine the predictive value to atherosclerosis in controlled and uncontrolled T2DM subjects by using the value of AIP, Ox-LDL/HDL ratio and Lp-PLA2/HDL ratio to provide prediction to atherosclerosis development in T2DM, especially uncontrolled T2DM.

METHODS

Study Design

This is a cross-sectional study comparing AIP, ratio of (Ox-LDL/HDL) and ratio of (Lp-PLA2/HDL) and various metabolic profiles between controlled and uncontrolled T2DM. Data collected by interview, medical records, physical examination, and laboratory testing (A1C, fasting plasma glucose, HDL-C, triglyceride, Ox-LDL, Lp-PLA2 level), from May to September 2009. The study protocol was approved by The Medical Ethics Committee of The Faculty of Medicine University of Hasanuddin Makassar, Indonesia, and all participat has given written informed consent

Subject

Subjects consisted of 80 T2DM patients who were divided into two groups based on A1C value. First group consisted of 40 individuals with A1C < 8 % as controlled T2DM, and the second group consisted of 40 individuals with A1C ≥ 8% as uncontrolled T2DM. Subject were consecutively recruited from Prodia clinical laboratory, Kramat, Jakarta. The inclusion criteria were 35-60 years of age with fasting blood glucose > 126 mg/dl, while the exclusion criteria were chronic kidney disease (serum creatinine > 2.4 mg/dl) and hepatic failure (AST > 66 U/L or ALT > 100 U/L). Subjects taking lipid lowering agents and antioxidant medications are also excluded.

Anthropometric Measurement

Body weight (BW) was measured in kilograms to the nearest 0.1 kg. Height (Ht) was measured in centimeters to the nearest 0.1 cm. Body Mass Index (BMI) was calculated by dividing body weight in kg by height in squared meter.

Waist circumference was measured in centimeters to the nearest 0.1 cm, using a flexible non-elastic tape made by Roche (Roche, Switzerland). Waist circumference was measured at stomach area in the middle of underside arcus costae and Iliacal Crist, in standing position.

Blood Pressure Measurement

Blood pressure was measured using a sphygmomanometer. Subjects were seated for at least 5 minute before the measurement. First and fifth Korotkoff sounds were taken as systolic and diastolic blood pressure, respectively.

Biochemical Assessments

Blood samples were analyzed for glycaemic control (blood glucose and A1C) and classified using local reference by PERKENI, 2006. A1C in blood EDTA samples were measured with High Performance Liquid Chromatography method using reagent manufactured by Biorad (Marnes-la-Coquette, France), serum blood glucose levels were measured by hexokinase method using reagent manufactured by Roche (Mannheim, Germany). HDL-C in blood serum sample were measured by homogenous method using reagent manufactured by Daiichi (Daiichi pure chemical, Japan), triglyceride (TG) in blood serum sample were measured by GPO-PAP method using reagent manufactured by Roche (Mannheim, Germany). Ox-LDL by ELISA method using reagent manufactured by Mercodia (AB, Uppsala, Sweden), and Lp-PLA2 in blood serum sample were measured by ELISA method using reagent manufactured by diaDexus (Inc., San Francisco, California).

Data Analysis

Statistical analyses were performed by SPSS for windows version 11.5. Univariat analyses were performed to calculate mean, maximum and minimum value and standard deviation (SD). Comparison of AIP, ratio of Ox-LDL/HDL and ratio of Lp-PLA2/HDL levels between controlled and uncontrolled group were analyzed using t test if normally distributed, or with Mann-Whitney non parametric test, if not normally distributed.

RESULTS

The study has recruited 80 subjects consisted of controlled T2DM (A1C < 8%) and 40 individuals with uncontrolled T2DM (A1C > 8 %)

Table 1 shows that both groups are comparable in demographic characteristics.

Table 1. Demographic Characteristics of the Subjects

Parameter	controlled DM	uncontrolled DM
	Mean ± SD	Mean ± SD
Age (year)	54.8 ± 6.1	52.1 ± 5.9
BMI (kg/m²)	24.6 ± 4.3	25.6 ± 3.6
WC (cm)	90.0 ± 11.5	91.9 ± 7.8
Systole (mm/Hg)	127.3 ± 19.4	133.4 ± 11.5
Diastole (mm/Hg)	82.3 ± 7.5	87.9 ± 13.0

BMI= Body Mass Index; WC = waist circumference

The uncontrolled T2DM subjects had higher, BMI, WC, Systole and Diastole than the controlled T2DM subjects. On the other hand, the uncontrolled T2DM subjects had lower age than their controlled counterpats.

Clinical chemistry data in Table 2 shows that fasting glucose, A1C, total cholesterol, triglyceride and HDL-cholesterol are significantly higher in uncontrolled T2DM compared to controlled T2DM subjects. Whereas the AST, ALT, Creatinine and LDL-cholesterol was not significantly different.

Table 3 shows the differential analysis between AIP, ratio of Ox-LDL/HDL and ratio of Lp-PLA2/HDL in controlled and uncontrolled T2DM patients**.** The uncontrolled T2DM subject had higher level of Ox-LDL, AIP and ratio of Ox-LDL/HDL. Whereas the Lp-PLA2 and ratio of Lp-PLA2/HDL were not significantly different in both groups.

Table 2. Biochemical Characteristic of the Subjects

Parameter	controlled DM	uncontrolled DM	*P*
	Mean ± SD	Mean ± SD	
Fasting glucose (mg/dl)	126.2 ± 34.5	230.1± 76.2	0.02
A1C (%)	6.7 ± 0.8	10.8 ± 2.1	<0.001
Total Cholesterol (mg/dl)	192.1 ± 31.5	214.9 ± 50.4	0.019
Triglyceride (mg/dl)	145.2 ± 66.5	216.3 ± 57.8	<0.001
HDL-C (mg/dl)	45.2 ± 8.7	40.7 ± 7.4	0.01
LDL-C (mg/dl)	115.9 ± 26.7	216.3 ± 57.8	0.089
AST (U/L)	25.0 ± 6.3	23.7 ± 7.8	0.06
ALT (U/L)	29.8 ± 17.0	24 ± 12.4	0.08
Creatinin (mg/dl)	1.1 ± 0,3	1.0 ± 4.0	0.47

Table 3. Differential Analysis between AIP, ratio of Ox-LDL/HDL and ratio of Lp-PLA2/HDL in controlled and uncontrolled T2DM patients

Parameter	controlled DM	uncontrolled DM	*P*
	Mean ± SD	Mean ± SD	
Ox-LDL (mU/L)	60350 ± 18358.5	76008 ± 20074.3	<0.001
Lp-PLA2 (ng/ml)	256 ± 122	224.1 ± 78.9	0.17
AIP	0.47 ± 0.22	0.72 ± 0.13	<0.001
Ratio of Ox-LDL/HDL	1418 ± 535.3	1738.8 ± 625.5	0.02
Ratio of Lp-PLA2/HDL	2.19 ± 0.99	1.84 ± 0.74	0.083

AIP=Atherogenic Index of Plasma; Lp-PLA2 = lipoprotein-associated phospholipase A2

DISCUSSION

Descriptive data showed that there was no significant difference regarding age, BMI, waist circumference, systolic & diastolic blood pressure between controlled and uncontrolled T2DM, indicating that both groups were comparable. Ox-LDL, AIP and ratio of Ox-LDL/HDL showed significant difference, because in uncontrolled T2DM worse diabetic dyslipidemia would occur, whereas Lp-PLA2 and ratio of Lp-PLA2/HDL were not significantly different.

The AIP value from these two groups was significantly different with p< 0. 001*. Similar result was obtained by a cohort study in 1433 patients by Dobiasova et al., with various risk of atherosclerosis, including T2DM, hypertension, and dislipidemia.[3] The AIP value increased significantly with increasing atherogenic risk (AIP from 0.24 to 0.51). In patient with T2DM, AIP was among the highest value.

Ratio of Ox-LDL/HDL in uncontrolled T2DM was significantly different from controlled T2DM (p = 0.02). This might be related to the worsen condition of diabetic dislipidemia in uncontrolled T2DM, compared with controlled T2DM, which might be due to degradation of cholesterol HDL and increased small dense LDL. The formation of Ox-LDL will be more likely to occur on small-dense LDL. These findings were supported by a study of small dense LDL by Physicians Health Study by Stampfer et al., on 266 male subjects with fatal and non fatal CHD for 7 years, that indicated significantly different in uncontrolled DM compared to controlled group awith relative risk of 1.38.[11] Therefore, LDL size was a strong predictor for the formation of Ox-LDL, and thus for CHD risk.[2]

AIP and ratio of Ox-LDL/HDL were significantly higher in uncontrolled than in controlled T2DM. The explanation is that the occurrence of Diabetes Mellitus is due to chronic hyperglycemia and disorder in carbohydrate, fat and protein metabolism due to the existence of absolute and relative insulin deficiency. The dyslipidemia condition commonly happen to T2DM patient is one of the factors in this risk. Diabetic dyslipidemia is generally accompagnied with the increase in triglyceride, small dense LDL and Apo-B, and the decrease in HDL-cholesterol. Diabetic dyslipidemia is associated with insulin resistance, a condition that has emerged as a predilection to type 2 diabetes. When people are insulin resistant, the body does not efficiently use the insulin, which adversely affects levels of blood lipids with increased trigycerides and decreased HDL cholesterol - thus increasing CVD risk.[12]

In uncontrolled T2DM, worse diabetic dyslipidemia would occur with hypertriglyceridemia as the primary dyslipidemia disorder. Other study showed a strong correlation of AIP with lipoprotein particle size which may explain its high predictive value.[3] Summarized data of AIP calculated in 8394 subjects from 6 populations and clinical studies demonstrated that AIP values increased with increasing cardiovascular (CV) risk. Thus, blood from umbilical cord, in young children, and in healthy women have values below 0.1, while in men and subjects with CV risk factors such as hypertension, diabetes, dyslipidemia, this value incresed up to 0.4. Based on these data was suggest that AIP values of -0.3 to 0.1 are associated with low, 0.1 to 0.24 with medium and above 0.24 with high CV risk. In that study population men had higher AIP values than women. In a cohort study on patients undergoing coronary angiography, AIP was the best predictor of positive findings in model that included age, BMI, waist circumference, T2DM, blood pressure, smoking, TG, TC, LDL-C, apoB, HDL-C, and TC/HDL-C. AIP was also a highly sensitive marker of differences of lipoprotein profiles in families of patients with premature myocardial infarction and control families. Treatment with ciprofibrate, and combination of statin and niacin dramatically decreased AIP. Combination with hypoglycemic therapy that included pioglitazone decreased AIP in patiens with T2DM.[13]

Epidemiology study shows that hypertriglyceridemia is the risk factor of CVD in T2DM. It is well known that triglyceride-rich lipoprotein (VLDL and LDL) is atherogenic, and the occurence of CHD has been shown to be related with the presence of negative correlation between hypertriglyceridemia and decrease in HDL value and increase in small dense LDL. Theese conditions are frequently found in T2DM patients and insulin resistance syndrome (central obesity).[14,15] Similar result was obtained by cohort study of relationship between Ox-LDL, T2DM and obesity-related traits in a bi-racial sample of 2985 subjects at baseline and after 7 years of follow-up. The results showed that Ox-LDL was positively correlated with T2DM fasting glucose, A1C, fasting insulin, and HOMA-IR and negatively correlated with adiponectin.[16]

Oxidized LDL (Ox-LDL) has been shown to play an important role in the initiation and development of atherosclerosis.[17] Individuals with T2DM exhibit enhanced LDL oxidizability and accelerated atherosclerosis.[18,19] Past studies demonstrated the association between LDL oxidation and atherosclerosis by "indirect" methods, such as lag times and propagation rates for LDL oxidation, and antibodies against oxLDL. Recently, some groups have developed "direct" methods for measuring circulating Ox-LDL.[20-22] Indeed, several lines of evidence have demonstrated that the level of circulating Ox-LDL is significantly higher in patients with T2DM, and becomes a marker and has a positive relationship with coronary artery disease (CAD) and acute coronary syndromes.[23,24]

However, the predictive value of circulating Ox-LDL for cardiac events in T2DM patients with CAD has not been investigated.

This study firstly, to the best of our knowledge, demonstrated that high levels of circulating Ox-LDL can serve as an independent and significant predictor for future cardiac events in T2DM patients with CAD. Therefore, measurement of circulating Ox-LDL may be helpful for identifying high-risk patients with T2DM and CAD. Level of ratio of Lp-PLA2/HDL in uncontrolled T2DM was lower but not significantly different from controlled T2DM. Similar result was obtained by a cohort study in 889 subjects from the population-based MONICA/KORA Augsburg survey from 1984 until 2002 (with mean follow-up time of 13.5 years). In this large population-based cohort study, elevated concentrations of Lp-PLA2 were not independently associated with incident T2DM in apparently healthy middle-aged men. Since Lp-PLA2 is associated with risk of future CHD but not with incident T2DM, it might represent a more specific marker of vascular inflammation. [25,26]

From the present study, it is concluded that AIP and ratio of Ox-LDL/HDL value were significantly higher in uncontrolled than in controlled T2DM. These parameters may be useful in predicting the risk of atherosclerosis in diabetic patients

Acknowledgments

We thank Prodia Foundation for Research and Training for their invaluable help in conducting the many procedures of this research.

REFERENCES

1. Detels R, McEwen J, Beaglehole R and Tanaka H. Oxford Textbook of Public Health. Forth Edition. New York : Oxford University Press, 2006; p. 1279 -1307.
2. Maassen JA. Mitochondrial diabetes: molecular mechanism and clinical presentation. Diabetes 20204;53 (Suppl 1):S103-9.
3. Dobiasova M, Frohlich J. The plasma parameter log (TG/HDL-C) as an atherogenic index: Correlation with lipoprotein particle size and esterification rate in Apo B-Lipoprotein-depleted plasma (FER_{HDL}). Clin Biochem. 2001;34:583-8
4. Jelesoff NE, Feinglos M, Granger CB. Outcomes of diabetic patients following acute myocardial infarction: A review of the major thrombolytic trials. J Cardiovasc Risk. 1974:100-11.
5. Bell DSH. Diabetes mellitus and coronary artery disease. J Cardiovasc Risk. 1997; 4:83-90.
6. Panahlao A, Yudkin JS. Diminished fibrinolysis in diabetes mellitus and its implication for diabetic vascular disease. J Cardiovasc Risk.1997;4:91-9.
7. Miller YL, Chang MK, Binder CJ. Oxidized Low Density Lipoprotein and innate immune receptors. Current Opinion in Lipidology. 2003;14:437- 45.
8. Iribarren C. Lipoprotein associated Phospholipase A2 and cardiovascular risk: State of the evidence and future directions. Atheroscl Thromb Vasc Biol. 2006;26: 5-6.
9. Dobiasova, M. Atherogenic Index of Plasma [Log (Triglycerides/HDL-Cholesterol)]: theoretical and practical implications. Clin Chem. 2004;50(7):1113-5.
10. Daniels LB, Laughlin GA, Sarno MJ. Lp-PLA2 is an independent predictor of incident coronary heart disease in appparently healthy older population. J Am Col Cardiol. 2008;51:913-9.
11. Stampfer MJ, Krauss RM, Blanche PJ, Holl LG, Sacks FM, Hennekens CH. A prospective study of triglyceride level, LDL particle diameter and risk of myocardial infarction. JAMA. 1996;276:882-8.
12. Management of dyslipidaemia in adults with diabetes. American Diabetes Association, Clinical Practice Recommendations. Diabetes Care. 2001; Jan;24 Suppl 1:S58-61.
13. Dobiasova, M. Atherogenic index of plasma as a significant predictor of cardiovascular risk: from research to practice. Vnitr Lek. 2006 Jan;52(1):64-71.
14. Tkac I, Kimball BP, Lewis G, et al. The severity coronary atherosclerosis in type 2 diabetes mellitus is related to the number of circulating triglyceride-rich lipoprotein particles. Artherioscler Thromb Vasc Biol.1997; 17:3633-8.
15. Tan MH, Johns D, Glazer NB. Pioglitazone reduces atherogenic index of plasma in patients with type 2 diabetes. Clin Chem. 2004;50(7):1184-8.
16. Njajou OT, Kanaya AM, Holvoet P, Connelly S, Strotmeyer ES, Harris TB, et al. Association between oxidized LDL, obesity and type 2 diabetes in a population-based cohort, the health, aging and body composition study. Diabetes Metab Res Rev. 2009 Nov;25(8):733-9.
17. Steinberg D, Witztum JL. Is the oxidative modification hypothesis relevant to human atherosclerosis? Do the antioxidant trials conducted to date refute the hypothesis. Circulation. 2002;105: 2107-11.
18. Fonseca VA. Management of diabetes mellitus and insulin resistance in patients with cardiovascular disease. Am J Cardiol. 2003;92:50J-60J,
19. Schwenke DC, D'Agostino RB Jr, Goff DC Jr, Karter AJ, Rewers MJ, Wagenknecht LE. Differences in LDL oxidizability by glycemic status: the insulin resistance atherosclerosis study. Diabetes Care. 2003;26:1449-55.
20. Itabe H, Takeshima E, Iwasaki H, Kimura J, Yoshida Y, Imanaka T, et al. A monoclonal antibody against oxidized lipoprotein recognizes foam cells in atherosclerotic lesions: complex formation of oxidized phosphatidylcholines and polypeptides. J Biol Chem. 1994;269:15274-9.
21. Palinski W, Horkko S, Miller E, Steinbrecher UP, Powell HC, Curtiss LK, et al. Cloning of monoclonal autoantibodies to epitopes of oxidized lipoproteins from apolipoprotein E-deficient mice: demonstration of epitopes of oxidized low density lipoprotein in human plasma. J Clin Invest. 1996;98:800-14

22. Holvoet P, Donck J, Landeloos M, Brouwers E, Luijtens K, Arnout J, et al. Correlation between oxidized low density lipoproteins and von Willebrand factor in chronic renal failure. Thromb Haemost. 1996;76:663-9.
23. Toshima S, Hasegawa A, Kurabayashi M, Itabe H, Takano T, Sugano J, et al. Circulating oxidized low density lipoprotein levels : a biochemical risk marker for coronary heart disease. Arterioscler Thromb Vasc Biol . 2000;20:2243-7.
24. Ehara S, Ueda M, Naruko T, Haze K, Itoh A, Otsuka M, et al. Elevated levels of oxidized low density lipoprotein show a positive relationship with the severity of acute coronary syndromes. Circulation. 2001;103:1955-60.
25. Kazunori S, Hiroshi M, Eriko M, Tetsuro M, Katsuhiko S, Atsumi K, et al. Predictive value of circulating oxidized LDL for cardiac events in type 2 diabetic patients with coronary artery disease. Diabetes Care. 2004 March; 27(3):843-4.
26. Natalie K, Jens B, Gerlinde T, Christa M, Hannelore L, Wolfgang K. Lipoprotein-associated phospholipase A2 does not predict risk of incident type 2 diabetes mellitus in apparently healthy middle-aged men: A more specific marker for vascular inflammation. Circulation. 2006;114:869-70.

Differences between several atherogenic parameters in patients with Controlled and Uncontrolled Type 2 Diabetes Mellitus

ORIGINALITY REPORT

24%	16%	21%	6%
SIMILARITY INDEX	INTERNET SOURCES	PUBLICATIONS	STUDENT PAPERS

PRIMARY SOURCES

1	Jussi Kosola. "Good Aerobic or Muscular Fitness Prevents Overweight Men from Elevated Oxidized LDL :", Medicine & Science in Sports & Exercise, 09/2011 Publication	2%
2	pdfs.semanticscholar.org Internet Source	2%
3	lipidworld.biomedcentral.com Internet Source	1%
4	Shimada, K.. "Circulating oxidized low-density lipoprotein is an independent predictor for cardiac event in patients with coronary artery disease", Atherosclerosis, 200406 Publication	1%
5	docplayer.net Internet Source	1%
6	Boulay, P.. "Risk factor management after short-term versus long-term cardiac	1%

rehabilitation program", Coronary Health Care, 200108
Publication

7	academic.oup.com Internet Source	1 %
8	worldwidescience.org Internet Source	1 %
9	ajpp.in Internet Source	1 %
10	www.freepatentsonline.com Internet Source	1 %
11	Durrington, . "Hypertriglyceridaemia", Hyperlipidaemia 3Ed Diagnosis and Management, 2007. Publication	1 %
12	Submitted to Higher Education Commission Pakistan Student Paper	1 %
13	Pantelis Aronis. "Effect of Fast-Food Mediterranean-Type Diet on Human Plasma Oxidation", Journal of Medicinal Food, 09/2007 Publication	1 %
14	ijmcmed.org Internet Source	1 %
15	Rina Amelia, Juliandi Harahap, Aznan Lelo, Hendri Wijaya, Novita Harahap, Zulham	1 %

Yamamoto. "Risk analysis for cardiovascular complication based on the atherogenic index of plasma of type 2 diabetes mellitus patients in Medan, Indonesia", Family Medicine & Primary Care Review, 2020
Publication

16	Chengzhi Lu. "The relationships between PON1 activity as well as oxLDL levels and coronary artery lesions in CHD patients with diabetes mellitus or impaired fasting glucose", Coronary Artery Disease, 12/2008 Publication	1 %
17	lib.bioinfo.pl Internet Source	1 %
18	www.massage-techniques.org Internet Source	1 %
19	Nichols, Timothy C., Elizabeth P. Merricks, Dwight A. Bellinger, Robin A. Raymer, Jing Yu, Diana Lam, Gary G. Koch, Walker H. Busby, and David R. Clemmons. "Oxidized LDL and Fructosamine Associated with Severity of Coronary Artery Atherosclerosis in Insulin Resistant Pigs Fed a High Fat/High NaCl Diet", PLoS ONE, 2015. Publication	1 %
20	Ebrahim Abbasi Oshaghi, Mohammad Taghi Goodarzi, Victoria Higgins, Khosrow Adeli. "Role of resveratrol in the management of	<1 %

insulin resistance and related conditions: Mechanism of action", Critical Reviews in Clinical Laboratory Sciences, 2017
Publication

21	www.nature.com Internet Source	<1 %
22	www.e-enm.org Internet Source	<1 %
23	"Monday, 1 September 2008", European Heart Journal, 09/02/2008 Publication	<1 %
24	B P A Thoonen. "Self-management of asthma in general practice, asthma control and quality of life: a randomised controlled trial", Thorax, 2003 Publication	<1 %
25	Shoichi Ehara, Makiko Ueda, Takahiko Naruko, Kazuo Haze et al. "Pathophysiological role of oxidized low-density lipoprotein in plaque instability in coronary artery diseases", Journal of Diabetes and its Complications, 2002 Publication	<1 %
26	www.spandidos-publications.com Internet Source	<1 %
27	www.openaccessjournals.com Internet Source	<1 %

28	Ebru Emekli-Alturfan, Isik Basar, A. Ata Alturfan, Faruk Ayan, Lale Koldas, Huriye Balci, Nesrin Emekli. "The Relation between Plasma Tissue Factor and Oxidized LDL Levels in Acute Coronary Syndromes", Pathophysiology of Haemostasis and Thrombosis, 2007 Publication	<1%
29	Wang, X.. "The hypolipidemic natural product Commiphora mukul and its component guggulsterone inhibit oxidative modification of LDL", Atherosclerosis, 200402 Publication	<1%
30	www.degruyter.com Internet Source	<1%
31	Giacomo Ruotolo, Barbara V. Howard. "Dyslipidemia of the metabolic syndrome", Current Cardiology Reports, 2002 Publication	<1%
32	S. Tsimikas. "Lipoprotein-associated phospholipase A2 activity, ferritin levels, metabolic syndrome, and 10-year cardiovascular and non-cardiovascular mortality: results from the Bruneck study", European Heart Journal, 11/19/2008 Publication	<1%
33	www.biomedscidirect.com Internet Source	<1%

34	Fubao Huang, Kai Wang, Jianhua Shen. "Lipoprotein‐associated phospholipase A2: The story continues", Medicinal Research Reviews, 2019 Publication	<1%
35	HANS HERLITZ, BJÖRN DAHLÖF, OLOF JO. "Relationship Between Salt And Blood Pressure In Hypertensive Patients On Chronic ACE-Inhibition", Blood Pressure, 2009 Publication	<1%
36	Rianita Rianita, Saptawati Bardosono, Andi A. Victor. "Relationship between plasma lipid profile and the severity of diabetic retinopathy in type 2 diabetes patients", Medical Journal of Indonesia, 2008 Publication	<1%
37	Omer T. Njajou. "Association between oxidized LDL, obesity and type 2 diabetes in a population-based cohort, the Health, Aging and Body Composition Study", Diabetes/Metabolism Research and Reviews, 11/2009 Publication	<1%

Exclude quotes	On	Exclude matches	< 5 words
Exclude bibliography	On		