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LYCOPENE AND ATHEROGENIC RISK FACTORS: A REVIEW

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ABSTRACT

Coronary heart disease is marked as the third–fourth largest global deaths worldwide by addressing the attributes of high increase hazard ratios across multiple variables: Hypertension, Dyslipidemia, Elevated cholesterol, chronic inflammation and metabolic syndrome expressing the unawareness of risk assessment. Lycopene as a superior carotenoid with antiatherogenic effect can be used consequently in preventions of long term cardiovascular risk reduction strategies. Clinical trials on animals and human studies indicate the antioxidant property in lycopene is beneficial on carotid plaques and aortic intima media thickness in vivo by stabilizing the effectiveness on extraneous factors in behaving equally to statin drugs but act alternatively natural reflex adjuvant therapy. The present review article support the therapeutic efficacy about lycopene in reducing coronary events significantly with respect to its protective role in cardiovascular health.

KEYWORDS: Lycopene, Carotenoid, Antioxidant, Coronary heart disease, Risk factors, Safety.

INTRODUCTION

Coronary Heart Disease risk factors formally established at early 1960s with the initial findings of Framingham Heart Study. Distinguishable evidences demonstrate invariably Systolic Hypertension, Prediabetic state, Dyslipidemia, Ischemic stroke, Smoking, obesity and family history are the Degenerative factors remaining deleterious on atherosclerotic inceptive thrombogenicity. The mortality rate is 30% worldwide every year. As the consequences detected loss of elasticity and interior flexibility lead to occlusions at physiological stress emphasizing modifiable and none modifiable risk factors origin of sudden death if not treated periodically with balanced nutritious diet or by drug therapy. A nutritional diet is an important factor in the expansion of disease.[1] The biological rationale entities focus on protective antioxidant property of plant derived carotenoids against atherosclerosis. Lycopene as a predominant phytosterol carotenoid in human plasma of fatty esters efficacy biosynthesis can be used as alternative traditional medicine in dealing with uncontrollable chronic specific components related to coronary heart disease, i e: coronary atherosclerosis, Heart failure, stroke, Cardiac arrest, congestive heart disease or chronic arterial insufficiency.

The importance of lycopene as chromogenic confers distinctive red color to lycopene crystals and follows up with homeostatic regulations in deriving oxidative process, triglyceride cholesterol, homocysteine and endothelial dysfunctions.[2,3] Molecular Sciences reveal the irreversible non-enzymatic degradation of lycopene with various oxidative metabolites affecting the blood plasma levels by the accumulation of 3-keto-apo-B and 1515-apo lycopenoids among cleavage products.[4] The action of carotenoids on immunity functionally neutralizes and inhibits cellular HMGCoA reductase via the realistic role in oversimplifying the regulation of immune functions, genes, apoptosis and angiogenesis with no pro-vitamin A activity remarkably correspond the hyper-reactivity of reactive oxygen species and Nitric Oxide generation throughout the critical stages of DNA, lipids and proteins containing Chylomicrons and other Apo-beta lipoproteins in blood circulation.[5]

Lycopene as a constant singlet oxygen quenching in-vitro with Polyunsaturated Fatty Acids compound (PUFAs) convert singlet state into triplet state by the dispersion of heat to convert the potency of anti-inflammatory mediators modulating the metabolism of active vasodilatations. Study on hypothesis alleged protection of the antioxidant from atherosclerosis at the least occurrence of antiatherogenic action through anti-inflammatory effect on endothelial vasoactivation with the inhibition of redox sensitivity and platelet aggregation detectable in vivo by shedding endothelial leukocyte molecules.[6,7] According to the Cochrane 2010-2013 reviews on cardiovascular disease conclude effectiveness in reducing homozygous deficiencies decline cognitive factor on statin drug therapy due to its side effects statistics in medicine report to treat just rare non-serious common reversible conditions.[8] This review highlight the reflex potency of lycopene as a natural carotenoid is purely virtue in medicine terminology at

maintaining effective adjustments on impulsive risk factors in both Molecular genetics and Evidence based pharmacology.

Carotenoids and Human Health

Most of the carotenoids have mono, or dicyclic compound structures in the form of cyclization comprise 30-90% of mixture total trans-cis isomers.[9] All Trans form 5-cis, 9-cis, 13-cis, 15-cis, 7-cis and 11-cis at stable sequence most commonly identified and referring as all E-lycopene.[9,10] As an Antioxidant it has the powerful ability of 10 times higher to trap peroxyl radicals than that of alpha tocopherol and butylated hydroxyl toluene.[11] And after ingestion increase lycopene concentration to its highest peak improving bioavailability within 24 to 48hrs.

The independent mechanism generates free hydroxyl radicals which destroy the cell membrane causing oxidative damage during phagocyte activity in suppressing circulating levels to form hydrogen peroxide and C-reactive proteins. Therefore, to maintain optimal oxidant antioxidant defensive mechanism eliminates ROS, reduce inflammatory marker CRP, inhibition against cardiovascular disorders by delicate the balance between intra and extra cellular milieu outcomes and hypothesize protective effect on immune responses to explore the interactions of carotenoids on cell system. Lycopene influence on cell growth factor with 40% of suppression in cancerous cells at Mammary (MCF-7), Lungs (NCI-H226), Human Leukemia (HL-60) and also inhibit certain genes (Raji Cells).[12,14] The highest Analytic concentration of lycopene is at Lung tissues (85 folds), Kidney (60 folds) and Adipose tissues (40 folds). It predominantly originates in human organs with the contribution of 60%-80% of carotenoids at Liver, Testes, Ovaries, Prostate and Adrenal glands.

The data from European Study of Antioxidants Myocardial Infarction and Cancer (EURAMIC) examine the association between the adipose tissues and lycopene concentration, the result is contrary, with high serum 7 beta-hydroxycholesterol concentration and the decrease antioxidant is susceptible to high risk mechanical injury on Cigarette smoking to molecules may progress the concentration of C-reactive protein causative in carotid atherosclerosis.[15,16] In supremacy, lycopene as a phytochemical strong biomarker of carotenoids tends to be a good fighter against myocardial infarction in the condition of smokers interpreting the desirable composition of lycopene epoxide and decline 80% direct exposure to hydrocarbon gas phase by the formation of buccal mucosal cells.[17,19] In termination, carotenoids as plausibility inhibit lung carcinogenesis by modulating the up regulation of insulin growth factor binding protein 3 and down regulation of phosphorylation to upgrade the synergistic effect on atherosclerotic plaques of (0.04 ± 0.065mmol/mol) at human carotid and iliac arteries in medicine.[20]

Lycopene and Atherogenesis

Scientific evidences specify the association of blood concentration of lycopene intake and the compensatory coronary enlargements with shrinkage calcium score at CCA-IMT nonsignificantly at case control study adjust the independent risk factors of hypercholesterolemia leading to hypertriglyceridemia.[10,11,21,24] On the population based subjects at CCA-IMT with the measurements of lycopene on prognostic CVD endpoints explains the susceptibility of LDL oxidation and prolonged inflammatory process of atherosclerosis adjusting the odd ratio on risk of MI, smokers and CAD mortality in the variance of both internal and external cholesterol health relevance.

Available affirmation from Kupio Ischemic Heart Disease (KIHD), reports reproduces ultrasonographic analysis track to detect intimae lumen and media adventitia interfaces to estimate the initial staging.[25] It begins with the intrusion of toxic lipid peroxides and iron crystals in aortic tissues constitute the pre-requisite of advance aortic plaques. The reduced lipid accumulation depositions at opposes the site lessen the risk of common carotid artery thickness and found enthusiastic advantageous to human leukocyte tissues against oxidative DNA damage.[26,27] Furthermore, double blind study on healthy human volunteers on 5.7mg lycopene pills on 25 days trials restricted TNFα production, restrain edema formation and liver injury induced by ischemia reperfusion with the consumable of 25 to 50mg/kg.[28]

Clinical trials are conducted on "Atherogenic lipoprotein phenotype" at animal model experiments indicating increase in LDL and triglycerides with decrease in HDL to measure regular lycopene extract serum level on 4-8weeks with uniquely discovered antiatherogenic lipid profiles decline 17% mortality rates of coronary events.[29] As summarized in Table 1 lycopene on various dosing /body weight influence the physiological concentration of lipid disposition at endothelium dependant relaxation strongly beneficial in suppression of high fat induced hyperlipidemia with the reduction of increased aortic cholesterol esters in tissues.[30] Hence, lycopene serum concentration quarter the risk factor by the adjusted mean and maximal/L ($P<0.001$) at clinical health authorities.

Table 1: Animal Studies using Lycopene in combination of Statin drugs to reduce Hypercholesterolemia.

Species	Lycopene Duration	Diet Composition	Lipid Profile	Comment Status	Result
Rat	Lycopene50mg/kg+ Atorvastatin 50mg/kg Orally for 45days.	High Cholesterol Standard Diet containing placebo.	Hypolipidemia	Decrease tot-C with LDL-C and triglycerides but increased lipoprotein cholesterol level significantly reduce HDL-C (P<0.05)	Type I lesion of atherosclerotic plaques with inflammatory and few foam cells from lycopene.
Rabbit	Lycopene 20mg/kg+10mg/kg Fluvastatin for 4-8wks intrgastrically	High Cholesterol Diet	Baseline values of homeostasis protecting vascular endothelium with anti-inflammatory effect.	50% decrease tot-C and LDL-C with decreased amount of cholesteryl esters in aorta with decrease significantly (P<0.05)	Decrease in plaques formation at aorta with no plaque rupture.
Porcine	Lycopene30mg/day+Streptozotocin(STZ) injection for 2-8weeks.	High Cholesterol Diet with restricted diet for 2weeks containing placebo.	Hyperlipoproteinemia and Hperglycemia.	Tot-C 5.5 ± 1.45mmol/L H-C 2.09 ± 0.23mmol/L C 5.03 ± 2.41mmol/L	Reduction in DNA oxidative damage with significant (P=0.007) and hyperlipidemia inducing histomorphological changes with no luminal narrowing in coronary arteries.

At Human interventional trials, the association of lycopene and atherogenesis are examined only in few studies. The study design on prevalence of carotid plaques and thickness of intima media with matched ages, races, BMI and case control study adjust the CVD risk factors and low CCA-IMT with correlated lycopene serum concentration relation as summarized in Table 2. The effect of lycopene on CCA-IMT in ASAP study is distinctly invulnerable on gender implications in association with endogenous antioxidant system and owing high levels of estrogen functions in women are more defensive against CVD. In recent years, the role of carotenoids as an impact of antioxidant property in the prevention of atherosclerotic-related risk factors amplifies the bioavailability of well-balanced diet and utilizes the ambient conditions in our everyday life by the substitution of vitamins and minerals i.e. Omega-3 fatty acids, Vitamin B3, Vitamin C, Vitamin D, Vitamin E, Vitamin K, Magnesium supplements, Zinc, Folic acid, Flavonoids, Fibers and sterols.

Table 2: Studies of Lycopene serum concentration with the Risk of CHD and Atherosclerosis.

Study, Publication, Years and Nationality of Subject	Type of Study	Sex	n	Variables	Sample	Mean Levels of Lycopene	Findings
ARIC-study Iribarren et al. 1997.[31] American	Case-control	Women and men	462	Intima-media thickness	serum	Cases 0.89 Jmol/1 controls 0.91 Jmol/l	Nonsignificantly lower odds of being case with increase in lycopene.
The Rotterdam Study Klipstein-Grobush et al. 2000.[32] Netherlanders	Case-control	Women and men	216	Plaques of the abdominal aorta	serum	Cases 0.121 Jmol/1 Controls 0.13 Jmol/1	Adjusted odds ratio 0.35 (0.13-0.94) the highest quarter compared with the lowest in smokers.
Bruneck study D'Orico et al. 2000.[33] Italian	Cross-sectional and prospective 5-year follow-up	Women and men	392	Prevalence and incidence of carotid plaques	serum	Means 0.53-0.76 J Jmol/1	Lycopene did not significantly predict the risk of atherosclerosis.
Street et al. 1994.[34] American	Nested case-control 14 years follow-up	Women and men	369	Myocardial Infarction	serum	Cases 39.0 J Jg/l Control 40.2 J Jg/l	The excess risk of MI in smokers with the serum level of lycopene lower than median.
EURAMIC-study Kohlmeier et al 1997.[35] Multicentre	Case-control	Men	1379	Myocardial Infraction	Adipose tissue	0.21-0.36 J Jg/1	Adjusted odds ratio 0.52 (0.33_0.82) in the 10th compared with 90th percentile
The Linkoping-Vilnus coronary disease risk assessment study Kristenson et al. 1997.[36] Swedish and Lithuania	Cross-sectional	Men	210	CHD mortality	plasma	Linkoping 0.62 J Jmol/l Vilnus 0.33 J Jmol/l	Lower plasma levels of lycopene and higher risk of CHD mortality in vilnus than in Linkoping

Effect of lycopene in predisposing risk factors

Hypertension and Hypercholesterolemia are the most important frequent risk factors for CVD in general population with prevalence of 60% - 80% systo-diastolic hypertension with increased total cholesterol according to different author's verifications.[37,42] Clinical case reports on previous hypertension type I concluded the supplementation of 10-15 mg lycopene serum in the age group of 45-65 yrs on 8-12 weeks study abruptly drop (SBP-144/134mmHg) and (DBP-91/84mmHg) with normal diet as summarized in Table 3 and firmly function well in endothelial vessels at maintaining a good status in cholesterol homeostasis.[43,44] And the other Arm Control Study on vasculatures separately measures the variations of primary ends on each arm to integrate the approximate arterial stiffness and venous occlusion.[45,46] Lycopene on exhortation of 10-20 mg supplementations in the form of Lyc-o-Mato soft gel capsules produced by Lycopene Red Ltd surprisingly lower LDL cholesterol. Hence, lately lycopene proven to be reliable and typically safe adjunct therapy.

Table 3: Lycopene Studies in Systo-Diastolic Hypertension Reduction on Clinical Trials.

Hypertensive Volunteers	Age	Lycopene Extract	Time phase	P value	Result Reduction
Baseline SBP >120-<120mmHg	45-65years	10-15mg	12weeks	P<0.001/0.02	144/134mmHg
Baseline DBP >80-<80mmHg	21-49years	10mg	8-12weeks	P<0.005/0.06	91/84mmHg

According to the number of prospective and retrospective studies on the hypothesis of non diabetic healthy subjects and type 2 diabetic subjects estimate the reduction level of oxidation on the homeostatic assessment of insulin resistivity by predicting the FPG status and evaluation of family history.[47] The unclear explanations between Males (91%) and Females (95%) conclude the relative risk by the exposure of cell damage under the physiological conditions with the sex interaction differences as summarized in the Table 4 showing the antioxidant effect on carotenoid supplements improving the oxidative stress balance with the protective measurements of CVD morbidity and mortality rates.[48,50]

Table 4: Study on Lycopene Supplementation of P value in Type 2 Diabetic Subjects.

Variables	Males Type 2 Diabetes	Females Type 2 Diabetes
Age	45-55 years	45-70 years
BMI/kg (Insulin dependence)	>40kg/m^2	>30kg/m^2
Lycopene Duration	8-10mg (8weeks – 2 months)	8-10mg (8weeks – 2 months)
HbA1c	14.5%	10.4%
Relative Risk	91%	95%
P value	P<0.0001	P<0.02

Comparison of Lycopene and Statin drugs effect on atherosclerosis

Based on the Interventional Experiments, the efficacy of lycopene with antioxidant property affects the absorption and bioavailability with the composition of high doses of lycopene/body weight in measuring the higher plasma levels.[51] As summarized in Table: 5 the lycopene intervention lowers the level of LDL cholesterol and oxidation modifications in the improvements of lipid metabolism biochemically in reducing adhesions and aggregations of platelets in controlling the vascular tone by clearance of free radicals in functions of anti-inflammatory actions which are essentials for anti-atherogensis.[56,57]

Table 5: Pharmacological Actions of Lycopene at Various Dose Levels.

S. No	Pharmacological Action	Experimental Studies	Effective Doses
1	Nitric Oxide scavenging	In Vitro (71)	5 and 10 µM
2	TNF- alpha inhibition (72)	Clinical	5.7mg/kg
3	Anti- inflammatory (73)	In Vivo	25 and 50mg/kg
4	Anti-Diabetic (74)	Animal	90mg/kg

In contrast, Statin drugs including (Simvastatin, Pravastatin, Fluvastatin and Atorvastatin) are generally accepted as anti-inflammatory and anti-atherosclerotic in vivo by inhibiting 3-hydroxy-3-methyl glutaryl-

coenzyme A reductase on morphological changes, it reduces lipids and cholesterol levels independently. It follows the parallel role with lycopene in preventing myocardial infarction, delaying the initial stages of atherosclerotic lesions and the plaques formation by the administration of 10mg statin drugs/body weight.[58] In result it shows less maintenance in Nitric Oxide levels which leads to the consequences of normal functioning of arteries in terms of complications of chronic diseases. Moreover Simvastatin and Pravastatin appear to be superior in causing myopathy, dyslipidemia in diabetes, rhabdomyolysis, renal insufficiency, heart failure and renal failure.

Future direction

In conclusion, there are much more unquestionable requisite interpretations needed to naïve the twisted interconnection of lycopene with Atherogenesis evolving gradual participation of acute vascular events for lifestyle remodeling. According to Epidemiological and pathopharmacological data survey, investigations are needed to focus on constant Sophisticated Replenishment System for the unknown internal absorption, departed glycated hemoglobin levels, covariate analysis on micro-albuminuria prevalence, unclear contradictory depletion phase and lastly the meticulous quantity of dosing of lycopene serum concentration for the rationale optimal long term beneficial in reducing residual cardiovascular risk incidences.

Conflicts of interest

The authors indicated no potential conflicts of interest.

REFERENCES

1. Rissanen TH, Serum Lycopene Concentrations and Carotid Atherosclerosis, 2003.
2. H. Jackson, C. L. Braun, and H. Ernst, “The chemistry of novel xanthophyll carotenoids,” The American Journal of Cardiology, 2008; 101(10): supplement, S50–S57.
3. Riccioni G, D’Orazio N, Speranza L, Di Ilio E, Glade M, et al. (2010) Carotenoids and asymptomatic carotid atherosclerosis. J Biol Regul Homeost Agents, 24: 447–452.

a. L. D. A. Ferreira, K.-J. Yeum, R. M. Russell, N. I. Krinsky and G. Tang, “Enzymatic and oxidative metabolites of lycopene,” Journal of Nutritional Biochemistry, 2003; 14(9): 531–540.

4. https://books.google.nl/books?isbn=3540276610
5. Palozza P, Parrone N, Simone RE et al. (2010) Lycopene in atherosclerosis prevention: an integrated scheme of the potential mechanisms of action from cell culture studies. Arch Biochem Biophys, 504: 26–33.
6. Marcotorchino J, Romier B, Gouranton E et al. (2012) Lycopene attenuate LPS-induced TNF-α secretion inmacrophages and inflammatory markers in adipocytes exposed to macrophage-conditioned media. Mol Nutr Food Res., 56: 725–732
7. "HIGHLIGHTS OF PRESCRIBING INFORMATION; LIPITOR (atorvastatin calcium) at www.accessdata.fda.gov" (PDF). Retrieved 1 May 2017.
8. amacneil.webfactional.com/wp-content/docs/hussey_etal_2012.pdf
9. H. Jackson, C. L. Braun and H. Ernst, “The chemistry of novel xanthophyll carotenoids,” The American Journal of Cardiology, supplement, 2008; 101(10): S50–S57.
10. N. J. Engelmann, S. K. Clinton, and J.W. Erdman, “Nutritional aspects of phytoene and phytofluene, carotenoid precursors to lycopene,” *Advances in Nutrition*, 2011; 2(1): 51–61.
11. Levy J, Bosin E, Feldmen B, Giat Y, Miinster A, Danilenko M, Sharoni Y. Lycopene is a more potent inhibitor of human cancer cell proliferation than either a-carotene or p-carotene. Nutr Cancer, 1995; 24: 257-66.
12. Countryman C, Bankson D, Collins S, Mar B, Lin W. Lycopene inhibits the growth of the HLpromyelocytic leukemia cell line (abstract). Clin Chem, 1991; 37: 1056.
13. Bankson DD, Countryman CJ, Collins SJ. Potentiation of the retinoic acid induced differentiation of HL-60 cells by lycopene (abstract). Am J Clin Nutr, 1991; 53(suppl): P- 13.
14. Conn PF, Schalch W, Truscott TG. The singlet oxygen and carotenoid interaction [published erratum appears in J Photochem Photobiol B, 1993; 17: 89]. J Photochem Photobiol B:, 1991; 11: 41 -7.
15. Salonen JT, Yla –Herttuala S, Yamamato R, et al. Autoantibody agent against oxidized LDL and Progression of Carotid atherosclerosis. Lancet, 1992; 339: 883-7.
16. Handelman GJ, Packer L, Cross CE. Destruction of tocopherols, carotenoids and retinol in human plasma by cigarette smoke. Am J Clin Nutr, 1996; 63: 559–65.
17. Salonen JT, Nyyssonenk, Salonen R, et al. Lipoprotein Oxidation and Progression of Carotid Atherosclerosis. Ciculation, 1997; 95: 840-5.
18. Pryor WA. Cigarette smoke and the involvement of free radical reactions in chemical carcinogenesis. Br J Cancer, 1987; 55: 19–23.
19. Pryor WA. Cancer and free radicals. In: Shankel DM, ed. Antimutagenesis and anticarcinogenesis: mechanisms. New York: Plenum Press, 1986; 45–59.
20. Austin MA. Plasma triglyceride and coronary heart disease. Arterioscler Thromb, 1991; 11: 2–14. Google Scholar.
21. Austin MA, Hokanson JE, Edwards KL. Hypertriglyceridemia as a cardiovascular risk factor. Am J Cardiol., 1998; 81: 7B–12B. Google Scholar.
22. Assman G, Schulte H, Funke H, von Eckardstein A. The emergence of triglycerides as a significant independent risk factor in coronary artery

disease. Eur Heart J., 1998; 19(suppl M): M8–M14. Google Scholar.
23. Verghese M, Richardson JE, Boateng J, Shackelford LA, Howard C, et al. (2008) Dietary lycopene has a protective effect on cardiovascular disease in New Zealand male rabbits. J Biol Sci., 8: 268–277.
24. M. VergheseJE RichardsonJ. BoatengLA ShackelfordC. Howard 2008 Dietary lycopene has a protective effect on cardiovascular disease in New Zealand male rabbits. J Biol Sci., 8268277. Google Scholar.
25. B. Burton-Freeman, J. Talbot, E. Park, S. Krishnankutty and I. Edirisinghe, "Protective activity of processed tomato products on postprandial oxidation and inflammation: a clinical trial in healthy weightmen and women," Molecular Nutrition and Food Research, 2012; 56(4): 622–631.
26. Heller FR, Descamps O, Hondekijn JC. LDL oxidation: therapeutic perspectives. Atherosclerosis, 1998; 137(Suppl): S25-31.
27. Delahoy PJ, Magliano DJ, Webb K, Grobler M, Liew D (2009) The relationship between reduction in low-density lipoprotein cholesterol by statins and reduction in risk of cardiovascular outcomes: An updated meta-analysis. Clin Ther., 31: 236–244.
28. Matos HR, Capelozzi VI, Gomes OF, Mascio PD, Medeiros MH. Lycopene inhibits DNA damage and liver necrosis in rats treated with ferric nitrilotriacetate. Arch Biochem Biophys, 2001; 396(2): 171-177.
29. Kohlmeier L, Kark JD, Gomez-Gracia E, Martin BC, Steck SE, Kardinaal AF, et al. Lycopene and myocardial infarction risk in the EURAMIC Study. Am J Epidemiol, 1997; 146: 618-26.
30. Iribarren C, Folsom AR, Jacobs DR, Gross MD, Belcher 10, Eckfeldt JH. Association of serum vitamin levels, LDL susceptibility to oxidation, and autoantibodies against MDA-LDL with carotid atherosclerosis. A case-control study. The ARIC Study Investigators: Atherosclerosis Risk in Communities. Arterioscler Thromb Vase BioI., 1997; 17: 1171- 1177.
31. Klipstein-Grobusch K, Launer LJ, Geleijnse JM, Boeing H, Hofman A, Witteman JC. Serum carotenoids and atherosclerosis: The Rotterdam Study. Atherosclerosis, 2000; 148: 49-56.
32. D'Odorico A, Martines D, Kiechl S, Egger G, Oberhollenzer F, Bonvicini P, Sturniolo GC, Naccurato R, Willeit J. High plasma levels of a- and l3-caroteneare associated with a lower risk of atherosclerosis: results from the Bruneck study. Atherosclerosis, 2000; 153: 231-239.
33. Street DA, Comstock GW, Salkeld RM, Schuep W, Klag MJ. Serum antioxidants and myocardial infarction. Are low levels of carotenoids and a-tocopherol risk factors for myocardial infarction? Circulation, 1994; 90: 1154-1161.
34. Kohlmeier L, Kark 10, Gomez-Gracia E, Martin BC, Steck SE, Kardinaal AF, Ringstad J, Thamm M, Masev V, Riemersma R, MartinMoreno JM, Huttunen JK, Kok FJ. Lycopene and myocardial infarction risk in the EURAMIC Study. Am J Epidemiol, 1997; 146: 618-626.
35. Kristenson M, Zieden B, Kucinskiene Z, Elinder LS, Bergdahl B, Elwing B, Alearavicius A, Razinkoviene L, Caltauskash H, Olsson AG. Antioxidant state and mortality from coronary heart disease in Lithuanian and Swedish men: concomitant cross sectional study of men aged 50. Br Med J., 1997; 314: 629-633.
36. Goff DC, Bertoni AG, Kramer H, et al. Dyslipidemia prevalence, treatment and control in the Multi-Ethnic Study of Atherosclerosis (MESA): gender, ethnicity and coronary artery calcium. *Circulation*, 2006; 113(5): 647–656. [PubMed].
37. Anderson KM, Castelli WP, Levy D. Cholesterol and mortality. 30 Years of follow-up from the Framingham Study. *Journal of the American Medical Association*, 1987; 257(16): 2176–2180. [PubMed].
38. Liakishev AA. Correction of lipid disorders in patients with arterial hypertension. *Russian Medical Journals*, 2002; 10(19): 878–882.
39. Novgorodtseva TP, Kantur TA, Karaman YK, Antonyuk MV, Zhukova NV. Modification of fatty acids composition in erythrocytes lipids in arterial hypertension associated with dyslipidemia. *Lipids in Health and Disease*., 2011; 10, article 18 [PubMed].
40. Goff DC, Bertoni AG, Kramer H, et al. Dyslipidemia prevalence, treatment and control in the Multi-Ethnic Study of Atherosclerosis (MESA): gender, ethnicity, and coronary artery calcium. *Circulation*, 2006; 113(5): 647–656. [PubMed].
41. Arnett DK, Jacobs DR, Luepker RV, Blackburn H, Armstrong C, Claas SA. Twenty-year trends in serum cholesterol, hypercholesterolemia, and cholesterol medication use: the Minnesota Heart Survey, 1980–1982 to 2000–2002. *Circulation*, 2005; 112(25): 3884–3891. [PubMed].
42. Graham I, Cooney MT, Bradley D, Dudina A, Reiner Z. Dyslipidemias in the prevention of cardiovascular disease: risks and causality. *Current Cardiology Reports*., 2012; 14(6): 709–720. [PubMed]
43. Martsevich SY. Treatment of lipid disorders in patients with coronary heart disease. *Treating Physician*., 2005; 5: 42–45.
44. Wilkinson IB, Webb DJ (2001) Venous occlusion plethysmography in cardiovascular research: methodology and clinical applications. Br J Clin Pharmacol, 52: 631–646.
45. Chen C-H, Nevo E, Fetics B, Pak PH, Yin FCP, et al. (1997) Estimation of Central Aortic Pressure Waveform by Mathematical Transformation of Radial Tonometry Pressure Validation of Generalized Transfer Function. Circulation, 95: 1827–1836. doi:10.1161/01.CIR.95.7.1827.

46. Plotnick GD, Correti MC, Vogel IRA. Effect ofantioxidant vitamins on the transient impairment ofendotheliumdependent brachial artery vasoactivity following a single high-fat meal. JAMA., 1997; 278: 1682-1686.
47. Salonen JT, Nyyssonen K, Salonen R. Antioxidant Supplementation in Atherosclerosis Prevention (ASAP) study: A randomized trial of the effect of vitamins E and C on 3-year progression of carotid atherosclerosis. J Intern Med., 2000; 248: 377-386.
48. Hertog MG, Feskens EJ, Hollman PC, et al. Dietary antioxidant flavonoids and risk of coronary heart disease: The Zutphen Elderly Study. Lancet., 1993; 342: 1007-1011.
49. Upritchard JE, Sutherland WH, Mann Jl. Effect of supplementation with tomato juice, vitamin E, and vitamin C on LDL oxidation and products of inflammatory activity in Wpe 2 diabetes. Diabetes Care., 2000; 23: 733-738.
50. Paolisso G, D'Amore A, Volpe C, Balbi V, Saccomanno F, Galzerano D, et al. Evidence for a relationship between oxidative stress and insulin action in non-insulin-dependent (type II) diabetic patients. Metabolism, 1994; 43: 1426-9.
51. Asberg A, Holdaas H. Fluvastatin and fluvastatin extended release: a clinical and safety profile. Expert Rev Cardiovasc Ther., 2004; 2: 641–52.
52. Riso P, Visioli F, Grande S, Guarnieri S, Gardana C. Effect of a tomato-based drink on markers of inflammation, immunomodulation and oxidative stress. *J Agr Food Chem.*, 2006; 54(7): 2563-2566.
53. Leticia B, Joao R, Bruno S, et al. Anti-inflammatory effect of lycopene on carrageenan-induced paw oedema and hepatic ischaemia-reperfusion in the rat. *Br J Nutr.*, 2009; 102: 126-133.
54. Ali MM, Agha FC. Amelioration of streptozotocin-induced diabetes mellitus, oxidative stress and dyslipidemia in rats by tomato extract lycopene. *Scand J Clin Lab Invest.*, 2009; 69(3): 371-379.
55. Berliner JA, Navab M, Fogelman AM, Frank JS, Demer LL, Edwards PA, et al. Atherosclerosis: basic mechanisms. Oxidation, inflammation, and genetics. Circulation, 1995; 91: 2488 –96.
56. Qiao C, Zhang K, Xia J. Influence of oxidized low density lipoprotein on the proliferation of human artery smooth muscle cells in vitro. J Huazhong Univ Sci Technolog Med Sci., 2007; 27: 20 –3.
57. Sudano I, Spieker LE, Hermann F, Flammer A, Corti R, Noll G, et al. Protection of endothelial function: targets for nutritional and pharmacological interventions. J Cardiovasc Pharmacol, 2006; 47(suppl 2): S136 –5.
58. Lee MT, Chen BH. Stability of lycopene during heating and illumination in a model system. *Food Chem*., 2002; 78: 425-432.