Original Research
Medical Journal of the Islamic Republic of Iran.Vol. 23, No. 1, May, 2009. pp. 14-22

Comparison of the effects of low calorie diet and lovastatin on serum lipoproteins, apob, homocysteine and total antioxidant capacity in hyperlipidemic obese persons

Farzad Shidfar[1],PhD., Javad Haji Miresmail[2],MD., Sharieh Hosseini[3],MSc.
Shahrzad shidfar[4],MD., Reza Homayonfar[5], MS.

Department of Nutrition, School of Health, Iran University of Medical Sciences., Tehran, Iran.

Abstract

Background: obesity is directly related to dyslipidemia which contributes significantly to the risk of coronary heart disease, a major cardiovascular disease and a serious health problem. The aim of this study was to compare the effects of low calorie diet and those of lovastatin on serum lipoproteins, apo B, homocysteine, and total antioxidant capacity (TAC) in hyperlipidemic obese patients.

Methods: In a randomized clinical trial, 41 obese patients were stratified by BMI, serum triglyceride (TG) and total cholesterol (TC) and randomly allocated to one of these groups: 1- Lovastatin tablet (40mg) 2-1200 calorie diet per day according to the therapeutic lifestyle change (TLC) dietary pattern for 8 weeks. Serum lipoprotein, apo B, homocysteine, and TAC were measured enzymatically, immunoturbidometrically, via EIA , and colorimetrically respectively.

Results: There were a significant decrease in mean of the serum TC (P=0.0001), LDL- c(p=0.0001), TG/HDL-c(p=0.03), apoB (p=0.0001) and significant increase in TAC (p=0.0001) in diet group at the end of the study compare to lovastatin group. TC, LDL-c, TG, LDL-c/HDL-c , TC/HDL-c , TG/HDL-c, homocysteine and apo B showed significant decrease but TAC showed significant increase in the diet group at the end of the study compared to beginning values (p=0.0001, p=0.0001, p=0.0001, p=0.001, p=0.0001, p=0.0001, p=0.0001, p=0.0001 and p=0.002, respectively). But in the lovastatin group only TC, LDL-C, TG, LDL-c/HDL-c, TC/HDL-c and apo B had significant decrease at the end of the study compared to beginning values (P=0.0001, P=0.0001, P=0.0001, P=0.01, P=0.02, P=0.002, respectively)

Conclusion: The study revealed that when compared to levostation 1200 kcal diet according to TLC dietary pattern had more beneficial effects on serum lipoproteins, apo B, homocysteine and TAC, so it may decrease CVD risk factors and mortality in hyperlipidemic obese patients.

Keywords: obesity, lipoprotein, lovastatin, low calorie diet, apo B.

Introduction

As the prevalence of obesity has increased over the past 20 years, the difficulties faced by overweight patients and their health care practitioners have become apparent [1]. In the year of 2006, about 56.4% of U.S. adults had a BMI of 25 or higher. Of these, 19.8% were considered obese, a 61% increase in obesity since 1991 up

1. **Corresponding author,** Associate Professor of Nutrition, School of Health, Iran University of Medical Sciences. Address: 3rd Floor, School of Medicine, Shahid Hemmat Expressway, Iran University of Medical Sciences, Tehran, Iran Tel:+98-21-88602218. Email: farzadshidfar@yahoo.com
2. Assistant Professor of Cardiology, School of Medicine, Iran University of Medical sciences, Tehran, Iran.
3. Master of chemistry, Islamic Azad University, Sari Branch, Sari, Iran.
4.Internist,University of Massachausetts, Memorial Hospital,Worcester, USA.
5. Master of Nutrition,School of Health, Iran University of Medical Sciences,Tehran, Iran.

to 2006 [2]. In the year of 2006 more than 115 million persons in developing countries were obese (BMI>30). In the same year prevalence of over weight (BMI=25-29.9) and obesity (BMI>30), according to a nationwide survey in Iran was 32% (men), 32.4% (women) and 10.9% (men), 24.5% (women) respectively [2] The economic burden of obesity was 70 billion dollar in 2004 in U.S.A at it was associated with 23% (95% confidence interval [CI], 10%-34%) of health plan health care charges and 27% (95% [CI], 10%-37%) of national health care charges.The total economic cost of obesity represented 2.2% of total health care cost in Canada [3]. Obesity is associated with increased risk of cardiovascular disease (CVD), type 2 diabetes mellitus, hypertension, cancer and osteoarthritis [4-7].

It has been shown that, for obese people, particularly those with abdominal obesity, there is an increased prevalence of dyslipidemia, manifested by increased fasting plasma triglyceride (TG) and decreased HDL-c [5] which is concomitant with increase of apo B-100 and small dense LDL and permeability of these particles in artery intima which leads to increasing plaque, atheroma formation and atherosclerosis [8,9]. The mainstay of treatment for obesity is dietary-induced weight loss [10,11]. American Diabetes Association (ADA), American Heart Association (AHA) and National Health, Lung and Blood Institute (NHLBI) recommend that weight loss is best accomplished by following a low-calorie diet with 30% of energy from fat [11-15]. Dansinger reported that low calorie diet can improve a number of risk factor for a atherosclerosis, including serum total cholesterol (TC) and TG levels [13]. However, according to Parenti and Redmon studies, its effect on HDL-c, apo A-I and apo B are controversial [16,17]. Samaha reported decrease of TG, TC and LDL-c in hyperlipidemic obese persons due to a low caloric diet [18].

Cholesterol-lowering therapy with 3-hydroxy-3-methylglutaryl coenzyme A (HMG-COA) reductase inhibitors or statin (because of favorable effects on serum lipoproteins) has been established as an effective method of reducing death and myocardial infarction among patients with CAD [19-21].

However, a significant number of patients receiving statin therapy continue to have high residual risk [22]. A wide gap still exists between the numerous scientific publications demonstrating the beneficial effects of statins and the low rate of implementing the guidelines in practice [23]. On the other hand, statins have some side effects (e.g. myopathy, peripheral neuropathy, lupus, tendinopthy and pancreatitis) [24,25]. Furthermore, statins do not substantially lower homocysteine levels as an independent risk factor for CVD [26-28] and no consistent evidence shows that statins overall have a benefical effect on serum antioxidant capacity [28-31]. However, low calorie diets do not cause the side effects statins do, but the effects of these diets on homocysteine and antioxidant capacity on human being is not clear [32-34]. In person with BMI of 30 and above, regardless of the drug used or category of risk, the therapeutic lifestyle changes underpin all treatment [34]. So we had no bias toward low calorie diet in this study.

The purpose of this study was, therefore, a comparison between the effects of low calorie diet and those of lovastatin on serum lipoproteins, apo B, homocysteine and total antioxidant capacity (TAC) in hyperlipidemic obese persons.

Method

Participants

Forty-four, nonsmoking, healthy obese men were recruited from the Endocrine Research Center (ERC) of Iran University of Medical Sciences in Tehran, Iran from May to November, 2006. All subjects completed a comprehensive medical examination and routine blood tests. Persons were informed of their rights as volunteers in this study and signed approved

consent forms. The procedures followed in this study were maintained in accordance with the Helsinki Declaration and the study was approved by the institutional review board of Iran University of Medical Sciences Health System. Participants received no monetary incentive. Inclusion criteria were an age of 18 to 55 years and a BMI of at least 25, desire to lose weight, and elevated lipid levels (total cholesterol level > 200 mg/dl, LDL-C level 160 mg/dl and triglyceride level 200-400 mg/dl). Exclusion criteria were chronic diseases (i.e., heart disease, cancer, diabetes, hepatic, kidney and thyroid disease), taken antihypertensive drugs, multivitamin or nutrient supplements, lipid lowering medications, antibiotics, or sex hormone treatment, pregnancy or breast feeding, use of any weight loss diet or diet pills in the last 6 months and base-line ketonuria.

Study design

A randomized clinical trial of parallel design was used to compare the effects of low-calorie diet with those of lovastatin on serum lipoproteins, apo B, homocysteine and TAC in hyperlipidemic obese people. During a 3- week time period, subjects continued their usual diet and then were stratified by sex, serum TC and TG and randomly assigned to one of two groups for 8 weeks: 1- lovastatin tablet with a dose of 40 mg/day, with no change in dietary intake and physical activity 2- A low calorie (1200 kcal) diet according to the therapeutic lifestyle change (TLC) dietary pattern [35], an enhanced National Cholesterol Education Program (NCEP) step II diet [35], with emphasis on lipid guidelines and portions with approximately 55 percent of calories from carbohydrate, 30 percent from fat (saturated fat less than 7%, polyunsaturated fat up to 10% and monounsaturated fat up to 20% of total calories) and 15 percent from protein. The daily dietary pattern consisted of 4 servings of bread and cereals, 3 servings of fruits, 4 servings of vegetables, 2 servings of low fat milk and dairy 3 servings of fats and oils, 6 oz of lean meat and legumes and less then 3 egg per week. No specific exercise program was recommended. In addition, subjects had an initial 1-2h of nutrition education by the research dietitians who used the exchange lists for meal planning for 2003 of ADA to implement each subject's individual macronutrient patterns. Subjects were specifically instructed to restrict exchange-list choices to low- saturated- fat items (eg, selecting only from nonfat or low fat dairy, monounsaturated and polyunsaturated fat, and very lean to lean protein food lists) and totally daily serving throughout each day to ensure consumption of prescribed serving from each food group. Subjects prepared their own food and kept detailed food records to enhance compliance and to enable monitoring.

Each week, subjects returned to the ERC for a weight check and a 15-20 min visit with the study dietitian to review their food records. Compliance with the assigned diet was assessed at weekly follow-up visits by evaluation of each food record for accuracy of macronutrient estimation and compliance with prescribed total calorie and macronutrient composition; this procedure used both exchange lists for meal planning and food processor software. Assessment of ease of adherence were rated on a scale of 1 to 10, in which 1 represented least and 10 represented complete ease of adherence. All persons in lovastatin group were assessed at weekly follow- up visits and compliance to lovastatin was based on the number of packets returned at the week 8 visit.

Data collection and measurement

Anthropometry data included measurement of height, waist circumference (WC) (using stadiometer) and weight (using a balance scale) was obtained at the beginning and end of the study. WC was the distance around the smallest area below the rib cage and above the umbilicus [35]. Dietary intake was monitored by the same dietitian throughout the study and subjects were asked to complete a 24 hour diet recall ques-

tionnaire in the beginning, forth and eighth week as well as a lifestyle questionnaire (e.g. physical activity, income, etc) at the beginning and end of the 8th week of intervention. Subjects were required to provide venous blood samples after fasting overnight (for 12-14 h) at the beginning and end of intervention. All samples were collected while the subject rested in a supine position for 10 minutes. Serum lipoproteins were assayed with a cobas MIRA analyzer (Roche Diagnostic, Basel, Switzerland). TC and TG levels were measured enzymatically with the triacylglycerol GPO-PAP-cholesterol CHOD-PP kit (MAN Co, Iran). Serum HDL-Cholesterol was determined enzymatically using the CHOD-PAP kit after precipitation of the chylomicrons, VLDL and LDL with phosphotungstic acid and mg+2. Serum LDL-cholesterol was determined enzymatically using the CHOD-PAP kit after precipitation of LDL with heparin and sodium citrates and then by utilizing the following formula: LDL-cholesterol= total cholesterol- cholesterol in the supernatant. Apo B, homocysteine, and TAC were measured by immunoturbidometry (Pars Azmon Kit, Iran), EIA (Randox kit, Great Britain) and colorimetry [36], respectively.

The within-assay CV (%) for these assays (n=10) were 0.8, 0.8 , 0.85, 1.2, 1.2, 1.2, 0.8 for TC, HDL-c, TG, Apo B, ApoA- I, TAC, and homocysteine respectively, and the between- assay CV (%) (n=10) were 0.9, 0.9, 0.95, 1.4, 1.4, 1.4 and 0.95 respectively.

The standard supplied with the kit was used for calibration. A 2 point calibration was used every 2 days, with charge of reagent lot/ bottle or as indicated by quality control procedures. The sensitivity was 0.5 mg/dl, the precision was based on reported CV (%), and the accuracy was based on dilution and recovery test.

Statistical analyses

This study was designed with 90% power, with 2- sided a=0.05 (type I error), to detect a 5% difference in weight loss between the 2 group. On the basis of SDs observed in the current study, the number of subjects needed to treat to detect this difference was 16/group. Given an anticipated dropout rate of 25 percent, we set the enrollment target at 20 subjects.

All data were expressed by means SD. The level of significance was chosen $P<0.05$. Statistical analyses were performed with PC SPSS 13.0. Normal distribution of the variables was checked by Kolmogorov Smirnov Test; student's t test was used to test whether the differences between the mean values of the items studied in both groups were significant. Differences in the same participants before and after 10 weeks of intervention were evaluated by paired t-test. Diet records were analyzed by using Food Processor II software. ANOVA was employed to compare the means in different intervals of 24-hour diet recall questionnaires and also the values of within-assay and between-assay of measurement. For qualitative variables (e.g. education, occupation, income, etc.), a chi square test was used. There was no missing data because all of persons ended the study successfully except 3 people who were ruled out.

Results

Forty-one of forty-four randomly assigned obese hyperlipidemic participants completed the study. 3 persons could not adhere to the group meeting schedule and were not included in analyses. Baseline characteristics of the participants confirmed that they were well matched for inclusion criteria (age: 44.1 ± 4.9 in diet group versus to 45.9 ± 5.6 in lovastatin group). Finally 8 men and 13 women in diet group versus to 7 men and 13 women in lovastatin group completed the study. Therefore there was no significant difference in these variables between two groups at the baseline.

Participants in diet group sustained a mean adherence level of at least 8 to 10,which appeared to delineate a clinically meaningful adherence level and had a excellent compliance(>90%) for lovastatin tablets. The results

Variable	Diet (n=21)		Lovastatin (n=20)	
	Baseline	After intervention	Baseline	After intervention
Weight (kg)	86.1±8.3A	73.9±4.9C	87.4±6.5	84.9±6.5
BMI ($\frac{kg}{m^2}$)	29.5±3.6B	25.3±3.2D	31.9±3.6	30.8±1.2
Waist/Hip	1.1±0.1	1.02±0.1	1.1±0.1	1.1±0.07
Waist circumference	95±1.1	92±1	96±1.2	95±1.1

C:P=0.02 Student's t-test A:P=0.01 Paired t-test
D:P=0.01 Student's t-test B:P=0.02 Paired t-test

Table 1. Anthropometric data at baseline and after intervention.

revealed that there were significant differences in weight and BMI between the two groups after intervention (P=0.02 and P=0.01, respectively) as well as in diet group after intervention compared to baseline values (P=0.01 and P=0.02 respectively) (Table 1). The expected potential confounders to the results of the study included age, body size and composition. None of these characteristics at baseline were significantly different between the two groups. Qualitative variables (e.g. education, physical activity, etc.) measured by valid questionnaire showed no significant difference between the two group. There was also no significant difference in dietary intake of the participants in lovastatin group during the study and also within-assay, between-assay had no significant difference. There were, however, significant decrease in LDL-c, TC, TG/HDL-c and apoB but significant increase in TAC after intervention in diet group compare to lovastatin group (p=0.0001, p=0.0001, p=0.03, p=0.0001 and p=0.0001, respectively) (Table 2). LDL-c TC, TG, LDL-c/HDL-c, TC/HDL-c and apoB showed significant decrease in diet and also in lovastatin groups at the end of the study compared to baseline values (p=0.0001 and p=0.0001, p=0.0001, p=0.001, p=0.0001, p= 0.0001 and p=0.0001, respectively in the diet group and p=0.0001, p=0001, p=0.0001, p=0.01, p=0.02 and p= 0.002, respectively in the lovastatin group) (Table 2).

Only in the diet group, there was a significant decrease in TG/HDL-c (P=0.0001), homocys-

Variable	Diet group (n=21)		Lovastatin group (n=20)	
	Baseline	After intervention	Baseline	After intervention
TC (mg/dl)	291.4±13.9A	227.2±10.8C	292.2±12.7B	213.3±9.3
LDL-c(mg/dl)	191.7±14.7A	153.4±11.8C	193.4±15.7B	135.3±11
HDL-c (mg/dl)	36.5±6.5	37.9±8.3	38.6±9.3	34.4±8.5
TG (mg/dl)	315.1±40.6A	239.5±30.9	300.7±36.4B	255.6±30.9
LDL-c/HDL-c	5.4±1.1D	4.2±1.1	5.4±1.9M	4.1±1
TC/HDL-c	8.1±1.4A	6.3±1.5	8±2.3E	6.5±1.6
TG/HDL-c	8.8±2A	6.5±1.4F	8.2±2.5	7.8±2.3
Homocysteine(µmol/l)	12.2±4A	10.5±3.4	11.5±4.8	11.4±4.7
TAC (µmol/l)	1±0.6G	1.6±0.3C	0.9±0.6	1.1±0.4
ApoB(mg/dl)	134.2±10.3A	92±7C	135.3±11K	121.2±10.1

A: P=0.0001 Paired t-test E: P=0.02 Paired t-test B: P=0.0001 Paired t-test F: P=0.03 student's t-test
C: P=0.0001 Student's t-test G: P=0.002 Paired t-test D: P=0.001 Paired t-test K: P=0.002 paired t-test
M: P=0.01 paired t-test

Table 2. Serum lipoprotein concentrations at baseline and after intervention in two groups.

teine (P=0.0001) and an increase in TAC (P=0.002) after intervention compared to baseline values (Table 2).

Discussion

The results of this randomized clinical trial demonstrate that in forty-one hyperlipidemic obese participants the low calorie diet (1200 kcal) produced greater decrease in weight, BMI, apo B, TG/HDL-c and, an increase in TAC compared to lovastatin tablet but homocysteine was decreased only in the low calorie diet group. To our knowledge, the present study is the first one which compared the effects of low calorie diet with statins. The magnitude of weight loss (14%) that we observed compares favorably with that achieved with use of weight loss medications approved by the U.S. Food and Drug Administration, such as orlistat (decrease of about 9% at 6 months)[37] and sibutramine (decrease of about 8% at 6 months) [38]. Studies in simple obese subjects have shown that diets providing 400, 600, and 800 kcal/day produce similar weight losses, but the safety of diets providing less than 800 kcal/day is questionable [8].

In both groups, there were significant decreases in LDL-c and TC but lovastatin caused more significant decrease compared to low calorie diet (p=0.0001). Decrease in LDL-c and TC due to low calorie diet, (p=0.0001) were similar to findings of other reports [8,16,18,39,40,41], but Mittendorfer and Yancy showed no change and increase in LDL-c, respectively [1,5].However, Mittendorfer had shorter period of study [5] and Yancy had utilized a low carbohydrate diet with a high fat intake [1]. Low carbohydrate diet generally leads to more weight loss compared to low fat diet [1] because of ketonuria and higher thermic effect due to high protein intake, but the greatest concern about the low carbohydrate diet is that increase in fat intake will have detrimental effects on serum lipids.

Low carbohydrate diet can have some side effects e.g. constipation, headache, muscle cramps, general weakness, halitosis [1]. Hence, it can be concluded that a balanced low calorie diet similar to the one we employed in our study is more advantageous compared to low carbohydrate or low fat diet.

TG was decreased significantly in both groups (p=0.0001) but HDL-c showed no significant change in our study which was consistent with other studies [1,5,18,41] although Harder and Foster reported decrease of HDL-c (essentially in HDL-3) because of lower intake of fat [8,12] compared to our study (15g versus to 40g). Also Foster et al [39] reported decrease of HDL-c, but duration of their study was smaller and the participants were obese but not hyperlipidemic and distribution of dietary fat was different compared to our study (In our study: saturated fat was 7%, MUFA 15%, PUFA 10% of total daily energy intake). Increase of HDL-c was seen in Fontana [40] and Redman [17] studies but in both studies, not only physical activity and lipid lowering drugs were used in addition to low calorie diet, but also the duration of studies much very longer compared to our study. The effects of statin on lipoproteins and apoB in other studies were similar to our study [21-23,40]. We observed no significant change in HDL-c in the lovastatin group but Mass reported an increase in HDL-C although in Mass study regular physical activity was added to statin intake [42]. In our study, however, the LDL-c/HDL-c decreased significantly in both groups (p=0.001 and p=0.01) which is a well-established risk factor for CAD but TG/HDL-c has been identified as a stronger predictor of myocardial infarction than either the TC/HDL-c or LDL-c/HDL-c[41].

The TG/HDL-c significantly decreased only in the diet group (P=0.0001) compared to the lovastatin group. Decrease of TG/HDL-c leads to an increase in LDL particle size and lower formation of small dense LDL particles. Both TG and HDL-c are major determinants of LDL particle size, partly because of the exchange of

TG from VLDL for cholesterol ester in LDL, which is mediated by cholesterol ester transfer protein (CETP) [43]. It is possible that as serum TG/HDL-c decreases after low calorie diet, fewer TGs are transferred to LDL by CETP reducing the formation of TG-enriched LDL, which minimizes the opportunity for lipoprotein lipase to convert large LDL particles to small LDL particles [43]. Small, dense LDL particles are associated with an increased risk of CAD [43]. On the other hand, apoB significantly decreased in the diet group compared to the lovastatin group (P=0.0001) showing a decrease of LDL particles [5]. Therefore it seems that, in our study CAD risk is lower in obese hyperlipidemic participants in the diet group compared to the lovastatin group at the end of study.

The TAC was increased in diet group compare to lovastatin group in our study (P= 0.0001). Findings of Vasankari and Beltowski about statin effects on TAC were similar to our study [29,31]. However Passi reported decrease of only vitamin E without affecting other antioxidants [30].

With regard to the above studies, it seems that lovastatin, compare to other statins, had less effect in decreasing TAC [29]. Homocysteine had no significant change in our study but in the diet group it was significantly decreased (P=0.0001). Avnell reported decrease of homocysteine compare to the control group but the duration of study was longer compare to our study (one year versus to 8 weeks). Sebestjen, Balk, Mass and Zemen reported similar results about effects of statin on homocysteine [20,28,40,44]. In addition, Balk reported that simvastatin had more increasing effect on homocysteine compare to lovastatin [28].

From this study, it can be concluded that according to TLC dietary pattern 1200kcal had more benefical effect than lovastatin on the serum TG, TG/HDL-c, apo B, hemocysteine and TAC in hyperlipidemic obese persons, but lovastatin had more beneficial effect on serum TC and LDL-c, however we found no evidence of clinically significant side effects of lovastatin in this study. We suggest to examine the effects of a regimen combining diet and lovastatin in future studies, because it seems this regimen probably enables more patients to achieve blood lipid goals than a statin-only regimen.

Acknowledgement

We acknowledge the valuable assistance of the staff of Endocrine Research Center of Iran University of Medical Sciences, Tehran, Iran and also we are grateful to all participants of the study for their helpful collaborations and Dr. Alireza Kalani for introducing suitable patients for this research.

References

1. Yancy WS, Olsen MK, Guyton JR, Bakst RP, Westmore EC. A Low-carbohydrate, ketogenic diet versus a low-fat diet to treat obesity and hyperlipidemia. Annals of Internal Medicine. 2004 May; 140(10): 769-777.

2. Janghorbani M, Amini M ,Willett WC, Gouya MM , Delavari A , Alikhani S. First nationwide survey of prevalence of overweight, underweight and abdominal obesity in Iranian adults. Obesity 2007:15(11):2797-28083.

3. Anderson LH, Martinson BC, Crain AL, Pronk NP, Whitebird RR, Oconner PJ, Fine LJ. Health care charges associated with physical inactivity,overweight and obesity. Prev Chronic Dis 2005: 2(4):90-115

4. Avenell A, Broom J, Brown TJ, Poobalan A, Aucott L, Stearns SC, Smith WCS. Systemic review of the long-term effects and economic consequences of treatments for obesity and implications for health improvement. Health Technology Assessment 2004; 8(21): 1-6.

5. Mittendorfer B, Patterson BW, Klein S.Effect of weight loss on VLDL-triglyceride and apoB-100 kinetics in women with abdominal obesity. Am J physiol Endocrinol Metab 2003 Dec; 284: E549-E556.

6. Cirqui MH. Obesity, Risk factors, and predicting cardiovascular events. Circulations 2005; 111(15): 1869-1870.

7. Raitakari M, Ilvonen T, Ahotupa M, Lehtimaki T, Harmoinen A. Weight reduction with very-low-Calorie diet and endothelial function in overweight adults: role of plasma glucose. Arteriosclerosis Thrombosis, and Vascular Biology 2004; 24 (1): 124-128.

8. Harder H, Dinesen B, Astrup A. The effect of a rapid weight loss on lipid profile and glycemic control in obese type 2 diabetic patients. International Journal of Obesity 2004 Jan, 28(1): 180-182.

9. Dominiczak MH. Obesity, glucose intolerance and

diabetes and their links to cardiovascular disease. Implications for laboratory medicine. Clin Chem Lab Med. 2003 Sep; 41(9): 1266-78.

10-Lang A, Froelicher ES. Management of overweight and obesity in adults: Behavioral intervention for long-term weight loss and maintenance. Eur J Cardiovasc Nurs. 2006 Jan; 5(2): 102-14.

11.Mclaughin T, Carter S, Lamendola C, Abbasi F, Yee G. Schaaf P.Effects of moderate variations in macronutrient composition on weight loss and reduction in cardiovascular disease risk in obese, insulin-resistant adults. American Journal of Clinical Nutrition. 2006; 84(4): 813-821.

12.Fleming RM. The effect of high, moderate-and low-fat diets on weight loss and cardiovascular disease risk factors. Prev Cardiol. 2002; 5(3): 110-8.

13.Dansinger ML, Gleason JA, Griffith JL, Selker HP, Schaefer EJ. Comparison of the Atkins, Ornish, Weight watchers and Zone diets for weight loss and heart disease risk reduction, a randomized trial. JAMA. 2005; 293(1): 43-53.

14. Heymsfield SB, Blackburn GL. Comparison of weight-loss diets. JAMA 2007; 298 (2): 173-174.

15. Melanson KJ. Nutrition Review: Dietary considerations for obesity treatment. American Journal of Lifestyle Medicine 2007; 1: 433-436.

16. Parenti M, Babini AC, Cecchetto ME, Bartolo PD, Luchi A. Lipid, lipoprotein and apolipoprotein assessment during an 8-wk very-low-calorie diet. Am J Clin Nutr 1992; 56 (1 suppl): 2685-705.

17. Redmon JB, Raatz SK, Reck KP, Swanson JE, Kwong CA. One-Year outcome of a combination of weight loss therapies for subjects with type 2 diabetes, A randominzed trial. Diabetes Care 2003; 26 (9): 2505-2511.

18. Samaha FF, Iqbal N, Seshadri P, Chicano KL, Daily DA, McGory J.A low-carbohydrate as compared with a low-fat diet in severe obesity. 2003 May; 348(21): 2074-2081.

19. Watts GF, Chan DC, Barrett PH, O'Neill FH, Thompson GR. Effect of a statin on hepatic apolipoprotein B-100 secretion and plasma campsterol levels in the metabolic syndrome. Int J Obes Relat Metab Disord 2003 Jul; 27(7): 862-5.

20. Sebestjen M, Keber I, Zegura B, Simicic S, Bozic M. Statin and fibrate treatment of combined hyperlipidemia: the effects on serum novel risk factors. Thromb Haemost 2004 Nov; 92(5): 1129-35.

21. Tsai TT, Nallamothu BK, Mukherjee D, Rubenfire M, Fang J, Chan P. Effect of statin use in patients with acute coronary syndromes and a serum low density lipoprotein < or=80 mg/dl. Am J Cardio 2005 Dec; 96(11): 1491-3.

22. Davidson MH, Reducing residual risk for patients on statin therapy: the potential role of combination therapy. Am J Cardiol 2005 Nov; 96(9A): 3K-13K.

23. Shechter M, Beigel R, Matetzky S, Freimark D, Chouraqui P. The intensive statin therapy myth. Isr Med Assoc J 2005 Nov; 7(11): 683-7.

24. Lupattelli G, Palumbo B, Sinzinger H. Statin induced myopathy does not show up in MIBI scintigraphy. Nucl Med Common 2001; 22(5): 575-8.

25. Tysk C, Al-Eryani AY, Showabkeh AA. Acute pancreatitis induced by fluvastatin therapy. J Clin Gasteroenterol 2002; 35(5): 406-8.

26. Milionis HJ, Papakostas J, kakafika A. Comparative effects of atrovastatin, simvastatin and fenofibrate on serum homocysteine level in patients with primary hyperlipidemia. J Clin Pharmacol 2003; 43(8): 812-30.

27. Ridker PM, Shih J, Cook IJ. Plasma homocysteine concentration, statin therapy and risk of first acute coronary events. Circulation 2002; 16; 105(15): 1776-9.

28. Balk EM, Lau J, Goudas LC, Jordan HS, kupelnick B. Effects of statin on nonlipid serum markers associated with cardiovascular disease, A systemic review. Ann Inter Med. 2003; 139 (8): 670-682.

29. Vasankari T, Ahotupa M, Viikari J, Nuotio I, Strandberg T. Effect of 12-month statin therapy on antioxidant potential of LDL serum antioxidant vitamin concentrations. Ann Med 2004; 36(8): 618-22.

30. Passi S, Stancato A, Aleo E, Dmitrieva A, Littarru GP. Statins lower plasma and lymphocyte ubiquinol/ubiquinone without affecting other antioxidants and PUFA. Biofactors 2003; 18(1-4): 113-124.

31. Beltowski J, Wojcicka G, Jamroz A. Differenctial effect of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors on plasma paraoxonase 1 activity in the rat. Pol J Pharmacology 2002 Nov-Dec; 54(6): 661-71.

32. Ugochukwu NH, Figgers CL. Dietary caloric restriction improves the redox status at the onset of diabetes in hepatocytes of streptozotocin-induced diabetic rats. Chem. Biol Interact 2007 Jan, 165(1): 45-53.

33. Ungvari Z, Parrado-Fernandez C, Cciszar A, De cabo R. Mechanisms underlying caloric restriction and lifespan regulation implications for vascular aging. Circ Res 2008 Mar; 102(5): 519-28.

34. Ugochukwu NH, Bagayoko ND, Antwi ME. The effects of dietary caloric restriction on antioxidant status and lipid peroxidation in mild and severe streptozotocin-induced diabetic rats. Clin Chim Acta 2004 Oct; 348(1-2): 121-9.

35. Krummel DA. Medical Nutrition Therapy for Cardiovascular Disease. P: 883-891. In: Krause's Food, Nutrition and Diet Therapy. Kathleen Mahan L, Escott-Stump S (eds.), 11th ed. Philadelphia: Lippincott Williams & wilkins; 2008.

36. Iris FFB, Strain JJ. The ferric reducing ability of plasma (FRAP) as a measure of antioxidant power: The

FRAP assay. Analytical Biochem 1996; 239-70-76.

37. Dovidson MH, Hauptman J, DiGirolamo M, Foreyt JP, Halsted CH, Heber D. Weight control and risk factor reduction in obese subjects treated for 2 years with orlistat: a randomized controlled trial. JAMA 1999 Jan; 281 (3): 235-42.

38. Bray GA, Ryam DH, Gordon D, Heidingsfelder S, Cerise F, Wilson K. A double-blind randomized placebo-controlled trial of sibutramine. Obes Res 1996; 4: 263-70.

39. Foster GD, Wyatt HR, Hill JO, McGuckin BG, Brill C. A randomized trial of a low-corbohydrate diet for obesity. The New England Journal of Medicine 2003; 384(21): 2082-2090.

40. Fontana L, Meyer TE, Klein S and Holloszy JO. Long term caloric restriction is highly effective in reducing the risk for atherosclerosis in humans. Proceeding of the National Academy of Sciences of USA, 2004; 101(17): 6659-6663.

41. Brooke RD, Bard RL, Glazewski, keher C, Bodary PF. Effect of a short-term weight loss on the metabolic syndrome and conduit vascular endothelial function in overweight adults. Am J Cardiol 2004; 93(8): 1012-6.

42. Mass R, Boger RH. Old and new cardiovascular risk factors: from unvesolved issues to new opportunities. Atheroscler Suppl. 2003; 4(4): 5-17.

43. Stark KD, Holub BJ. Differential eicosapentaenoic acid elevations and altered cardiovascular disease risk factor responses after supplementation with docosahexaenoic acid in postmenopausal women receiving and not receiving hormone replacement therapy. Am J Clin Nutr 2004; 79(5): 765-77.

44. Zeman M, Zak A, Vacka M, Turzicka E, Pisarikova A. N-3 fatty acid supplementation decreases plasma homocysteine in diabetic dyslipidemia treated with statin-fibrate combination. J Nutr Biochem 2006 Jan; 17(6): 379-84.