THE EFFECT OF LOW-DOSE NIACIN ADDED TO SIMVASTATIN ON LIPOPROTEIN PROFILE

AR Khosravi[(1)], A Abdi[(2)], N Sarrafzadegan[(3)], R Ansari[(4)]
G Kiani Mehr[(5)], F Roghani[(6)], ZD Siadat[(7)]

Abstract

INTRODUCTION: Different studies have demonstrated that low levels of high-density lipoprotein (HDL) cholesterol in serum are significantly related to the progression of coronary artery disease (CAD) and its related mortality. This study was performed primarily to assess the effectiveness of supplementing treatment with statins with low-dose (100 mg, bid) fast-release nicotinic acid (the only form of this drug produced in Iran) in increasing HDL; we also aimed to evaluate the effect of this regimen on other lipoproteins, and to investigate any possible side effects.

METHODS: This double-blind placebo-controlled randomized clinical trial was conducted on patients who were treated with simvastatin (20 mg/daily) for at least four weeks and did not receive any other lipid-lowering medications. The patients were divided into two groups of 50. The case group was treated with niacin tablets (100 mg, bid) and simvastatin (20 mg/daily). The control group was treated with placebo tablets (bid) and simvastatin (20 mg/daily). All patients underwent two 6-week crossover periods and a 2-week washout period. Liver-function biomarkers (ALK-P, SGPT, SGOT), serum lipids, uric acid, CPK and fasting blood sugar (FBS) were measured before and after each course of treatment. Data were analyzed with chi-square test and paired t-test.

RESULTS: Serum HDL increased from 42.44±8.5 to 44.01±8.39 mg/dl in the case group, with a mean increase of 2.56 mg/dl ($P<0.05$). HDL decreased from 41.5±9.1 to 40.9±9.4 mg/dl in the control group ($P>0.05$). Mean serum HDL was significantly different between the case and control groups ($P<0.05$). The increase in mean total cholesterol and low-density lipoprotein (LDL) cholesterol in the control group, and the decrease in triglyceride (TG) in both groups were not statistically significant ($P>0.05$). In follow-up, flushing was reported in 44.4% of case patients, resulting in discontinuation of treatment in 38.5% of patients. Flushing was reported in 5.6% of controls, resulting in discontinuation of treatment in 20% of patients. Muscle pain was reported in 24.4% of the case patients, resulting in discontinuation of treatment in 47.6% of the patients. Only 3.3% of the controls reported muscle pain, which led to discontinuation of treatment by the physician in 66.7% of the patients.

CONCLUSIONS: Low-dose fast-release niacin led to significant HDL increase; hence we recommend that treatment of dyslipidemic patients with statins be supplemented with low-dose niacin, which is available in Iran.

Keywords: Niacin, simvastatin, lipoprotein.

***ARYA Atherosclerosis Journal* 2007, 3(1): 8-13**

Date of submission: 10 Feb 2007, ***Date of acceptance:*** 01 Apr 2007

Introduction

The effect of decreasing serum low-density lipoprotein (LDL) cholesterol on reduction of cardiovascular disease (CAD)-associated mortality and morbidity is well recognized.[1] It has also been demonstrated that low serum high-density lipoprotein (HDL) cholesterol is significantly related to the progression of CAD and its related mortality.[2-5]

Nearly 50% of patients untreated for hyper-cholesterolemia have low HDL levels. Cases of isolated low HDL are also common. Low HDL is the commonest form of dyslipidemia in patients with premature CAD.[6] Studies have shown that even slight increases in serum HDL concentration can reduce cardiovascular mortality.

1) Alireza Khosravi, MD, Assistant Professor of Cardiology, Isfahan Cardiovascular Research Center (ICRC), Isfahan University of Medical Sciences (IUMS), Isfahan, Iran. E-mail: *alikh108@yahoo.com*, Tel: +98 (913) 314-3710
2) Ahmadnoor Abdi, MD, Assistant of Cardiology, IUMS, Isfahan, Iran.
3) Nizal Sarrafzadegan, MD, Professor of Medicine, Cardiologist, ICRC, IUMS, Isfahan, Iran.
4) Rezvan Ansari, M.Sc., Research Assistant, ICRC.
5) Gilda Kiani Mehr, MD, Research Assisitant, ICRC.
6) Farshad Roghani, MD, Assistant Professor of Cardiology, IUMS. Isfahan, Iran
7) Zahra Dana Siadat, MD, Research Assistant, Community Medicine Specialist, ICRC.

Corresponding author: Alireza Khosravi MD.

Schectmor and colleagues demonstrated that an increase of 1 mg/dl in HDL reduces the risk of CAD by 2% in men and 3% in women.[7,8]

Among drugs used to treat hyperlipidemia, niacin is the most effective in increasing HDL.[7]

Concurrent administration of statins and low-dose niacin is more effective in reducing LDL-to-HDL ratio than any single medication.[9]

The effective dose of niacin for treatment of dyslipidemia as proposed in reference textbooks is close to 3000 mg.[10] Prescription of this drug is limited by its side effects, including flushing, gastrointestinal disturbances and liver dysfunction; nearly 50% of patients administered niacin stop taking the drug in the first year owing to undesirable side effects. At doses higher than 1500 mg/dl, niacin lowers LDL in a dose-dependent fashion; however, it has been reported to increase serum HDL at lower doses (750-1500 mg).[9]

In view of the unavailability of slow-release niacin in Iran's pharmacopoeia, the primary goal of this study was to assess the effectiveness of supplementing therapy with statins with low-dose (100 mg, bid) fast-release nicotinic acid (the only form of this drug produced in Iran) in increasing HDL; other objectives of this study were to assess the effect of this regimen on other lipids and serum biomarkers and to investigate possible clinical complications.

Materials and methods

This double-blind placebo-controlled randomized trial was conducted on patients who presented to the outpatient clinics and were treated with simvastatin (20 mg/daily) for at least four weeks. Using simple randomization and the table of random numbers, the patients were divided into two groups of 50.

The case group was treated with niacin tablets (100 mg, bid) and simvastatin (20 mg/daily). The control group was treated with placebo tablets (bid) and simvastatin (20 mg/daily).

Niacin tablets were purchased from city pharmacies. The niacin and placebo tablets were both produced by Sobhan Pharmaceutical Co., Iran. The tablets were placed in separate containers and coded by a person who was unaware of the study. A third person distributed the containers among patients who had been randomized using the table of random numbers. Sample size was measured according to formula and 50 patients were assigned to each group.

The inclusion criteria were as follows:

- Age ≥ 20 years
- Primary hyperlipidemia treated with simvastatin for at least 4 weeks

Exclusion criteria were as follows:

- Uncontrolled diabetes
- Gout
- Liver disease
- Secondary hyperlipidemia
- Being under treatment with antihyperlipidemic drugs other than simvastatin

Contraindications of nicotinic acid administration were excluded in the subjects.

The patients gave their informed written consent after being briefed about the study objectives, medications to be prescribed, and possible side effects. They were instructed to remain in fasting state for 12 hours before presenting to clinic.

A trained nurse completed a questionnaire on disease and drug history for each patient. The patients were sent to Isfahan Cardiovascular Research Center, where they gave 10 cc venous blood sample for measurement of total cholesterol, HDL, LDL, triglyceride (TG), liver-function biomarkers (SGPT, SGOT, ALK-P), serum uric acid, fasting blood sugar (FBS) and CPK.

The patients remained on the diet prescribed by their physicians. This study was conducted in three stages. In the first stage, the patients were divided into two groups.

The first group (cases) was treated with simvastatin (20 mg/daily) + nicotinic acid (FR) (100 mg, bid) and the second group (controls) with simvastatin (20 mg/daily) + placebo tablets (bid).

To monitor compliance and check for side effects, the patients were telephoned everyday; they also visited Isfahan Cardiovascular Research Center once every two weeks to receive medication (or placebo) and to be examined for possible drug side effects and/or intolerance.

In each visit, the number of consumed tablets (drug or placebo) was counted and patients who had used at least 80% of their tablets were considered to have completed the course of treatment. Each time, the patients were given enough tablets for two weeks.

The patients who experienced flushing were encouraged to tolerate the side effect as much as they could; otherwise they were instructed to take a 325 mg aspirin tablet every morning.

In case of intolerance and/or severe side effects, the signs were recorded, the drugs were discontinued, and the patient was followed up.

The patients were also asked about other side effects in daily telephone calls and appropriate decisions were made by the physician on whether to discontinue treatment or to treat the patient for side effects. Six weeks later, serum lipoproteins, liver enzymes, serum uric acid, FBS and CPK were measured and the patients entered the second stage of the study which consisted of a two-week washout period.

Treatment with simvastatin (20 mg/daily) continued in this stage, but treatment with nicotinic acid or placebo was stopped. At the end of the two-week washout period, serum lipoproteins, liver enzymes, serum uric acid, FBS and CPK were measured and the results were recorded in the patients' files.

The third stage of the study was conducted in a crossover fashion, i.e. nicotinic acid was dropped from the treatment regimen of the case group and was added to that of the control group, while placebo was discontinued in the control group and was added to the treatment regimen of the case group. The drugs were administered and the patients were followed up as in earlier stages for six weeks. At the end of this stage, serum lipoproteins, liver enzymes, serum uric acid, FBS and CPK were measured and the results were recorded (Flowchart). The effects of drugs on lipoprotein components and laboratory findings were compared by t-test in the case and control groups; paired t-test was used for pre- and post-intervention comparison. Differences in clinical side effects between the two groups were compared by chi-square test. P values less than 0.05 were considered as statistically significant.

Results

Given the type of study and crossover of samples in both groups in the third stage, the patients who were studied at the end of the trial numbered 100 in both case and control groups.

The mean ages of patients were the same in the two groups (56.45±12.7 years) and 36.9% of patients in each group were female. Mean LDL showed an insignificant decrease in the case group and a significant increase in the control group (Table 1).

Although TG and total cholesterol in the cases decreased compared to controls, the difference was not statistically significant (P>0.05).

On the other hand, HDL showed a significant increase from 42.44±8.5 mg/dl to 44.01±8.39 mg/dl in the case group (P<0.0.5), with a mean increase of 2.56 mg/dl.

However, the decrease in HDL in the control group was not statistically significant (P>0.05) (Table 1). The difference in mean serum HDL between the case and control groups at the end of the first 6-week period was significant (P<0.05) (Table 2).

The incidence of side effects was 52.2% and 6.7% in the case and control groups, respectively, showing a significant difference (P<0.05).

TABLE 1. Mean levels of lipoproteins in the study groups.

Variable	Group1	Group2	P value
LDL-cho (mg/dl)	-1.55	+5.37	0.08
HDL-cho (mg/dl)	+2.56	-0.58	0.01
TG (mg/dl)	-1.2	-7.1	0.64
Total cho (mg/dl)	-1.48	2.70	0.4

Group 1: Patients received simvastatin plus niacin, Group 2: Patients received simvastatin plus placebo
LDL-cho: Low-density lipoprotein cholesterol, HDL-cho: High-density lipoprotein cholesterol
TG: Triglyceride, Total cho: Total cholesterol

TABLE 2. Changes in mean lipoprotein levels in the study groups.

Variable	Group 1			Group 2		
	Before mean±SD	After mean±SD	P value	Before mean±SD	After mean±SD	P value
LDL-cho (mg/dl)	102.52 ± 35.52	100.96±32.63	0.6	103.4±31.1	108.8±33.6	0.02
HDL-cho (mg/dl)	42.44±8.5	44.01±8.39	0.03	41.5±9.1	40.9±9.4	0.4
TG (mg/dl)	173.07±77.59	161.7±81.3	0.06	170.01±73.2	162.9±73.9	0.2
T-cho (mg/dl)	178.03±40.1	176.55±34.8	0.6	175.2±86.5	177.9±36.3	0.4

Group 1: The patients received simvastatin + niacin, Group 2: The patients received simvastatin + placebo
LDL-cho: Low-density lipoprotein cholesterol, HDL-cho: High-density lipoprotein cholesterol
TG: Triglyceride, Total cho: Total cholesterol

Nearly 80% of the cases and 92.2% of the controls completed the treatment course (P<0.05). The frequency of flushing was 44.4% in the case group, resulting in discontinuation of the drug in 38.5% of patients. Flushing occurred in 5.6% of controls, resulting in discontinuation of the drug in 20% of patients. Nearly 24.4% of the cases reported muscle pain which resulted in discontinuation of the drug in 47.6% of patients. By contrast, of the 3.3% of controls reporting muscle pain, the majority were instructed by their physicians to stop taking the drug (Table 5).

At the end of treatment, liver enzymes, serum uric acid and FBS in the case and control groups did not show any significant difference compared to before treatment (Tables 3 and 4).

Discussion

Decrease in serum HDL is an independent risk factor for progression of atherosclerosis. HDL increase is known to reduce cardiovascular morbidity and mortality.[11] In the VA-HIT trial which investigated the HDL-increasing effect of gemfibrozil, a 2 mg/dl increase in HDL was shown to be associated with a 22% decrease in CAD mortality.[12] Niacin is the most effective HDL-increasing drug.

The primary goal of this study was to assess the effect of adding fast-release nicotinic acid (100 mg, bid) to simvastatin (20 mg/daily) on serum HDL. We found a mean HDL increase of 2.56 mg/dl, which based on results of earlier studies, could significantly contribute to reduction of CAD-related mortality and morbidity.[8] Rubind and colleagues demonstrated that low-dose niacin does not have any significant effects on serum LDL;[12] the latter finding was also confirmed in the present study, i.e. LDL decreased in the group receiving simvastatin and low-dose niacin, but this decrease was not significant.

In this study, supplementing simvastatin with low-dose fast-release niacin reduced TG by 11.2 mg/dl (P=0.06); this decrease was 7.1 mg/dl in the control group (P=0.2).

Flushing, a well known side effect of fast-release niacin, has restricted its consumption.[13,14]

Earlier studies on fast-release niacin have shown that different degrees of flushing and pruritus are experienced by nearly all patients, resulting in discontinuation of the drug in almost a quarter of the cases.[15-17]

Vasodilator side effects of niacin such as flushing have been minimized to less than 50% and discontinuation of drug to less than 10-15% thanks to the development of new forms of niacin including those with sustained release, administering gradually increasing doses of the drug, and the use of aspirin.[18,19]

TABLE 3. Serum mean levels of other biochemical variables in the studied groups before and after intervention.

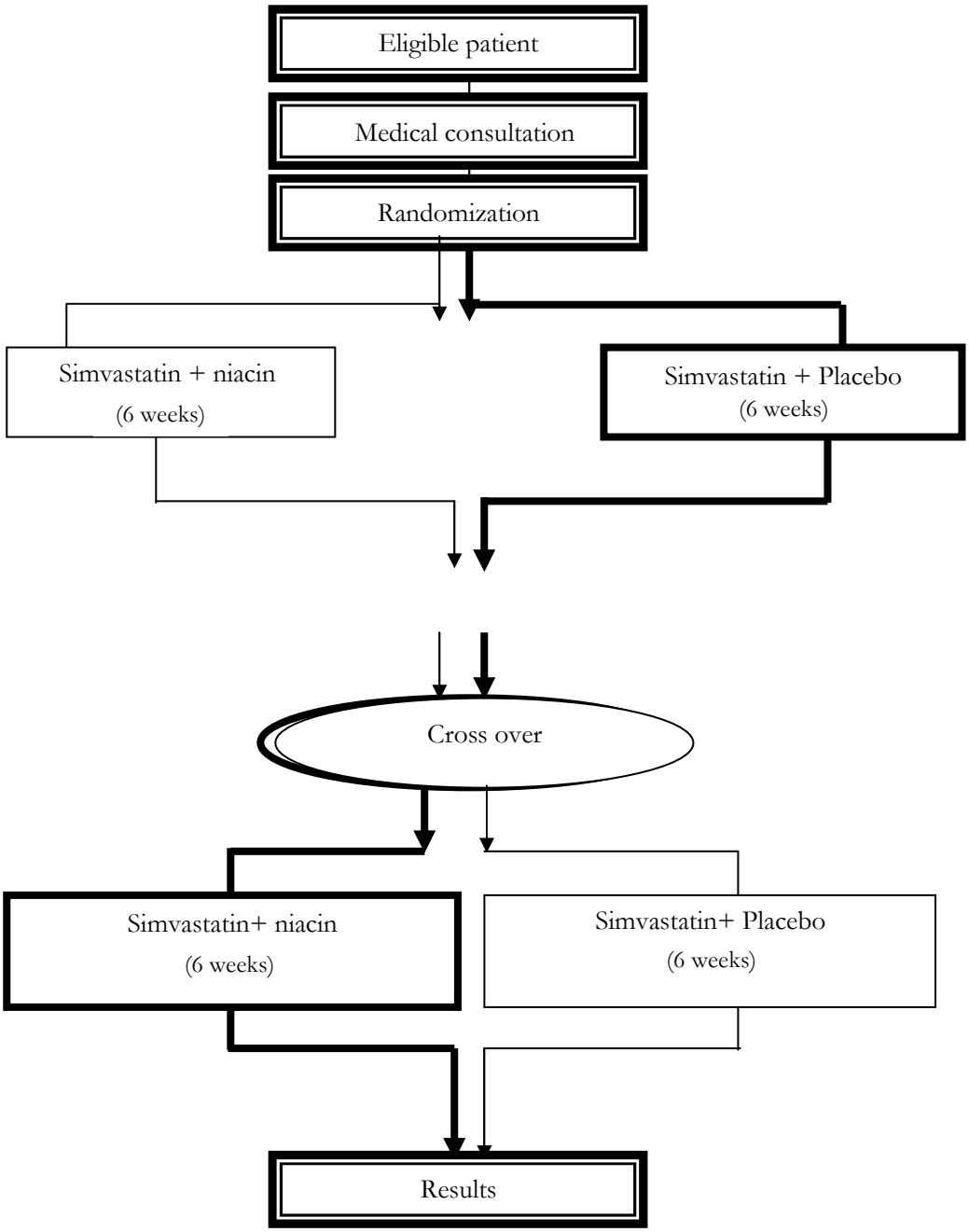
Variable	Group 1			Group 2		
	Before mean±SD	After mean±SD	P value	Before mean±SD	After mean±SD	P value
SGOT (mg/dl)	34.75±9.68	33.3±9.35	0.18	34.7±9.3	34.8±10.8	0.9
SGPT (mg/dl)	30.6±7.23	29.69±2.16	0.7	28.7±8.01	29.2±8.3	0.6
ALK-P (mg/dl)	168.7±44.7	169±55.7	0.85	176.6±59.9	172.6±57.1	0.4
CPK (mg/dl)	85.5±51.09	81.44±39.5	0.27	84.2±43.9	105.17±89.1	0.04
FBS (mg/dl)	108.9±36.8	109.4±34.4	0.85	110.42±33.2	107.8±37.6	0.3
Uric acid (mg/dl)	5.89±1.37	5.68±1.25	0.04	5.7±1.4	5.8±1.19	0.10

Group 1: The patients received simvastatin + niacin, Group 2: The patients received simvastatin + placebo
SGOT: Serum glutamic oxaloacetic transaminase, SGPT: Serum glutamic pyruvic transaminase, ALK-P: Alkaline phosphatase, CPK: Creatine phosphokinase, FBS: Fasting blood sugar

TABLE 4. Changes of mean levels of other serum biochemical variables in the studied groups before and after intervention

Variable	Group 1	Group 2	P value
SGOT (mg/dl)	-1.4	+0.06	0.3
SGPT (mg/dl)	-0.92	+0.4	0.6
ALK-P (mg/dl)	+0.93	-3.9	0.5
CPK (mg/dl)	-4.1	+20.9	0.02
FBS (mg/dl)	+0.54	-2.59	0.4
Uric acid (mg/dl)	-0.21	+0.10	0.05

Group 1: The patients received simvastatin + niacin, Group 2: The patients received simvastatin + placebo
SGOT: Serum glutamic oxaloacetic transaminase, SGPT: Serum glutamic pyruvic transaminase,
ALK-P: Alkaline phosphatase, CPK: Creatine phosphokinase, FBS: Fasting blood sugar



Flowchart

TABLE 5. Frequency of clinical side effects in the studied groups.

Variable	Group 1 % (frequency)	Group 2 % (frequency)	P value
Total side effect	52.2(47)	6.7(6)	0.001
Flashing	44.4(40)	5.6(5)	0.001
Cut	38.5(15)	20(1)	0.07
Muscle pain	24.4(21)	3.3(3)	0.001
Cut	47.6(10)	66.7(2)	0.5

In this study, flushing was the most frequently reported side effect; it was seen in 44.4% of the cases and 5.65% of the controls and led to discontinuation of drug in 38.5% of patients in the case group. In this study, flushing was seen more frequently than in some other studies;[20] this may be accounted for by the genetic differences of the subjects studied.

Adding niacin to simvastatin did not result in a significant increase in liver and/or muscle enzymes; this may be due to the low dose of the drug and its fast release.

Educating the patients is probably of the greatest importance in increasing their cooperation. Using a patient crossover design to reduce the effect of genetic or metabolic factors was a considerable advantage; however, it was offset by the small number of patients studied.

To better evaluate the effect of the proposed drug combination, we recommend further studies with larger sample sizes and more diabetic and elderly patients.

In view of the HDL increase observed in this study following the administration of nicotinic acid, the potentially beneficial effects of increased HDL on the prognosis of patients with cardiovascular disease, and the unavailability of slow-release forms of niacin products in Iran, we recommend adding low-dose niacin to statins in the treatment of dyslipidemia in order to increase serum HDL.

References

1. Randomized trial of cholesterol lowering in 4444 patient with coronary heart disease: the Scandinavian survey study. lancet1999; 34:1383-9.
2. Wilh m, Gumsj G. Isolated low high density lipoprotein cholesterol. Ann pharmacol 1997; 31:89-97.
3. Rubins HB, Robinss ji, Collins D, et al. Hemfibrosil for the prevention of coronary artery disease in men with low high density lipoprotein cholesterol. EMJM 1994;34, 408-410.
4. Fordon DJ, Probshifild D, Garrison Rj, et al. High density lipoprotein cholesterol and disease, four prospective American study. Circulation 1992;85:22-9
5. Bring j. Lonner G, Huld H et al. Decrease HDL2 and HDL3 cholesterol: ApoA1 and ApoA II and increase prevalence of MI. Circulation 1992;86:839-48.
6. Rubins HB. Rubins SJ. Collins D, et al. Distribution of lipid in 8500 men with coronary artery disease; department of veteran's affairs HDL-C intervention trial group. Am J Cardial1995; 75:1196-201.
7. Schectmor G. Hiatt A. Evaluation of effectiveness of lipid lowering therapy for treating hypercholesterolemia in veterans. BMJ Cardial1993; 71:758-65.
8. Can Pl, Berg K, Winger NK, et al. Fifteen year mortality in coronary drug project patient; Long term benefit with niacin. JAM Cardial1986; 8:1242-55.
9. Schectman G, Hiatt G. Drug therapy for hypercholesterolemia in patient with cardiovascular disease. Factor limiting achievement of lipid goal. Am J Medicine 1996; 700. 197-204.
10. Braunwalds. Heart disease a text book of cardiovascular medicine 7th edition 2005;1025.
11. Nissen SE, Tsunoda T, Tuzcu EM, Schoenhagen P, Cooper CJ, et al. Effect of recombinant ApoA-I Milano on coronary atherosclerosis in patients with acute coronary syndromes: a randomized controlled trial. JAMA 2003;290:2292-2300
12. Rubind HB, Pubins SJ, Collin D, Fyecl, Anderson JW. Elom MB et al. For the veterans affairs high density lipoprotein cholesterol. Intervention trial study group, Gamfibrusil for prevention of coronary heart disease in man with low HDL cholesterol. N Engl J Med 1999; 341:40-8.
13. Berge KG, Achor RW, Christensen AN, Nason HL, Barker NW. Hypercholesterolemia and nicotinic acid. Am J Med 1961; 31: 24-35.
14. Keenan JM, Fontaine PL, Wenz JB, Myers S, Huang Z, Ripsin CM, Niacin revisited: a randomized, controlled trial of wax-matrix sustained-release niacin in hypercholesterolemia. Arch Intern Med 1991; 151: 1424-1432.
15. Goldberg A, Alagona P, Capuzzi Jr, Guyton J, Morgan JM, Rodgers J, Sachson R, Samuel P. Multiple-dose efficacy and safety of an extended-release form of niacin in the management of hyperlipidemia. Am J Cardiol 2000; 85:1100-1105.
16. Berge KG, Achor RW, Christensen AN, Nason HL, Barker NW. Hypercholesterolemia and nicotinic acid. Am J Med 1961; 31: 24-35.
17. Keenan JM, Fontaine PL, Wenz JB, Myers S, Huang Z, Ripsin CM. Niacin revisited: a randomized, controlled trial of wax-matrix sustained-release niacin in hypercholesterolemia. Arch Intern Med 1991; 151: 1424-1432.
18. Kashyap ML, McGovern ME, Berra K, Guyton JR, Kwiterovich PO, Harper WL, et al. Long-term safety and efficacy of a once-daily niacin/lovastatin formulation for patients with dyslipidemia. Am J Cardiol 2002; 89: 672-678.
19. Goldberg P, Alagona Jr, Capuzzi DM, Guyton J, Morgan JM, Rodgers J, et al. Multiple-dose efficacy and safety of an extended-release form of niacin in the management of hyperlipidemia. Am J Cardiol 2000; 85:1100-1105.
20. American Diabetes Association, American Diabetes Association position statement: evidence-based nutrition principles and recommendations for the treatment and prevention of diabetes and related complications. J Am Diet Assoc 2002; 102:109-118.