National Cholesterol Treatment Guidelines in Korean Population

- Setting-up the cutpoints for high blood cholesterol -

National Cholesterol Treatment Guidelines are different according to race and country, and change year by year, because the distribution of lipid and lipoprotein levels are different by genetic background, dietary habit and life style. So it is mandatory to set-up the national cholesterol treatment guidelines based on the epidemiologic results. To establish the cutpoints for hypercholesterolemia specific to the Korean population, we selected the laboratories, whose inaccuracies of cholesterol measurement were less than 5%, in the external laboratory quality assessment survey, and performed epidemiological survey on the distribution of cholesterol levels, and other risk factors of coronary heart disease(CHD). As a result, prevalence of CHD risk factors was very high in hypertension(28.0%) and relatively low in diabetes(2.8%). Smokers were 42.6% of total subjects. Thirteen percent of subjects had a family member(s) who was suffering from or had of hypertension, stroke, and heart diseases. The average cholesterol level of a Korean was 187mg/dL, which was about 25mg/dL lower than that of United States. The 75th percentile of total cholesterol was 210mg/dL and 90th percentile 235mg/dL. The cutpoint for borderline-high cholesterol levels provide a major guideline for initiation of dietary and exercise therapy. We propose the cutpoint for borderline-high cholesterol levels as 200 instead of 210mg/dL to initiate more active dietary and exercise therapy, and we also propose the temporary cutpoint for high blood cholesterol levels as 240mg/dL instead of 235mg/dL, which is a reasonable cutpoint considering medical insurance policy of the country. In conclusion, we suggest the cutpoints for borderline-high and high serum cholesterol levels as 200 and 240mg/dL, respectively. ***(JKMS 1997;12:17~22)***

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INTRODUCTION

Atherosclerosis of the coronary arteries is the most severe form of atherosclerosis and is one of the major causes of early mortality and morbidity. In Western countries such as Great Britain, coronary heart disease (CHD) is the leading cause of adult death. The death rate of ischemic heart diseases in Korean males was 1.8 per 100,000 population and 1.0 in females in 1981, which increased in 5.2 folds to 9.4 in male, 6.2 folds to 6.2 in female in 1991 (1). These are closely related to the increase of cholesterol levels during the specified interval. Rapid increase of ischemic heart disease in Korea seems to be the major threatening factor in national heath. Early detection and management of CHD risk factors, especially hypercholesterolemia, are emerging as major task for national health care.

In 1985, NIH Consensus Development Conference Statement stratified cholesterol into moderate-risk and high-risk categories according to age-related 75th and 90th percentiles for the United States (US) population (2). In 1988, The Expert Panel of the US National Cholesterol Education Program (NCEP) proposed a classification of hypercholesterolemia based on total and LDL cholesterol values, unrelated to age. Total cholesterol was defined as 'desirable' (<200mg/dL), 'borderline-high'(200-239mg/dL) and 'high'(≥240mg/dL) (3). These cutpoints are somewhat arbitrary. The 240mg/dL cutpoint for total serum cholesterol is a level at which CHD risk is almost double that at 200mg/dL, and is rising steeply. In 1993, the Second Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel II or ATP II) presented the NCEP's updated recommendations for

cholesterol management (4, 5). The report contained new features that distinguish it from the first. These included the following : Increased emphasis on CHD risk status as a guide to type and intensity of cholesterol-lowering therapy, more attention to high-density lipoproteins (HDL) as a CHD risk factor, increased emphasis on weight loss and physical activity as components of the dietary therapy of high blood cholesterol.

'Under what circumstances and at what level of blood cholesterol should dietary or drug treatment be started?' or 'setting-up cutpoints to differentiate normal and high blood cholesterol' are most important issues in establishing the national cholesterol treatment guidelines. As accurate statistics of CHD incidence has not been available and no prospective epidemiological study of the relationship between CHD and hypercholesterolemia has been reported in Korea, patients have been treated according to US NCEP guidelines. But due to the difference in CHD mortality rate, distribution of cholesterol levels, dietary habits, and genetic background between Koreans and Westerners, it is not appropriate to use US NCEP guidelines in Korean population.

To establish the cutpoints for high blood cholesterol specific to the Korean population, we selected the laboratories which had inaccuracies of less than 5% on the external laboratory quality assessment survey. And epidemiological survey on the distribution of cholesterol levels and other CHD risk factors in those laboratories selected was done. We propose the cutoff value of hypercholesterolemia in the Korean population based on the above data, which can be used as a basis for establishing the future Korean National Cholesterol Treatment Guidelines.

MATERIALS AND METHODS

1. Quality control and standardization of the clinical laboratory

With survey program of the Korean Association of Quality Assurance for Clinical Pathology, we twice sent the survey materials for cholesterol measurement to 1600 laboratories nationwide. At each survey, we made 16 batches of quality control materials and randomly chose and sent 2 of them to each laboratory.

Inaccuracy of cholesterol measurement was calculated with formula described below ;

$$\text{Inaccuracy} = \frac{\text{Measured value} - \text{Designated value}}{\text{Designated value}} \times 100$$

2. Survey for Korean cholesterol level and CHD risk factors

1) Subjects

Included in the study were 987,820 who took a routine health check in 1994. Data of whole group was compared with those from the laboratories with inaccuracy within 5%, which amounted to 588,082.

2) Methods

Analysis of CHD risk factors were done through the questionnaire, physical examinations and blood tests of parameters including sex, age, body weight, height, total cholesterol, hypertension, diabetes and family history for hypertension, stroke and heart diseases. Hypertension was defined as systolic pressure over 140mmHg or diastolic pressure 90mmHg and diabetes was defined as fasting blood sugar over 140mg/dL or positivity of urine glucose stick test.

Serum total cholesterol were determined by a cholesterol oxidase enzymatic method, triglyceride by a glycerol oxidase enzymatic method and HDL cholesterol by precipitation.

We calculated mean, standard deviation, 5th, 10th, 25th, 50th, 75th, 90th and 95th percentile value of each lipid parameter using the SAS (Statistical Analysis System) program.

RESULTS

1. Distribution of laboratories according to the inaccuracies of cholesterol measurement

Inaccuracy distribution among 1477 clinical laboratories are listed in Table 1. We selected the laboratories with an inaccuracy of less than 5% (54.23%) to survey the Korean cholesterol levels and CHD risk factors.

2. Survey for Korean cholesterol levels and CHD risk factors

Analysis of total cholesterol level distribution was done in two groups. One consisted of 987,820 subjects who took a the routine health check in 1994, and the other consisted of the subjects checked by the laboratories with

Table 1. Distribution of laboratories according to their cholesterol measurement inaccuracy

Cholesterol inaccuracy	No. of Laboratories(%)	
<3%	293	(19.84)
3-5%	508	(34.39)
5-10%	518	(35.07)
≥10%	158	(10.70)

Table 2. Mean, S.D. and selected percentiles of serum cholesterol levels by age and sex in whole subjects

No of Persons				Percentile						
Age (year)	examined	Mean	S.D.	5th	10th	25th	50th	75th	90th	95th
Total	987820	186.6	36.3	134	144	162	184	208	234	250
				Men						
≥ 20	763696	188.7	36.4	145	145	164	186	210	235	251
20-34	188640	178.8	33.8	139	139	155	176	199	223	238
35-44	271241	188.4	35.7	146	146	164	186	210	234	250
45-54	201661	194.4	37.1	150	150	170	192	217	241	257
55-64	99541	196.2	37.3	152	152	171	194	219	243	258
65-74	2565	197.9	37.5	153	153	173	196	221	244	259
≥ 75	48	207.5	38.8	152	152	182	203	233	254	271
				Women						
≥ 20	224124	179.6	35.1	130	139	156	176	200	225	242
20-34	119277	173.0	32.9	126	135	151	170	191	214	231
35-44	69016	179.4	32.2	132	141	158	177	199	221	236
45-54	27129	197.9	36.8	143	154	173	195	221	245	260
55-64	8495	215.8	38.9	157	169	189	214	240	263	283
≥ 65	207	219.5	39.4	157	168	196	218	240	268	278

unit ; mg/dL

Table 3. Mean, S.D. and selected percentiles of serum cholesterol levels by age and sex in subjects which were examined in the laboratories of less than 5% inaccuracy of cholesterol measurement

No of Persons				Percentile						
Age (year)	examined	Mean	S.D.	5th	10th	25th	50th	75th	90th	95th
Total	588082	186.6	36.2	134	144	162	184	208	234	250
				Men						
≥ 20	455546	188.7	36.3	135	145	164	186	210	235	251
20-34	111970	178.8	33.6	130	139	156	176	199	223	239
35-44	161224	188.5	35.6	136	146	164	186	210	234	250
45-54	120333	194.3	37.0	139	150	169	192	217	241	257
55-64	60366	196.0	37.2	140	152	171	194	218	243	258
65-74	1623	197.8	37.0	141	153	173	195	222	244	258
≥ 75	30	209.5	37.9	123	151	188	213	235	250	260
				Women						
≥ 20	132536	179.6	35.3	130	139	155	176	200	225	242
20-34	71317	173.0	32.9	127	135	151	170	191	214	231
35-44	40567	179.4	32.3	132	141	157	177	199	221	236
45-54	15520	198.5	37.0	143	154	173	196	222	246	260
55-64	5014	216.9	39.6	157	169	190	215	241	266	285
≥ 65	118	219.7	38.9	166	171	194	215	240	268	285

unit ; mg/dL

an inaccuracy of less than 5%, which amounted to 588,082. As shown in Tables 2 and 3, total cholesterol level distribution was very similar between two groups.

The serum total cholesterol levels showed a rising trend with age, and they were higher in males until early 40's but in females after late 40's. The 75th percentile of total cholesterol was 210mg/dL and 90th percentile 235mg/dL.

Prevalence of CHD risk factors are listed in Table 4. It was very high in hypertension (28.0%) which might be due to the criteria of hypertesion (≥140/90mmHg) by single measurement of blood pressure, and relatively low in diabetes (2.8%). Smokers were 42.6% of total subjects. Thirteen percent of subjects had a family member (s) who were suffering from or had died of hypertension, stroke, and heart diseases.

Table 4. Prevalence of coronary heart disease risk factors by age and sex in the Korean population.

Group	No.	Hypertension	Diabetes	Smoking	CHD Family Hx
Total	588082	164772(28.0)*	16505(2.8)	250673(42.6)	77530(13.2)
			Men		
≥ 20	455546	149727(32.9)	15708(3.4)	250400(55.0)	57327(12.6)
20-34	111970	24432(21.8)	990(0.9)	68418(61.1)	11447(10.2)
35-44	161224	44103(27.4)	3571(2.2)	92074(57.1)	22329(13.8)
45-54	120333	48604(40.4)	6262(5.2)	61933(51.5)	15676(13.0)
55-64	60366	31616(52.4)	4750(7.9)	27386(45.4)	7615(12.6)
65-74	1623	957(59.0)	135(8.3)	580(35.7)	254(15.7)
≥ 75	30	15(50.0)	0(0.0)	9(30.0)	6(20.0)
			Women		
≥ 20	132536	15045(11.4)	797(0.6)	273(0.2)	20203(15.2)
20-34	71317	4515(6.3)	186(0.3)	96(0.1)	8675(12.2)
35-44	40567	4239(10.4)	209(0.5)	62(0.2)	7753(19.1)
45-54	15520	4051(26.1)	230(1.5)	72(0.5)	2822(18.2)
55-64	5014	2172(43.3)	168(3.4)	42(0.8)	937(18.7)
≥ 65	118	68(58.6)	4(3.4)	1(0.9)	16(13.8)

* Number (percentage)

DISCUSSION

The laboratory Standardization Panel for Cholesterol of NCEP at NIH in the US recommended that inaccuracy and imprecision of less than 5% by the year 1992 (6). In Korea, the national average of inaccuracy was 9.1% in 1990 and 5.95% in this study, which showed an almost 3% improvement (7). It is very similar to the overall average of CAP Survey, which is 5.6%. But these figures are still higher than 5% (1992), or 3% (after 1992) recommended by NCEP Laboratory Standardization Panel for Cholesterol (6).

The total cholesterol level distribution was very similar between whole subjects (n=987,820) and the subjects (n=588,082) checked by the laboratories with an inaccuracy of less than 5%, which proved the fact that inaccuracies in cholesterol measurement did not affect the distribution of total cholesterol level, when number of the study subjects were extremely high.

Cholesterol levels in this study were lower than those of the US. The average cholesterol level of the US was 211mg/dL and that of Korea was 187mg/dL, which showed about 25mg/dL of difference (Fig. 1) (8). We applied our data to US NCEP guidelines, and got the result that 67.2% were in desirable cholesterol level, 24.9% were in borderline high, and 7.3% were in high (Table 5). The prevalence of hypercholesterolemia was lower in Korea than in the US (11%) (9).

In 1984, the National Heart, Lung, and Blood Institute(NHLBI) and NIH Office of Medical Application of Research convened a Consensus Development Conference on Lowering Blood Cholesterol to Prevent Heart Disease (2). They agreed on answers to the following questions :

1) Is the relationship between blood cholesterol levels and coronary heart disease causal? 2) Will reduction of blood cholesterol levels help prevent CHD? 3) Under what circumstances and at what level of blood cholesterol should dietary or drug treatment be started? 4) Should an attempt be made to reduce the blood cholesterol levels of the general population? 5) What research directions should be pursued regarding the relationship between blood cholesterol and CHD?

A wealth of congruent results of genetic, experimental pathologic, epidemiological and intervention studies gave the answer to the first and second questions (10～12). To the fourth question, a public health program, designed to reduce cholesterol levels, including mass screening of the general population and early detection and management of hypercholesterolemic patients has reduced the morbidity and mortality of CHD in US and many European countries (8). To the last question, much about lipid metabolism and about the mechanisms of the atherosclerotic process remains unknown and under investigation.

However the third question, 'Under what circumstances and at what level of blood cholesterol should dietary or drug treatment be started?', depends on National Cholesterol Treatment Guidelines. It is different according to races and countries, and changes from year to year, because the distribution of lipid and lipoprotein levels are different by genetic background, dietary habit and life style. For example, the Japanese population, in comparison with the US population, is characterized by

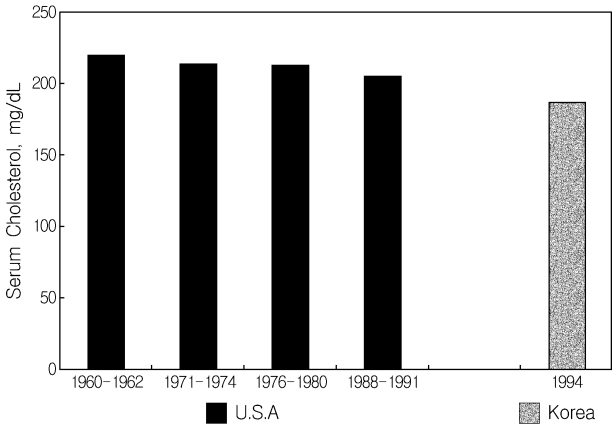

Fig. 1. Comparison of average cholesterol levels between Korean and American population.

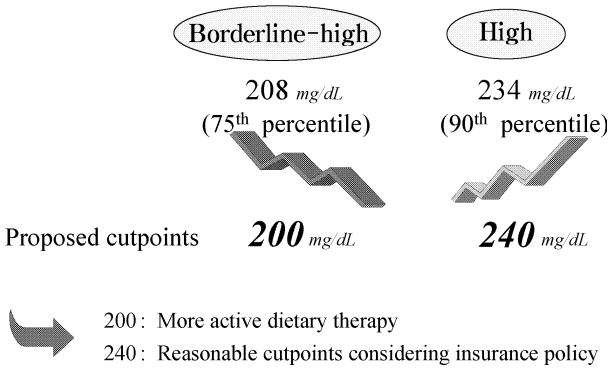

Fig. 2. Interim cutpoints for high blood cholesterol to establish National Cholesterol Treatment Guidlines in Korean population.

Table 5. Prevalence of serum cholesterol levels in the Korean population by age and sex which were examined in the laboratories of less than 5% inaccuracy of cholesterol measurement

Group	No.	Desirable blood cholesterol (<200mg/dL)	Borderline-high blood cholesterol (200-239mg/dL)	High blood cholesterol (≥240mg/dL)
Total	588082	394887(67.1)*	146867(25.0)	46328(7.9)
		Men		
≥ 20	455546	295680(64.9)	121192(26.6)	38674(8.5)
20-34	111970	84668(75.6)	21954(19.6)	5348(4.8)
35-44	161224	105238(65.3)	43041(26.7)	12945(8.0)
45-54	120333	70671(58.7)	36570(30.4)	13092(10.9)
55-64	60366	34212(56.7)	19080(31.6)	7074(11.7)
65-74	1623	881(54.3)	534(32.9)	208(12.8)
≥ 75	30	10(33.3)	13(43.3)	7(23.3)
		Women		
≥ 20	132536	99207(74.9)	25675(19.4)	7654(5.8)
20-34	71317	58439(81.9)	10327(14.5)	2551(3.6)
35-44	40567	30659(75.6)	8197(20.2)	1711(4.2)
45-54	15520	8376(54.0)	5100(32.9)	2044(13.2)
55-64	5014	1695(33.8)	2001(39.9)	1318(26.3)
≥ 65	118	38(32.8)	50(43.1)	30(25.9)

* Number (percentage)

a much lower average cholesterol level and a much lower frequency of CHD. The Finnish, on the other hand, have a much higher average cholesterol level and a much greater risk of CHD than do US citizens. Furthermore, Japanese who have migrated to Hawaii and San Francisco have higher cholesterol levels and a higher risk of CHD than nonmigrants.

Koreans, in comparison with US population, have a much lower death rate of ischemic heart diseases (about one tenth) and a 10-20mg/dL lower average cholesterol level. So management of Korean hypercholesterolemic patients according to the US NCEP or EAS guidelines is not reasonable. So it is mandatory to set-up the national cholesterol treatment guidelines based on the epidemiological results on the prevalence of CHD risk factors including distribution of cholesterol levels in the Korean population.

To establish the cutpoint for total serum cholesterol specific to Korean population, there should be judicious and deliberate discussion among lipidologists based on "Distribution of total serum cholesterol levels in the Korean population" and "Prospective epidemiological survey on the relationship between serum cholesterol levels and CHD". But there has been no prospective study to establish the cutpoints for total serum cholesterol specific to the Korean population, which makes it even more difficult to establish the cutpoints. Some investigators reported scattered efforts to establish the cutpoints.

Kwon et al.(13) reported that the diagnostic sensitivity and specificity for CHD were 25.9% and 83.0% when the cutpoints for cholesterol was 220mg/dL. Kim et al. (14) proposed the cutpoints for moderate and high risk groups at 220 and 245mg/dL of serum cholesterol. But these data were collected in the metropolitan areas, which estimated the cutpoints at too high levels. The data were too small in number and too narrow in sampling area to be a representative data for Korea.

The Japanese cutpoint is 220mg/dL in a population whose cholesterol distribution and CHD mortality are similar to those of Korea.

In this survey, we performed the external quality assessment of the participating laboratories nationwide to improve the accuracy and precision of cholesterol measurement and performed large-scale nationwide analysis of about 1 million subjects. So, we believe, this data is representative of true Korean cholesterol status.

The 75th percentile level of total cholesterol in the Korean population was 210mg/dL and 90th percentile, 235mg/dL. Therefore it might be reasonable to set up the cutpoints for borderline-high and high serum cholesterol levels at 210 and 235 respectively. But now a day dietary habit and life style in Korean are rapidly westernized and the incidence of CHD are increasing tendency, so more intensive dietary and exercise therapy to control the hyperlipidemia is needed. The cutpoint for borderline-high cholesterol levels provide a major guideline for initiation of dietary and exercise therapy, therefore we propose the cutpoints for borderline-high cholesterol levels at 200 instead of 210mg/dL to initiate more active dietary and exercise therapy.

The cutpoint for high cholesterol levels give a major guideline for drug therapy. Considering that the 250 mg/dL is the level approved for drug therapy by medical insurance so far, we propose a temporary cutpoint for high blood cholesterol levels as 240mg/dL which is reasonable cutpoint considering medical insurance policy.

In conclusion, we suggest the cutpoints for borderline-high and high serum cholesterol levels at 200 and 240 mg/dL, respectively. Lipid experts including cardiologists, endocrinologists, nutritionists, clinical pharmacologists and clinical chemists should establish the national cholesterol treatment guidelines based on the above cutpoints. They should also evaluate the effect of the treatment by these guidelines to reduce the morbidity and mortality of CHD.

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