Acta Medica Okayama

Volume 33, *Issue* 4 1979 *Article* 9

AUGUST 1979

Effect of nicomol on HDL cholesterol level.

Makoto Watanabe* Kazuhisa Taketa†

Hideo Nagashima‡ Yoshio Yamamoto**

*Okayama University,

†Okayama University,

‡Okayama University,

**Yamamoto-Naika-Hospital,

Effect of nicomol on HDL cholesterol level.*

Makoto Watanabe, Kazuhisa Taketa, Hideo Nagashima, and Yoshio Yamamoto

Abstract

In cardiovascular diseases with potential atherosclerosis, the serum concentration of HDL cholesterol as determined by a precipitation method with dextran sulfate and Mg++ was lower while that of total cholesterol was normal or elevated. Treatment with a daily dose of 1,200 mg of Nicomol, a derivative of nicotinic acid, for 1 to 3 months increased the mean HDL cholesterol level by 3 to 5 mg/dl and reduced the total cholesterol level by 14 to 15 mg/dl and total/HDL cholesterol ratio by 0.8 (3 months) to 0.9 (1 month, p less than 0.05). Similar decreases in HDL cholesterol concentration were also found in parenchymal and obstructive liver diseases with normal total cholesterol values except in fulminant hepatitis and intrahepatic cholestasis.

KEYWORDS: HDL cholesterol, nicomol, atherosclerosis, liver diseases

---

*PMID: 227232 [PubMed - indexed for MEDLINE]

Acta Med. Okayama **33**, (4), 323—326 (1979)

BRIEF NOTE

EFFECT OF NICOMOL ON HDL CHOLESTEROL LEVEL

Makoto WATANABE, Kazuhisa TAKETA, Hideo NAGASHIMA and Yoshio YAMAMOTO*

First Department of Internal Medicine, Okayama University Medical School, Okayama 700, Japan (Director: Prof. H. Nagashima) : and
**Yamamoto-Naika-Hospital, Onomichi 729-01, Japan*

Received June 11, 1979

Abstract. In cardiovascular diseases with potential atherosclerosis, the serum concentration of HDL cholesterol as determined by a precipitation method with dextran sulfate and Mg^{++} was lower while that of total cholesterol was normal or elevated. Treatment with a daily dose of 1,200 mg of Nicomol, a derivative of nicotinic acid, for 1 to 3 months increased the mean HDL cholesterol level by 3 to 5 mg/dl and reduced the total cholesterol level by 14 to 15 mg/dl and total/HDL cholesterol ratio by 0.8 (3 months) to 0.9 (1 month, $p<0.05$). Similar decreases in HDL cholesterol concentration were also found in parenchymal and obstructive liver diseases with normal total cholesterol values except in fulminant hepatitis and intrahepatic cholestasis.

Key words : HDL cholesterol, Nicomol, atherosclerosis, liver diseases

The importance of low HDL concentrations as a negative risk factor for atherosclerosis has been re-evaluated recently since Miller and Miller reported a close association between a low HDL cholesterol level and the development of ischemic heart diseases (1–4). These findings are largely based on the development of a simplified technique by Burstein *et al.* (5) for rapid separation of HDL from other lipoproteins.

In the present study, HDL cholesterol concentrations in sera of 162 cases of atherosclerotic disorders and in 68 cases with liver diseases were determined by the method of Kostner (6) with dextran sulfate (molecular weight, 500,000; Pharmacia Fine Chemicals AB, Sweden) and magnesium chloride as precipitating agents and by an enzymatic method with T-Choles (Enzymatic, International Reagent Corp., Kobe).

The results confirmed significantly lower levels of HDL cholesterol in ischemic heart diseases and its related conditions and in cerebrovascular disorders with normal or elevated mean concentrations of total cholesterol (Table 1). Similar reductions in HDL cholesterol concentration were also found in patients with parenchymal and obstructive liver diseases with a significantly

lower mean concentration of total cholesterol only in fulminant hepatitis (Table 2), indicating the importance of HDL cholesterol as a more sensitive marker of hepatic injury than total cholesterol. Variable levels of HDL cholesterol were found in intrahepatic cholestasis. Although Slow-migrating HDL was precipi-

TABLE 1. SERUM LEVELS OF TOTAL AND HDL CHOLESTEROL IN ATHEROSCLEROTIC DISORDERS AND THEIR RELATED CONDITIONS

Diseases		Cholesterol (mg/dl)	
		Total	HDL
Control	(19)	187.2±22.8	59.3±9.7
Hyperlipoproteinemia (II)	(28)	264.7±50.9***	47.3±11.5***
(III)	(1)	253.0	25.4
(IV)	(3)	192.8±17.9	33.3±12.3***
Myocardial Infarction	(7)	225.8±52.9	37.7±6.9 ***
Angina Pectoris	(16)	212.6±39.7	41.8±11.1***
Myocardial Injury	(12)	202.7±30.5	46.1±12.0 **
Essential Hypertension	(45)	200.2±32.5	46.1±14.8***
Cerebrovascular Disorders	(16)	206.2±41.4	44.3±12.7***
Diabetes Mellitus	(29)	203.7±50.3	41.7±10.3***
Obesity	(5)	174.5±21.3	45.9±9.9 **

*, $p<0.05$; **, $p<0.01$; and ***, $p<0.001$ against control values. Control subjects consisted of 14 males and 5 females, ranging in age from 20 to 60 and having no apparent diseases. The numbers of cases studied are given in parentheses.

TABLE 2. SERUM LEVELS OF TOTAL AND HDL CHOLESTEROL IN LIVER DISEASES

Diseases		Cholesterol (mg/dl)	
		Total	HDL
Control	(19)	187.2±22.8	59.3±9.7
Fulminant Hepatitis	(2)	107.2±27.9***	22.7±1.1 ***
Acute Hepatitis	(5)	176.0±21.5	35.0±10.9***
Chronic Hepatitis	(21)	174.1±48.2	41.0±12.8***
Liver Cirrhosis	(15)	168.5±67.7	40.0±16.0***
Fatty Liver	(6)	195.2±34.3	37.9±6.3 ***
Alcoholic Liver Diseases	(5)	143.6±57.6	39.0±18.7 *
Intrahepatic Cholestasis	(11)	279.3±118.6 *	50.5±22.5
Biliary Obstruction	(4)	176.9±44.7	24.0±10.7***

*, ** and ***; see the legend to Table 1. Acute hepatitis, icteric stage; chronic hepatitis, mostly inactive; liver cirrhosis, postnecrotic type and mostly compensated; fatty liver, hyperalimentary but not alcoholic; intrahepatic cholestasis, 4 primary biliary cirrhosis and its related condition and 3 suspected drug-induced cholestasis included; and biliary obstruction, malignant and extrahepatic.

tated by dextran sulfate and magnesium ion (7), cases of intrahepatic cholestasis with this cholestatic HDL tended to have higher HDL cholesterol levels.

Besides physiological factors affecting HDL cholesterol levels, such as alcohol intake (8), physical exercise (9), age (9), or sex (3) as positive factors and smoking (9), high-carbohydrate diet (10) or obesity (3) as negative factors, nicotinic acid is one of the drugs known to increase the level of HDL_2 (10). The effect of Nicomol (2, 2, 6, 6-tetrakis (nicotinoyloxymethyl) cyclohexanol; Cholexamin®, Kyorin Pharmaceutical Co. Ltd.), a derivative of nicotinic acid and having a choleretic action, was thus studied in patients with the cardiovascular disorders given in Table 3.

TABLE 3. EFFECT OF NICOMOL ON CHOLESTEROL VALUES IN PATIENTS WITH CARDIOVASCULAR DISEASES

Treatment	Period	Lipoprotein	Cholesterol (mg/dl)	
			Before	After
Control (17)	4 weeks	Total	227.6±46.6	218.7±44.7
		HDL	45.2±11.9	44.2±9.7
Nicomol (14)	4 weeks	Total	216.0±38.3	202.0±43.6
		HDL	37.7±8.7	40.7±7.8
Control (13)	3 months	Total	206.9±43.2	209.7±39.7
		HDL	46.0±17.1	43.3±9.0
Nicomol (8)	3 months	Total	233.9±58.1	219.1±53.5
		HDL	40.3±4.1	45.2±9.7

Control and Nicomol groups received drug treatment for basal diseases. No changes in dietary intake and personal habits (smoking and alcohol intake) were made during the period of this study. The numbers of patients studied are given in parentheses.

The administration of a daily dose of 1,200 mg of Nicomol for 4 weeks confirmed our previous results (11); namely, there was a mean increase of 3 mg/dl HDL cholesterol in the treated group with no practical change in the control group. In relatively long-term treatment for 3 months with the same daily dose, the mean HDL cholesterol concentration rose by 5 mg/dl, while the control group showed a mean reduction of 3 mg/dl. In 3 of 14 cases (4-week treatment) and 3 of 8 cases (3-month treatment), consistent increases over 10 mg/dl of HDL cholesterol were observed. Total cholesterol values were lowered by 14 to 15 mg/dl in those treated groups. No untoward effect of Nicomol was observed during the periods of treatment. One case tolerated a transient development of skin rash. In no cases under treatment did myocardial infarction or angina pectoris develop or recur. The change in HDL cholesterol concentration following Nicomol treatment did not correlate with either the initial

value of HDL cholesterol or the change in total cholesterol values. However, the mean total/HDL cholesterol ratio decreased from 6.1 to 5.2 and from 6.0 to 5.2 in 1- and 3-month treatments, respectively. The difference reached a statistically significant level in the 1-month group ($p<0.05$ in paired t test). Nicomol was thus considered to have a beneficial effect in preventing the development of atherosclerosis.

The mechanism, by which Nicomol increases the HDL cholesterol level, may be analogous to that of nicotinic acid, namely retardation of HDL turnover, since Nicomol has several of the pharmacological effects of nicotinic acid. Although Nicomol is also an alcohol, it does not enhance the activity of the microsomal system (12). Thus, the mechanism whereby Nicomol increases the HDL cholesterol level appears to differ from that of ethanol.

REFERENCES

1. Miller, G. J. and Miller, N. E.: Plasma-high-density-lipoprotein concentration and development of ischemic heart disease. *Lancet* **i**, 16-19, 1975.
2. Rhoads, G. G., Gulbrandsen, C. L. and Kagan A.: Serum lipoproteins and coronary heart disease in a population study of Hawaii japanese men. *N. Engl. J. Med.* **294**, 293-298, 1976.
3. Gordon, T., Castelli, W. P., Hjortland, M. C., Kannel, W. B. and Dawber, T. R.: High density lipoprotein as a protective factor against coronary heart disease. The Framingham study. *Am. J. Med.* **62**, 707-714, 1977.
4. Castelli, W. P., Doyle, J. T., Gordon, T., Hames, C. G., Hjortland, M. C., Hulley, S. B., Kagan, A. and Zukel, W. J.: HDL cholesterol and other lipids in coronary heart disease. The Cooperative Lipoprotein Phenotyping Study. *Circulation* **55**, 767-772, 1977.
5. Burstein, M., Scholnick, H. R. and Morfin, R.: Rapid method for the isolation of lipoproteins from human serum by precipitation with polyanions. *J. Lipid Res.* **11**, 583-595, 1970.
6. Kostner, G. M.: Enzymatic determination of cholesterol in high-density lipoprotein fractions prepared by polyanion precipitation. *Clin. Chem.* **22**, 695, 1976.
7. Watanabe, M.: Lipoprotein abnormalities in cholestasis. II. Isolation, characterization and clinical evaluation of an additional cholestatic lipoprotein (Slow-migrating HDL). *Acta Med. Okayama* (in press).
8. Castelli, W. P., Doyle, J. T., Gordon, T., Hames, C. G., Hjortland, M. C., Hulley, S. B., Kagan, A. and Zukel, W. J.: Alcohol and blood lipids. The Cooperative Lipoprotein Phenotyping Study. *Lancet* **ii**, 153-155, 1977.
9. Enger, S. C., Herbjornsen, K., Erikssen, J. and Fretland, A.: High density lipoproteins (HDL) and physical activity: the influence of physical exercise, age and smoking on HDL-cholesterol and the HDL-/total cholesterol ratio. *Scand. J. Clin. Lab. Invest.* **37**, 251-255, 1977.
10. Blum, C. B., Levy, R. I., Eisenberg, S., Hall, M., III, Goebel, R. H. and Berman, M.: High density lipoprotein metabolism in man. *J. Clin. Invest.* **60**, 795-807, 1977.
11. Watanabe, M., Taketa, K. and Nagashima, H.: Effect of Nicomol on HDL cholesterol level in short term administration. *Geriatric Med.* **16**, 1019-1024, 1978 (in Japanese).
12. Akamatsu, K., Shimamura, J., Takesue, A. and Taketa, K.: Effects of Tetrakis (nicotinoyloxymethyl) Cyclohexanol (Nicomol) and Ethyl Chlorophenoxyisobutyrate (Clofibrate) on Lipid Metabolism and Drug-Metabolizing and other Enzymes. *Acta Hepatol. Jpn.* **15**, 236-247, 1974 (in Japanese).