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Dyslipidemia and Cardiovascular Disease

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1. Introduction

Four non-communicable diseases (NCDs) including cardiovascular disease (CVD), cancer, chronic respiratory disease, and diabetes were announced by World Health Organization (WHO) as the major causes of mortality in the world in 2008(Alwan, 2008). According to WHO prediction, in the next 10 years, mortality rate caused by NCDs will increase by 17 percent with the highest mortality rate in the regions of Africa (27 percent) and Eastern Mediterranean (EMRO, 25 percent) (Alwan, 2008). Fortunately more than 80 percent of heart disease, stroke, and type 2 diabetes mellitus incidence and almost one third of cancers could be prevented with appropriate interventions to reduce the effect of risk factors (Alwan, 2008).

Dyslipidemia, as a risk factor of CVD, is manifested by elevation or attenuation of plasma concentration of lipoproteins. Several methods have been used to classify the lipoproteins in respect to their density, physical, and chemical properties. Based on these classifications, different types of lipoproteins, including chylomicrones, IDL[1], VLDL[2], LDL[3], and HDL[4], and apolipoproteins (Apo), including Apo A, Apo B, Apo C, and Apo E, have been introduced. Generally, dyslipidemia is defined as the total cholesterol, LDL, triglycerides, apo B or Lp (a) levels above the 90th percentile or HDL and apo A levels below the 10th percentile of the general population (Dobsn et al., 1996).

CVD is the most common health problem worldwide. This disease is often manifested as coronary heart disease (CHD). According to the international reports, mortality of CHD in the developed countries is expected to reach almost 29 percent in women and 48 percent in men in years 1990-2020. These figures have been estimated to increase by 120 percent in women and 137 percent in men (Thom et al., 1998) in the developing countries.

Atherosclerosis is the most common cause of CHD. According to recent epidemiological studies, hypercholesterolemia and possibly coronary atherosclerosis are suggested as the sole risk factors of ischemic stroke. The results of a meta-analysis of 10 large cohort studies (Law et al., 1994) showed that for each 0.6 mmol/l reduction in serum cholesterol levels in

[1] Intermediate Density Lipoprotein
[2] Very Low Density Lipoprotein
[3] Low Density Lipoprotein
[4] High Density lipoprotein

those aged 60 years, the risk of CHD decreased by 27 percent, which manifested a calculated relative risk of 0.73. With three times reduction in serum cholesterol (1.80 mmol/l or 70mg/dl), the relative risk of CHD was 0.39 $(0.73)^3$ and risk reduction reached to 61 percent. The expected benefits of total cholesterol and LDL reduction seem to be in both primary and secondary prevention of CHD. Protective effects of HDL against initial coronary events in secondary prevention (Barter et al., 2007; Rosenson, 2007) was even observed in levels of higher than 75 mg/dl with long lifetime protection (Longevity Syndrome) and emancipation of the relative risk of coronary disease. Based on these observations, current attempt for stroke prevention is mostly focused on intensive treatment with lipid-lowering drugs (Gorelick et al., 1997).

In spite of a decline in cardiac events and coronary mortality rates, many people who are under appropriate treatment are still exposed to these events. In a population-based study regarding hypercholesterolemia awareness (Nieto et al., 1995), only 42% of population were informed of their hypercholesterolemia and only 4% were under lipid-lowering drug treatment. Need assessment to better understand the role of lipids and its subgroups including; VLDL, Small dense LDL, lipoprotein (a), and subgroups of HDL in pathogenesis of CVD calls for a general awareness regarding these topics. In this context, the major challenges would be: 1 – to identify those who need treatment (with or without past history of coronary artery disease), 2 – to develop more effective treatment strategies for patients with coronary artery disease (whether individuals were treated with lipid-lowering drugs or people who have not received adequate treatment), 3 – to adequately treat other high risk individuals such as diabetic, hypertensive, and old subjects.

1.1 Objective

Main objective of this chapter is to express the relationship between lipid disorders and CVD according to the top epidemiological studies in the world. Other minor objectives include; evaluation of role of dyslipidaemia in the incidence of CVD, and also assessment of the role of different types of lipoproteins in this area.

1.2 Expected outcomes

- To increase general awareness regarding the relationship between lipid disorders and CVD
- To reduce the morbidity and mortality of CVD (by primary or secondary prevention)

2. World epidemiological evidences of association between dyslipidemia and CVD

CVD is widespread among general population. Reports received from late 1990s indicate that the ultimate cause of death in adults is CVD (Murray & Lopez, 1997). It has been predicted that CVD will become the ultimate cause of disability in the world between years 2000-2025 (Murray & Lopez, 1997). Common lifestyle determinants such as western diet, physical inactivity, tobacco consumption and also increase in life expectancy are linked to elevation of CVD prevalence (Critchley et al., 1999).

According to data published from the autopsy studies in 1960s, the origin of early lesions of atherosclerosis in adults is mostly caused by consumption of Western diet. The prevalence

and severity of fibroid plaques and calcified lesions as signs of CVD were significantly lower in Asia, underdeveloped countries and consumers of Mediterranean diet (Eggen et al., 1964).

2.1 Total and LDL cholesterol

Two decades after World War II, large population studies had been performed in different countries in order to determine risk factors of heart disease. The most famous studies include the Framingham Study, Chicago and Tecumseh in USA (Butler et al., 1985; Dawber et al., 1951; Dyer et al., 1981; Keys, 1970) and Seven Country Studies including studies in England, Sweden and Norway (Fager et al., 1981; Keys et al., 1984; Miller et al., 1977) in European countries. The major finding of these cohort studies was that in addition to serum cholesterol levels, other factors also are involved in development of coronary heart disease. Among the main risk factors, dyslipidemia, especially increase in LDL levels and decrease in HDL concentrations were considered as the important factors. Table-1 demonstrates the Population Attributable Factors (PARs) with its 99 percent confidence interval (CI) associated with lipids by sex and geographic region (Labarthe, 2011; Yusuf et al., 2004). In some countries, PAR estimation in women is based on small numbers which makes them less reliable.

Region	Lipids in men % (CI 99%)	Lipids in women % (CI 99%)	Lipids in both sexes % (CI 99%)
West Europe	36.7 (10.7-73.8)	47.9 (20.3-76.8)	44.6 (23.5-67.8)
Central & eastern Europe	38.7 (20.0-61.4)	26.8 (5.9-68.2)	35.0 (19.2-54.9)
Middle East	72.7 (58.8-83.2)	63.3 (32.0-86.3)	70.5 (57.8-80.7)
Africa	73.7 (55.2-86.4)	74.6 (49.1-90.0)	74.1 (59.7-84.6)
South Asia	60.2 (42.5-75.6)	52.1 (19.0-83.5)	58.7 (42.7-73.1)
China	41.3 (32.4-50.7)	48.3 (36.9-59.9)	43.8 (36.7-51.2)
Southeast Asia and Japan	68.7 (51.2-82.1)	64.5 (29.5-88.7)	67.7 (52.0-80.2)
Australia & New Zealand	48.7 (17.5-80.9)	14.9 (0.0-99.6)	43.4 (16.0-75.6)
South America	41.6 (20.2-66.6)	59.3 (30.5-82.9)	47.6 (29.6-66.2)
North America	60.0 (22.2-88.8)	32.2 (1.1-95.1)	50.5 (18.2-82.4)
Overall adjusted for age, sex & smoking	53.8 (48.3-59.2)	52.1 (44.0-60.2)	54.1 (49.6-58.6)
Overall adjusted for risk factors	49.5 (43.0-55.9)	47.1 (37.4-57.0)	49.2 (43.8-54.5)

Legend: CI: Confidence Interval.

Table 1. Population Attributable Factors (PARs) associated with lipids in men & women by geographic region.

In parallel to these large population studies, a series of case studies were also performed. In one study, serum lipid levels were evaluated in 500 men with a prior history of myocardial infarction. Overall 30 percent of study population had abnormal blood lipid levels (Goldstein et al., 1973). High levels of cholesterol in 8 percent, triglycerides in7 percent and concomitant high cholesterol and triglycerides in15 percent were reported by this study.

In normal individuals from different communities, plasma levels of lipids vary due to differences in genetic background and diet. For example, the average cholesterol levels, according to age, in western and Chinese men are 202 mg/dl and165 mg/dl, respectively (Caroll et al., 2005; Wu et al., 2004). Based on results of the National Health and Nutrition Examination Surveys (NHANES) from 1999 to 2004, the percentage of adults with triglyceride levels above 150 and 200 mg/dl in the United States, were 33 and 18 percent, respectively (Ford et al., 2009). In the United States, the NHANES from 2005 to 2008 found that 98.8 million adults have total cholesterol levels ≥ 200 mg/dl, 33.6% of them having a total cholesterol level ≥ 240 mg/dl (American Heart Association [AHA], 2011).

Table-2 shows the prevalence of high levels of total cholesterol (cholesterol ≥ 200 mg/dl), LDL (LDL cholesterol ≥130 mg/dl), and HDL (HDL cholesterol≤ 40 mg/dl) in adults aged ≥20 years, according to NHANES (American Heart Association [AHA], 2011).

	Non-Hispanic White		**Non-Hispanic Black**		**Mexican-American**	
	M	**F**	**M**	**F**	**M**	**F**
Total cholesterol						
200-239 mg/dl	41.2	47.0	37.0	41.2	50.1	46.5
≥ 240 mg/dl	13.7	16.9	9.7	13.3	16.9	14.0
LDL cholesterol						
≥130 mg/dl	30.5	32.0	34.4	27.7	41.9	31.6
HDL cholesterol						
≤ 40 mg/dl	29.5	10.1	16.6	6.6	31.7	12.2

Legend: M: Male; F: Female; LDL: Low Density Lipoprotein; HDL: High Density Lipoprotein.

Table 2. Proportion of USA adults aged ≥ 20 years with dyslipidemia by ethnicity and gender

In MONICA[5] project designed for more than 30 countries in different regions of WHO coverage except the US, the percentage of hypercholesterolemia for individuals aged between 35-64 years and total cholesterol levels between 5.2-7.8 mmol/l (approximately 200-300 mg/dl) was found to be lowest (20%) among the men in China-Beijing and highest (76%) in France-Strasbourg. The lowest percent of women with hypercholesterolemia (5%) was in Australia-Perth population and the highest percent (76%) was observed in Germany-Bremen (WHO MONICA project, 2008). However, these figures were different when the total cholesterol level >7.8 mmol/l was considered as hypercholesterolemia. None of the China-Beijing's men had the serum cholesterol levels >7.8 mmol/l (0%) while 15% of Switzerland-Ticino men had hypercholesterolemia (highest percent). for women these figures were 0% in China-Beijing and 14% in Lithuania-Kaunas (WHO MONICA project, 2008).

[5] Multinational MONItoring of trends and determinants in CArdiovascular disease

The WHO MONICA project showed (WHO MONICA project, 1989) that the average of total cholesterol in 30 studied areas varied from 158 mg/dl (in the Beijing, China) to 246 mg/dl (Loczamburk, Germany) for men and from 162 mg/dl (Beijing, China) to 246 mg/dl (Glasgow, UK) in women. In addition, there was a difference in prevalence of hypercholesterolemia in different regions, from 2 percent in Beijing, China to nearly 50 percent in Lille, France (WHO MONICA project, 1989). An intermediate reduction in cholesterol level of MONICA project study populations during 5-6 year follow-up was observed. The mean annual decrease in total serum cholesterol was 0.4-3 mg/dl (Dobsn et al., 1996).

The highest incidence of hyperlipidemia is shown in patients with premature coronary artery disease, which occurs before age 55 years in men and 65 years in women. Prevalence of dyslipidemia in these patients is equal to 80-88 percent, compared to 40-48 percent in age-matched controls without CHD (Genest et al., 1992; Roncaglioni et al., 1992). In these conditions, 12.5 percent of patients with a prior history of premature coronary disease and 58.5 percent of age-matched controls without prior history of coronary disease have normal lipid profiles.

MRFIT[6] study performed in more than 350,000 middle-aged men demonstrated (Stamler et al., 1986) that a sigmoid relationship (curvilinear) between total serum cholesterol level and prevalence of coronary artery disease especially in total cholesterol more than 240 mg/dl is presented (Figure-1).

The strongest association was found in population from United States and Finland, the intermediate association was observed in European population, and the least correlation was related to Japanese men and rural area of Greece. The relationship between serum cholesterol and incidence of CVD become stronger when the number of risk factors was increased (Kannel, 1983).

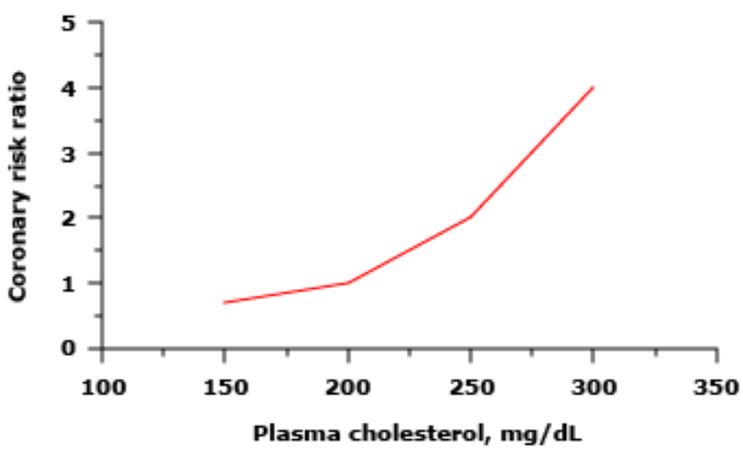


Fig. 1. Association between plasma cholesterol and coronary risk among MRFIT study

[6] Multiple Risk Factor Intervention Trial

Similar results were obtained from Framingham and Migration studies (Kannel et al., 1971, 1979). The Migration study is one of the strong studies evaluating the relationship between increased serum cholesterol and risk of CVD. This study was done in 1960 and compared Japanese men residing in Japan with immigrated Japanese to Honolulu and San Francisco. In Japanese men living in their native country, the mean total cholesterol levels and CHD rate were lower compared to immigrated population. In immigrated Japanese, those who live in Hawaii had lower lipid levels than those in San Francisco. Considering race similarity in this study, the reason for observed differences in rate of CHD and cholesterol levels can be related to differences in dietary cholesterol and fat consumption (Kagen et al., 1974).

However the results of other studies on immigrants were not always similar to the Migration study. In one study (Kushi et al., 1985), diet produced no effect on cholesterol levels or heart disease mortality. In General, the importance of age, sex and race on levels of cholesterol has been shown in population-based studies.

Invention of ultracentrifuge has facilitated measurement of the various lipid parameters. LRCP (Lipid Research Clinics Program) was one of the first surveys during 1970 that was conducted to determine the total cholesterol, HDL cholesterol, LDL cholesterol and triglyceride levels in American adults (Heiss et al., 1980). In another study, difference in distribution of cholesterol and its components in the blood in accordance to age were described (Glueek & Stein, 1979). In both sexes, the slope of total cholesterol curve is increased by increase in age until the end of middle-age. After that, by increasing the age, slope of the curve is downward until reaching the old age. Mean total cholesterol in men and women aged between 20 -50 years is similar, however, the levels of HDL cholesterol in women after puberty is higher than men (Rifkind & Segal, 1983).

Among patients with a prior history of myocardial infarction, an elevated total cholesterol following recovery was a major independent risk factor for reinfarction, death from heart disease and total mortality. Cardiovascular mortality is varied in different populations. The highest and lowest mortality rate was found in Finland and Japan, respectively, with a direct relationship to serum cholesterol levels (Rosenson, 2011).

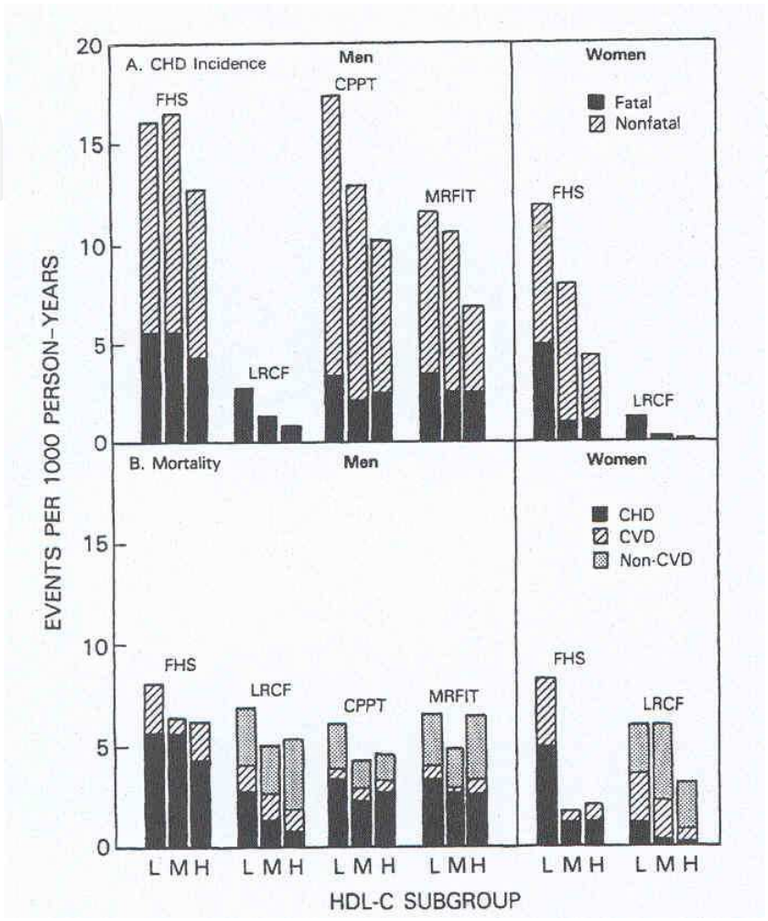
2.2 HDL cholesterol

The negative relationship between low HDL cholesterol and the risk of heart disease is well stablished in the general population (Abbott et al., 1988; Abbott et al., 1998; Castelli, 1983; Gordon et al, 1989; Harper & Jacobson, 1999; Rosenson, 2005) (figure-2). In the Framingham Heart study, the protective role of HDL has been well described (Kannel et al., 1971).

Based on results of this study, by each 5 mg /dl decrease in serum levels of HDL (compared to mean normal values for men and women), the risk of myocardial infarction was increased by 25 percent.

Predictive role of HDL against coronary events was also well documented in patients with known heart disease. The results of Lipid and Care clinical trial showed that low levels of HDL cholesterol is a stronger predictor of heart disease incidence in presence of serum LDL cholesterol < 125 mg/dl than LDL cholesterol ≥ 125 mg/dl (Sacks et al., 2002). They also found that in serum LDL<125 mg/dl, each 10 mg /dl increase in HDL level, will cause 29 percent reduction in the incidence of cardiovascular events , while with the serum LDL cholesterol ≥ 125 mg/dl, this attenuation will be lowered to 10 percent. This association was

also seen in post hoc analysis of TNT[7] study, in which 10000 known cases of CVD were under-treatment with different doses of statins (Barter et al., 2007).



Legend: CHD: Coronary heart disease; L M H HDL: Low, middle, high, high density lipoprotein; CVD: Cardiovascular disease; FHS: Framingham Heart Study; LRCF: Lipid Research Clinics Prevalence Mortality Follow-up Study; CPPT: Lipid Research Clinics Coronary Primary Prevention Trial; MRFIT: Multiple Risk Factor Intervention Trial.

Fig. 2. Inverse association between HDL and CVD events.

As mentioned previously, the cardioprotective effect of HDL was shown to be present at serum levels higher than 60 mg/dl (Castelli et al., 1983). These effects are more prominent when the serum levels of HDL cholesterol reach 75 mg/dl and higher (Table-3).

In assessment of 18 relatives with familial hyperalfa–lipoproteinemia, the life long of these men and women were found to be 5 and 7 years, respectively, more than general population (Glueck et al., 1976).

[7] Treating to New Targets trial

In the Lipid Research Clinics study, the Framingham heart Study and the HHS[8] the ratio of LDL to HDL was shown to be the best predictor of cardiovascular events (Manninen et al., 1992; Kinosian et al., 1994). In HHS study, the risk of new coronary events such as myocardial infarction and sudden cardiac death in patients with LDL/HDL ≥ 5 and a concomitant serum triglycerides ≥ 200 mg /dl, was fourfold more than patients with lower LDL/HDL ratio and triglycerides levels. Overall, among men, an LDL/HDL ratio of ≥ 6.4 had 2–14 percent higher predictive value than serum total cholesterol or LDL levels. Among women the predictive value of LDL/HDL ≥ 5.6 was 25–45 percent greater than serum total cholesterol or LDL level (Kinosian et al., 1994).

HDL (mg/dl)	**Multiplier for cardiovascular risk**	
	men	**women**
30	1.82	----
35	1.49	----
40	1.22	1.94
45	1.00	1.55
50	0.82	1.25
55	0.67	1.00
60	0.55	0.80
65	0.45	0.64
70	----	0.52
75	Longevity syndrome	Longevity syndrome

Legend: HDL: High Density Lipoprotein.

Table 3. Inverse relation between plasma HDL-cholesterol levels and cardiovascular risk in men and women.

2.3 Triglycerides

The relationship between hypertriglyceridemia and CVD was determined in the population-based Stockholm prospective study (Carlson et al., 1979). In this study, 3,486 subjects were followed for 14.5 years. An independent relation between hypertriglyceridemia and CVD was observed in this study, which was stronger than the relationship between hypercholesterolemia and CVD. Meta-analysis of several large population–based prospective studies showed similar results (Hokanson & Austin, 1996). Based on this study, the univariate risk ratio (RR) of triglyceride, independent of HDL and other CVD risk factors, among men was 1.32 (95 percent CI, 1.26 to 1.39) and among women was 1.76 (95 percent CI, 1.50 to 2.07).

As mentioned previously in the HHS study, not only there is an interaction between triglycerides and total cholesterol/HDL ratio, but also an inverse association between triglycerides and HDL levels exists (Rosenson, 2011). Additionally, hypertriglyceridemia is associated with increased mortality in patients with known CHD and also reduces the

[8] Helsinki Heart Study

event–free survival after coronary artery bypass graft surgery (CABG) (Haim et al., 1999; Sprecher et al., 2000).

Nevertheless, because hypertriglyceridemia is an independent risk factor for CVD, measurement of triglycerides as a part of routine cholesterol screening is recommended by NECP ATPIII guidelines (Haim et al., 1999). Fasting triglyceride measurement is important for evaluating the risk of heart disease especially in cases who are suffering from diabetes, glucose intolerance, insulin resistance syndrome, obesity and low HDL. Although, triglyceride measurement is commonly done after 8–12 hours fasting, an association between nonfasting triglyceride levels and CVD is also present (Nordestgaard et al., 2007; Bansal et al., 2007).

2.4 Non-HDL cholesterol

Non–HDL cholesterol is defined as the difference between total and HDL cholesterols. Thus it includes LDL, Lp (a), IDL and VLDL (Ballantyne et al., 2000). In both LRCP study and the Women's Health Study non-HDL cholesterol has been suggested as a better tool for risk assessment of CVD than LDL levels (Cobbaert et al., 1997; Ridker et al., 2005). In the LRCP study in which the patients were followed for an average of 19 years, a 30 mg/dl difference in non–HDL and LDL concentrations, produced 19 and 15 percent, increase in mortality risk of CVD among men, respectively, and 11 and 8 percent, among women, respectively, (Cobbaert et al., 1997).

2.5 Lipoprotein (a)

Lipoprotein (a), also called Lp (a), is established as an independent risk factor for CVD. Lp (a) is a modified form of LDL with a structure similar to plasminogen (Steyrer et al., 1994) that could interfere with fibrinolysis by competing with plasminogen for binding to cells (Loscalzo et al., 1990; Palabrica et al., 1995). Lp (a) also binds to macrophages to promote foam cell formation and deposition of cholesterol in atherosclerotic plaques (Zioncheck et al., 1991). Thus, Lp (a) accelerates atherosclerosis process by impairing fibrinolysis and increasing LDL oxidation (Stein & Rosenson, 1997). Evidences of association between Lp (a) excess [Lp (a) levels above the 95th percentile] and CVD mostly come from 2 large meta-analyses that found positive continuous correlation between Lp (a) and risk of CVD events (Bennet et al., 2008; Emerging et al., 2009). The 24 cohort studies in the meta-analysis (Bennet et al., 2008) found a risk ratio of 1.13 (95 percent CI, 1.09 to 1.18) between the top and third bottom baseline Lp (a) levels after adjustment for multiple traditional cardiovascular risk factors. Lp (a) excess concentration is usually detected in patients with premature CHD. In one study 18.6 percent of patients with premature CHD had excess levels of Lp (a), while 12.7 percent of them had no dyslipidemia (Genest et al., 1992).

LP (a) increases the risk of cerebrovascular disease, peripheral vascular disease, myocardial infarction (MI), re–stenosis after angioplasty, and failure after CABG (Rosengren et al., 1990; Schaefer et al., 1994). 12 years and more follow–up of patients in the Framingham Heart study showed that Lp (a) can increase the risk of premature coronary heart disease by two-times (Bostom et al., 1996), and augment the risk of MI, intermittent claudication, cerebrovascular disease, and coronary artery stenosis. In the 4S[9] study an association between increased Lp (a) levels and overall mortality rate was also observed (Bostom et al., 1994).

[9] Scandinavian Simvastatin Survival Study

2.6 Apolipoproteins & atherogenic lipoprotein phenotype

There are limited prospective studies about the relationship between apolipoproteins (apo A-I and apo B) and the CVD risk. The QCS[10] was studied 2155 men aged between 45-76 years and reported a direct correlation between apo B levels and prevalence of ischemic heart disease over the future 5 years, [relative risk (RR) 1.4; 95 percent CI, 1.2 to 1.7] (Lamarche et al., 1996), independent of other risk factors of CVD. For apo A–I, a negative correlation (RR = 0.85; 95 percent CI, 0.7 to 1.0) was reported.

Since the measurement of apo B and apo A–I is an indicator of total atherogenic (lDL, VLDL, and LDL) and antiatherogenic particles (HDL), some studies (Lamarche et al., 1996; Meisinger et al., 2005; Yusuf et al., 2004; Walldius et al., 2001, 2005) proposed that measurements of apo B and apo A are more important predictors of the CVD than above measurements. The AMORIS[11] study evaluated this relationship in 175,553 subjects with 65 months follow up (Walldius et al., 2001). In the multivariate analysis the apo B concentration was significantly higher than LDL levels and served as a better predictor of CVD than LDL.

The results regarding the role of apolipoproteins in prediction of CVD risk are conflicting. Two studies; Women's Health Study and the Framingham Study obtained a similar predictive value for apo B/A–I ratio versus total cholesterol/ HDL ratio (Ridker et al., 2005; Ingelsson & Schaefer, 2007). However, in contrast to Health Professionals Follow-up Study (Pischon et al., 2005; Sniderman, 2005) and AMORIS study, apo A–I and apo B did not have any predictive value for CHD risk in ARIC[12] study (Sharrett et al., 2001). The explanation for these disparate results is not clear. However, it seems apolipoproteins have a potential role in CHD risk stratification. Standardization of laboratory methods and measurements to the same reference system, and establishing threshold and target values for diagnosis could help recognize the full potential of apolipoproteins (Srinivasan & Berenson, 2001; Denke, 2005).

Apo E is important in plasma lipid metabolism and Apo E gene affects plasma levels of LDL. Three major apo E isoforms are E2, E3, and E4, which are encoded by three common alleles at the APO E locus. The less common and the most common isoforms in society are E2 and E3, respectively. E4 allele is associated with higher plasma total cholesterol and LDL cholesterol levels and with risk of heart attack. In contrast, subjects with E2 allele have lower risk of heart attack compared to people with E4 isoform (Song et al., 2004).

Some clinical researches have focused on the relationship between small dense LDL particles and risk of CVD. This status, also called atherogenic lipoprotein phenotype, is usually associated with increased triglyceride, VLDL and LDL levels (Krauss, 1994). The Physician's Health Study showed that small dense LDL particles can increase three times the risk of CVD more than LDL cholesterol (Zambon et al., 1996). In QCS study, during 5 year follow up, 114 cases from a total of 2103 were diagnosed with heart disease. In this study, in multivariate analysis small dense LDL was more important predictor of CVD [odds ratio (OR) = 3.7; 95 percent CI, 1.4 to 9.7) than LDL (OR = 1.8; 95 percent CI, 1.2 to 2.9) (Lamarche et al., 1997). The Familial atherosclerosis Treatment Study (FATS) found that LDL subclasses were the most important predictor of coronary progression (Zambon et al., 1999). In the Pravastatin Limitation of Atherosclerosis in the Coronaries (PLAC–I) study showed that

[10] Quebec Cardiovascular Study
[11] Apolipoprotein-related MOrtality RISk
[12] Atherosclerosis risk in Communities

small LDL particle size (≤ 20.5 nm) could increase rate of coronary progression with OR= 5.0 and 95 percent CI, 1 to 9. High numbers of small LDL particles (>30 mg/dl) was the most important lipoprotein predictor in multivariate analysis (OR = 9.1; 95 percent CI, 2.1 to 39) (Otvos et al., 2002).

In the FATS[13] study 95 percent variance in regression of atherosclerosis in coronary arteries were related to changes in lipid profile. Adding the LDL density to the equation showed that almost 45 percent of the variance was related to changes in LDL density (Lamarche et al., 1997). In contrast, the CHS[14] reported that LDL particle concentration and not LDL size acted as a significant predictor of MI and angina in women, in which by every 100 nmol/l increase in LDL particle number, the OR of MI and angina increased by 11 percent (Kuller et al., 2002).

In Women's Health Study which assessed LDL particle size and concentration by NMR[15] , the LDL particle concentration was a strong predictor of CVD after adjustment for traditional risk factors (Blake et al., 2002).

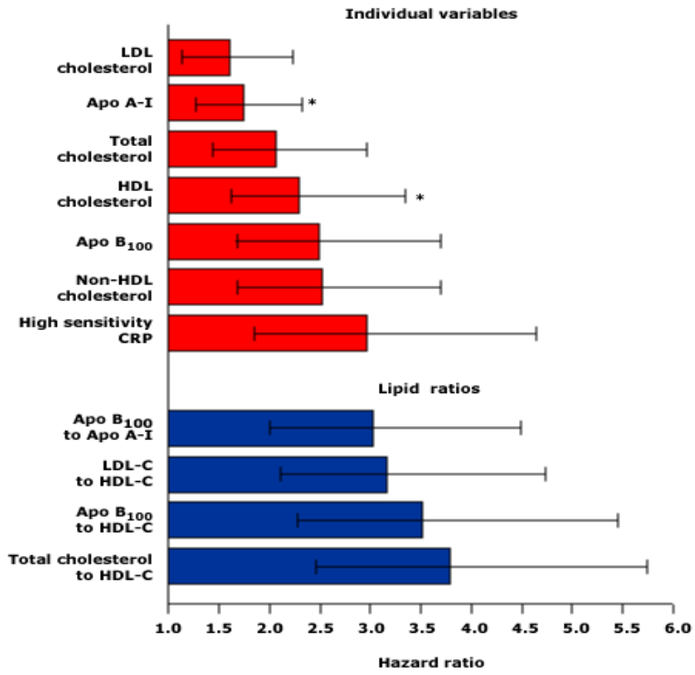
EPIC[16]- Norfolk prospective Population Study examined NMR-measured LDL particle size and concentration (EI Harchaoui et al., 2007) and found that LDL particle concentration did not increase the prediction of CHD. After LDL particle concentration adjustment, LDL size was no longer associated with CHD.

Recently, some scientists from the University of Warwick in UK discovered a modified form of LDL, MGmin-LDL, also called super-sticky LDL, or very-bad LDL, that promotes CVD (Rabbani et al., 2011). High levels of this lipid are more common in diabetics and elderly patients. Diabetic subjects present almost four times more serum levels of MGmin-LDL than normal subjects. This may explain the high frequency of CVD in diabetics and elderly patients. Rabbani et al (Rabbani et al., 2011) found that secondary to hyperglycemia, LDL is glycated with methylglyoxal (MG) and makes a type of LDL with smaller, stickier and more atherogenic LDL than normal LDL. The MGmin-LDL can help to build fatty plaques. When these plaques grow, the wall of arteries become narrower and the blood flow reduces. Plaque rapture, an event that would eventually happen, triggers the blood clot cascades that could cause a heart attack or stroke. In elderly, the activity of the enzyme for detoxification of MGmin-LDL is reduced. They (Rabbani et al., 2011) also showed that metformin can block the glycation processes which might explain the cardioprotective effects of this drug. This discovery could lead to invention of new treatments for CVD prevention especially in type 2 diabetics and the elderly subjects.

3. Summary

The relationships described above can be summarized in the figure-3 (Ridker et al., 2005). This figure shows the adjusted Hazard ratios of future cardiovascular events among patients who are in the extreme quintiles of each measured marker. Black bars present 95 percent CI.

[13] Familial Atherosclerosis Regression Study
[14] Cardiovascular health Study
[15] Nuclear Magnetic Resonance
[16] European Prospective Investigation into Cancer and Nutrition



Legend: LDL: Low Density Lipoprotein; Apo A-I: Apolipoprotein A-I; HDL: High Density Lipoprotein; Apo B100: Apolipoprotein B100; CRP: C - reactive protein.

Fig. 3. Adjusted Hazard ratios for future cardiovascular events.

Today, interventional studies have investigated the effects of augmentation of HDL levels. The clinical trials which deal with this matter will be discussed in a separate part. In assessment of dyslipidemia two points should be stipulated:

1. Decline of coronary events could be possible by modifying the serum lipid levels in order to prevent or delay the reduction of vessel diameter, and also to stabilize atheroma plaques. Small plaques are mostly filled with lipid and are prone to disposable rupture, thrombosis, acute, serious and ultimately fatal atherosclerosis. Reduction of LDL leads to removal of fatty deposits from the inside of the atheroma plaque and makes them more stable. In addition, lowering the lipids levels can return the normal activity of vessel wall endothelium and its ability to produce nitric oxide, the main mediator of coronary vasodilation (Krauss, 1994).
2. During lipid-lowering drug therapy the cost-effectiveness of the treatment should be considered. This depends on the price of drugs as well as patient's risk. For example, at least cost-effectiveness includes patients with intermediate elevation of serum cholesterol, who, without any other risk factors, are under- lipid lowering agent therapy. In 4S study which was performed in patients with high risk of CVD, cost per year of life gain, was depended on age, sex and baseline levels of lipid. The range of this cost was varied from 3,800 $ U.S. for men aged 70 years and the mean serum cholesterol 309 mg/dl, to 27,400 $ U.S. for women aged 35 years and the average serum cholesterol 213 mg/dl (Johannessonet al., 1997). In other studies these figures were different from 19,000 $ U.S. to 56,000 $ U.S. which depends on drug dose and formulation used. Also, these costs were three folds, two folds and 1.3 folds more in women at age 40, 60 and 70 years, respectively, when compared with the men at age 40 years (Martens & Guibert, 1994; Thorvik et al., 1996).

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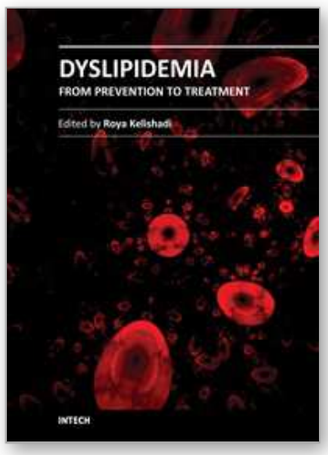

Dyslipidemia - From Prevention to Treatment

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Dyslipidemia has a complex pathophysiology consisting of various genetic, lifestyle, and environmental factors. It has many adverse health impacts, notably in the development of chronic non-communicable diseases. Significant ethnic differences exist due to the prevalence and types of lipid disorders. While elevated serum total- and LDL-cholesterol are the main concern in Western populations, in other countries hypertriglyceridemia and low HDL-cholesterol are more prevalent. The latter types of lipid disorders are considered as components of the metabolic syndrome. The escalating trend of obesity, as well as changes in lifestyle and environmental factors will make dyslipidemia a global medical and public health threat, not only for adults but for the pediatric age group as well. Several experimental and clinical studies are still being conducted regarding the underlying mechanisms and treatment of dyslipidemia. The current book is providing a general overview of dyslipidemia from diverse aspects of pathophysiology, ethnic differences, prevention, health hazards, and treatment.

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