INTRODUCTION
High serum cholesterol has been known as being a main risk factor for coronary heart disease (CHD). A number of types of evidence support the cholesterol-CHD link, these include researches in laboratory animals, epidemiological studies, findings of premature CHD in genetic forms of hypercholesterolemia, laboratory investigations, and clinical trials of cholesterol-lowering therapy. Most people with high serum cholesterol also have elevated LDL because much of the serum cholesterol is transported in LDL. Therefore, the emerging concept is that the predominant atherogenic lipoprotein is LDL.1a

THE DISEASE PROCESS1
Understanding the pathogenesis of atherogenic dyslipidemia, it becomes clear that the prevalence of low HDL-C levels, hypertriglyceridemia, and a predominance of small, dense LDL particles will increase in direct relation to the growing rate of obesity. As abdominal obesity increases, free fatty acids are delivered through portal circulation to the liver and serve as substrates for the production and release of very low-density lipoprotein (VLDL) particles into the bloodstream. The longer these particles remain in circulation, the greater the opportunity for them to be acted on by cholesteryl ester transport protein, which transfers cholesterol from LDL and HDL particles to VLDL particles in exchange for triglycerides. This cholesterol transfer results in large VLDL particles that are enriched in cholesterol and small LDL and HDL particles that are cholesterol-depleted. Besides, triglyceride-enriched HDL particles are more easily cleared by the kidney, which reduces the number of HDL particles in the bloodstream.

It is no wonder that three key components of the metabolic syndrome are obesity, low HDL-C levels, and hypertriglyceridemia. Atherogenic dyslipidemia results in increased atherosclerotic plaque formation because of an inequity between an increased number of small, dense LDL particles (which carry cholesterol to the vascular endothelium) and a decreased number of HDL particles (which remove cholesterol from atherosclerotic vessels).

LOW-DENSITY LIPOPROTEIN (LDL) AND THE ASSOCIATION WITH AHEROGENIC DYSLIPIDEMIA
Between the different risk factors for CHD, a raised LDL level appears to be crucial. High LDL concentrations initiate atherogenesis and promote atherosclerosis at every stage. The remarkable finding that LDL-lowering therapy reduces risk for subsequent coronary events even in patients with advanced atherosclerotic disease discloses a role for LDL in late stages of atherogenesis.2 Moreover, populations devoid of some elevations of LDL levels exhibit relatively low prevalence of CHD even when other coronary risk factors, e.g., cigarette smoking, hypertension, and diabetes mellitus, are common.3 An elevated LDL, thus, is at the core of atherogenesis. Table 1 classifies LDL-cholesterol levels according to NCEP guidelines; approximate corresponding values for total cholesterol also are listed. In the United States, most CHD occurs in patients who have borderline high-risk or high-risk LDL levels; CHD rarely develops when LDL-cholesterol levels are optimal (ie, <100mg/dL).4

<table>
<thead>
<tr>
<th>Category</th>
<th>LDL Cholesterol, mg/dL</th>
<th>Total Cholesterol, mg/dL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Optimal</td>
<td>&lt;100</td>
<td>&lt;160</td>
</tr>
<tr>
<td>Desirable</td>
<td>100-129</td>
<td>160-199</td>
</tr>
<tr>
<td>Borderline high</td>
<td>130-159</td>
<td>200-239</td>
</tr>
<tr>
<td>risk</td>
<td>High risk</td>
<td>&gt;160</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt;240</td>
</tr>
</tbody>
</table>

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Association between plasma level of low-density lipoprotein cholesterol (LDL-C) and the risk of coronary heart disease (CHD) is beyond argument. As emphasized in the recently updated Canadian guidelines for the management and treatment of dyslipidemia, a variety of major clinical trials over the past decade have reported that lowering LDL-C levels has a clear benefit in reducing the risk of CHD events. Although significant, the risk reduction afforded by pharmacologic lowering of LDL-C has generally been limited to 30%.6

Despite overwhelming evidence that LDL is an atherogenic lipoprotein, the precise mechanisms whereby LDL promotes atherosclerosis remain unknown. According to current concepts, circulating LDL particles filter into the arterial wall, where they elicit an atherogenic response. Most investigators believe that LDL particles must undergo modification before they become pathogenic. Several postulated modifications include oxidation, aggregation, glycation, and enzymatic degradation. A final answer as to which of these or other modifications impart atherogenicity to LDL expects further research.

Nowadays, to make LDL cholesterol as the principal target of therapy, several points must be made about LDL in general.

1. LDL-cholesterol concentration fails to precisely count the number of LDL particles; this number derives instead from the LDL–apolipoprotein B (apo B) level. There is one apo B molecule per LDL particle; therefore, the LDL–apo B level accurately defines LDL particle number. The ratio of cholesterol to apo B varies from person to person; this explains why the LDL-cholesterol level does not necessarily indicate the number of LDL particles in a given volume of serum.7

2. Usual estimates of LDL cholesterol include the cholesterol content of IDL as well as true LDL. IDL typically contributes about 10% to 15% of the cholesterol in the estimated “LDL-cholesterol” value. This seems acceptable, however, because IDL probably rivals LDL in atherogenic potential.

However, the LDL+IDL fraction may not include all atherogenic lipoproteins; some lipoproteins within the class of VLDLs probably promote atherosclerosis too. The total apo B level gives the total number of lipoprotein particles in LDL+IDL+VLDL; if most apo B–containing lipoproteins in each fraction are atherogenic, then the total concentration of apo B should indicate CHD risk better than the LDL-cholesterol level does. Furthermore, studies reveal that the cholesterol content of LDL+IDL+VLDL correlates strongly with total apo B levels.8 This cholesterol value equates to total cholesterol minus HDL cholesterol. Therefore, LDL+IDL+VLDL cholesterol may be called non-HDL cholesterol.

Some investigators8, 9 suggest that the non-HDL cholesterol, a marker for all apo B–containing lipoproteins, better represents “atherogenic cholesterol” than does LDL cholesterol. Even now, the relative atherogenic potentials of LDL is still unknown, IDL, and VLDL. Fisher10 first reported heterogeneity within LDL. He used the term “polydisperse” to describe LDL having a wide range of particle sizes; this contrasted to “monodisperse” LDL, which has a narrow range of particle size. Later, Krauss and Burke11 and Austin et al12 simplified the approach to defining LDL particle size; these workers divided the LDL pattern into two categories: pattern A and pattern B. The former signifies a predominance of larger particles; the latter denotes a preponderance of smaller LDL particles. Pattern A typically contains “monodisperse” LDL, whereas pattern B often reflects “polydisperse” LDL; most particles in polydisperse LDL consist of small LDL. Pattern A is the most common and most normal LDL pattern. Several retrospective surveys16 suggest that the more abnormal pattern B confers increased risk for CHD.

In addition, prospective studies such as the Quebec Cardiovascular Study12 uphold this hypothesis; they disclose that high levels of small LDL particles (pattern B) are associated with increased risk of subsequently developing CHD in men. The data further imply that this associated risk is partly independent of other lipoprotein abnormalities. Moreover, they have reported marked overlap in the distribution of LDL-C levels at baseline between men who went on to experience CHD and those who remained asymptomatic over the 5-year follow-up period. Thus, additional factors must modulate the risk of CHD associated with LDL-C.

The Quebec cardiovascular study12 provides additional support for the concept that small LDL particles are unusually atherogenic. Its major finding is the apparent independence of the association between LDL particle size and CHD risk. Austin et al11 make similar claims but without the benefit of such a large prospective study. Despite their apparent “independence,” small LDLs often coexist with other lipoprotein abnormalities, notably slightly raised triglycerides and low HDL cholesterol. Actually, these three abnormalities are metabolically intertwined. Each one may be atherogenic, but separation of their relative contributions to atherogenesis is difficult. Because of this, the coexistence of slightly raised triglycerides, small LDL, and low HDL cholesterol has called forth the umbrella
term “atherogenic lipoprotein phenotype”.\(^4\)

The togetherness of raised triglycerides, small LDL, and low HDL, are not enough to justify the term “atherogenic” independently of some elevation of LDL cholesterol. In populations without raised cholesterol, CHD risk remains low even in the presence of the so-called “atherogenic lipoprotein phenotype”. An alternative term that includes LDL cholesterol as a component may be “atherogenic dyslipidemia”. The word dyslipidemia implies that lipoproteins are abnormal but plasma total lipids (cholesterol and triglycerides) are in the accepted “normal” range.

Therefore atherogenic dyslipidemia can be defined as a fourfold entity. Include borderline high-risk LDL cholesterol (130 to 159 mg/dL), moderately raised (often highnormal) triglycerides, small LDL particles, and low HDL cholesterol. In the Quebec study\(^{12}\) most patients who developed CHD showed this constellation of lipoprotein abnormalities. Atherogenic dyslipidemia probably imparts a risk for CHD at least equals to that of isolated, moderate hypercholesterolemia, the latter is for primary prevention. Moreover, atherogenic dyslipidemia may equal or exceed moderate hypercholesterolemia in prevalence.

Detection of small LDL particles frequently means that more LDL particles are present than indicated by LDL-cholesterol levels and it is possible that the number of LDL particles is more closely related to CHD risk than are levels of LDL cholesterol. The Quebec study\(^{12}\) and previous investigations\(^{16}\) suggest that a reduced particle size for LDL adds independently to the risk accompanying atherogenic dyslipidemia. This excess of LDL particles could account in part for the independent increment in risk accompanying small LDL. On the other hand, the Quebec data\(^{12}\) imply that the presence of small LDL per se enhances risk more than what can be explained by higher apo B levels alone. Smaller LDL particles may be more atherogenic than larger ones. The full picture is not clear. Possibly smaller LDL particles filter more readily into the arterial wall than the larger ones. Perhaps they are more prone to modification once they enter the wall.

Low level of high-density lipoprotein cholesterol (HDL-C), which is included in the Framingham algorithm for predicting multivariate CHD risk, is also a well-recognized risk factor,\(^{13}\) and there may be others as well.

Despite the results of the Quebec study, it is still difficult to define the independent contributions of several interrelated abnormalities in lipoproteins to atherogenesis. The problem is compounded by the fact that the multiple lipoprotein changes of atherogenic dyslipidemia commonly aggregate with other CHD risk factors,\(^{11}\) including hypertension, insulin resistance (with or without non–insulin-dependent diabetes mellitus), and a procoagulant state. This frequent aggregation of abnormalities in a single person can be called the syndrome of multiple metabolic risk factors or, for simplicity, the metabolic syndrome. (Table 2)

<table>
<thead>
<tr>
<th>Component Risk Factors</th>
<th>Contributing Causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atherogenic Dyslipidemia</td>
<td>Obesity (especially abdominal obesity)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Physical inactivity</td>
</tr>
<tr>
<td>Insulin resistance ± DM type 2</td>
<td>Cholesterol-raising nutrients</td>
</tr>
<tr>
<td>Procoagulant state</td>
<td>Aging</td>
</tr>
</tbody>
</table>

### THE METABOLIC SYNDROME

The “metabolic syndrome” is a cluster of risk factors including insulin resistance, elevated plasma triglyceride concentrations, low HDL-C levels and presence of small, dense LDL.\(^5\) The metabolic syndrome has a multifactorial etiology and results from the combination of obesity (especially abdominal obesity), physical inactivity, high intakes of cholesterol-raising nutrients, aging, and various genetic factors. All of these factors frequently coexist in single individuals in our society. Thus, any attempt to delineate the independent atherogenicity of one lipoprotein abnormality presumably requires adjustment for all the components of the metabolic syndrome. Such an attempt will undoubtedly prove problematic because of uncertainty in defining the severity of each risk factor. Indeed, it may ultimately be impossible to accurately delineate the independent contributions of each of the elements of the metabolic syndrome to CHD risk because of the confounding effects of the others.

The importance of the metabolic syndrome in terms of both prevalence and risk of CHD was also recognized in the recently published recommendations of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (also known as the Adult Treatment Panel)\(^{14}\). Unfortunately, this highly prevalent atherogenic condition is not currently considered in the Framingham algorithm. However, the risk of CHD may actually be much higher for this abdominally obese man, who has the features of the metabolic syndrome. Asymptomatic men with elevated waist circumference and moderate hypertriglyceridemia\(^{15}\) are characterized by an atherogenic triad of metabolic abnormalities (hyperinsulinemia, elevation of
apolipoprotein B and small, dense LDL particles) that substantially increases their risk for CHD, even in the absence of elevated cholesterol, elevated LDL-C and other traditional risk factors.16

Due to low HDL-C levels, the total cholesterol: HDL-C ratio of these abdominally obese, insulin-resistant men is often elevated to 7 or more. Data from the Quebec Cardiovascular Study8 indicate that elevation of the ratio to this level may be associated with an increased risk of CHD, even in the absence of elevated LDL-C levels. When the men in the Quebec Cardiovascular Study were stratified into tertiles according to baseline total cholesterol: HDL-C ratio and were further classified on the basis of median LDL-C level, there was a clear relation between total cholesterol: HDL-C ratio and risk of CHD, irrespective of LDL-C level (Table 3). Indeed, despite a highly significant difference in LDL-C (more than 38.46 mg/dL) between men below and those at or above the median LDL-C level, there was no significant difference in risk of CHD between these 2 groups, for any category of total cholesterol: HDL-C ratio (Table 3). These results further emphasize the importance of calculating the total cholesterol: HDL-C ratio and making it a therapeutic target.5

Thus, they also remind us that, irrespective of whether LDL-C level is elevated, a high total cholesterol: HDL-C ratio indicates higher risk of CHD. Elevation of the total cholesterol: HDL-C ratio in the absence of marked elevation of LDL-C level is a salient feature of insulin-resistant, abdominally obese patients, as well as of type 2 diabetic patients, most of whom are abdominally obese.15

Among men in the top tertile for total cholesterol: HDL-C ratio (ratio at least 6.4), there was a high prevalence of the metabolic syndrome (almost 40%), but there was no difference in the prevalence of this syndrome between subjects with low and high LDL-C levels (Table 4). Furthermore, the group with elevated total cholesterol: HDL-C ratio but low LDL-C level had a higher prevalence of obesity (defined as body mass index of at least 30) than those with elevation of both total cholesterol: HDL-C ratio and LDL-C levels (26.2% vs. 13.5%). Thus, elevation of the total cholesterol: HDL-C ratio is often accompanied by an underlying metabolic syndrome resulting from obesity, a condition that may not be associated with elevated LDL-C level. Pharmacotherapy aimed at lowering LDL-C is legitimate; however, given that the risk of CHD associated with elevation of the total cholesterol: HDL-C ratio does not vary substantially with LDL-C level, propose that more attention should be paid to the management of the causal factor responsible for atherogenic dyslipidemia in these patients: abdominal obesity.

Therefore, it is recommended that waist circumference “the best and simplest correlate of abdominal obesity”15 be measured and recorded for these patients. Furthermore, given that the Veterans Affairs High Density Lipoprotein Intervention Trial17 has reported the benefits of therapy to increase HDL-C among diabetic and abdominally obese hyperinsulinemic patients, strong efforts should be made to reduce waist girth and increase HDL-C levels in these high-risk “normocholesterolemic” patients.

Reducing body weight by reducing the caloric density of foods consumed and increasing energy expenditure through a more active lifestyle thus appear to be legitimate objectives for better management of propensity for CHD in high-risk patients with the metabolic syndrome.18

**Metabolic Syndrome in Asia**

Metabolic syndrome pandemic and the rapidity with which the disorder develops together with the
Pan19 compared the age-standardized prevalence of the metabolic syndrome among 2500 Taiwanese adults (during 1993-1996) with Americans of African or Caucasian origin (during 1988-1994). The waist circumference criteria were reduced for Taiwanese to 80 cm and 90 cm, respectively, for women and men. The metabolic syndrome was found in 14% of Taiwanese compared with 20% of African Americans and 23% of the US whites. The data for American adults during the period from 1988 to 1994 showed an overall 24% prevalence of the metabolic syndrome, which affected approximately half of elderly Americans.20 Among the Taiwanese, the most commonly occurring components were hypertension (23%), large waist (18%), and hypertriglyceridemia (>200 mg/dL: 11%). Individual components of the metabolic syndrome compiled for 4541 adults in the Philippines in 199921 showed obesity (body mass index (BMI), >25 kg/m² among 19% of these adults, a low HDL-C level (<35 mg/dL) in 65%, raised blood pressure (>140/90) in 17%, and raised TG levels in 9% of these Philippine adults.

While in Indonesia, research by the Indonesian Society for The Study of Obesity (ISSO) has come up with a BMI value that suitable for Indonesia male and female. The research finds that the Indonesian BMI for Obesity is 24.9 kg/m² and weight circumference for obese male is 88.7 cm.23 The latest study by Soegondo24 showed that BMI 25 kg/m² is more appropriate. A cross sectional study on male population, aged 30 years old or older, with obese and non obese condition, was taken in Jakarta, West Java, and Banten. Approximately 205 obese subjects and 92 non-obese subjects from 297 subjects have been studied. This study revealed that the appropriate BMI cutoff is 27.17 kg/m². This means that the metabolic syndrome develops in this cut off. Using that value, this study found the metabolic syndrome in 13.13% subjects. This study statistically proved that Indonesian population should use the Asia Pasific criteria (BMI 25 kg/m²), despite the WHO criteria (BMI 30 kg/m²), in order to prevent the CHD.

Hypertension and reduced HDL-C were, thus, the two main components of the metabolic syndrome. With a different set of criteria based on the International Atherosclerosis Society’s harmonized guidelines, the prevalence of metabolic syndrome components increased substantially with an overall 19.3% prevalence of the metabolic syndrome.

Multietnic population (e.g. Singaporean Indians, Chinese, and Malays) striking differences have been reported.22 The Malays were the fattest and most hypertensive of these three groups, while the Singaporean Indians had the largest waist, which was associated with the most insulin resistance (raised plasma insulin concentration, low HDL-C, and raised TG and plasminogen activator inhibitor I [PAI-I] concentrations). The complexity of dissociating genetic predisposition from different patterns of eating, which may explain differences among ethnic groups, has not been attempted adequately.

Tan and Tai25 examined the interrelationships between nutritional and genetic influences on biomarkers of the metabolic syndrome among the three ethnic populations of Singapore. They demonstrated that the associations between the HDL-C concentration and polymorphisms in several key regulatory genes, such as cholesteryl ester transfer protein (CETP). Perhaps the most revealing information of the rapid rise in the metabolic syndrome among Asians has come from China. The China multiprovince cohort study was recorded among 29,488 adults during 1992 to 2002. In the Beijing cohort. The prevalence of the syndrome increased from 9% to 21%, and abdominal obesity (Asian criteria for waist circumference) rose from 8% to 23%. Hypertriglyceridemia (>150 mg/dL) increased from 19% to 33%, and hypertension 130/85) from 43% to 61%.18

In a short time period. The metabolic syndrome in Asia seems to have reached the prevalence reported for European populations.

The Indonesian Society of Endocrinology has proposed new guidelines for dyslipidemia management in Indonesia26. This guideline contains basic and advances adequate therapy for dyslipidemia management, particularly in Indonesia. In Indonesia, dyslipidemia characterized into 3 (three) major categories (Table 5).

By these standards, Physicians in Indonesia are hoping to be an ‘early bird’ to catch and prevent CHD, by managing dyslipidemia in early state.
Table 5. Classification of Dyslipidemia in Indonesia

<table>
<thead>
<tr>
<th>Total Cholesterol (mg/dL)</th>
<th>LDL-C (mg/dL)</th>
<th>HDL-C (mg/dL)</th>
<th>Triglyceride (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Desirable level</td>
<td>&lt; 200</td>
<td></td>
<td>Normal</td>
</tr>
<tr>
<td>Borderline high</td>
<td>200 – 239</td>
<td>Low</td>
<td>&lt; 150</td>
</tr>
<tr>
<td>High level</td>
<td>&gt; 240</td>
<td>High</td>
<td>150 – 199</td>
</tr>
<tr>
<td>LDL-C (mg/dL)</td>
<td></td>
<td></td>
<td>High</td>
</tr>
<tr>
<td>Optimal</td>
<td>&lt; 100</td>
<td>&lt; 40</td>
<td>&gt; 200 – 499</td>
</tr>
<tr>
<td>Near optimal</td>
<td>100 – 129</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Borderline high</td>
<td>130 – 159</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>160 – 189</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Very high</td>
<td>≥ 190</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HDL-C (mg/dL)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>&lt; 40</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>≥ 60</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Triglyceride (mg/dL)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>&lt; 150</td>
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<td>Borderline high</td>
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<tr>
<td>High</td>
<td>200 – 499</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Very high</td>
<td>≥ 500</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CONCLUSION

The overall impact of the metabolic syndrome on atherogenesis, nevertheless, is a need of increasing importance. It is well established that hypercholesterolemia promotes atherosclerosis and enhances CHD risk. Effective therapeutic modalities for reducing elevated LDL are now in place. Establishing the role of hypercholesterolemia and the development of effective management are major steps forward. The next step in prevention of CHD should focus on control of the metabolic syndrome, which appears to rival hypercholesterolemia in atherogenic potential. Other metabolic risk factors assume increased importance once the LDL-cholesterol level are raised. Therefore, decreasing LDL levels is the centerpiece of therapy for reducing CHD risk in patients with the metabolic syndrome as well as in the treatment of hypercholesterolemia. This strategy gives appropriate attention to raised LDL as the primary cause of coronary atherosclerosis.

An additional need is to develop therapeutic strategies that will modify the metabolic syndrome as a whole. The possibility of discovering new drugs that can strike at the heart of the metabolic syndrome has been proposed. From a public health perspective, the major causes of the metabolic syndrome are unhealthy life habits. Hence, for the general public, the best approach to favorably modifying the whole syndrome is through weight control, increased physical activity, and decreased intake of LDL-raising nutrients. For individuals, one or another metabolic abnormality may predominate. When this occurs, genetic aberrations most likely are at fault. In such cases, drug therapy directed toward individual risk factors may be needed. It must be recognized, however, that for many patients this bit by bit approach will incompletely control several coexisting risk factors.

More investigation of the key metabolic steps that affect multiple pathways simultaneously thus will be required to yield a satisfactory therapy for high-risk patients exhibiting the metabolic syndrome.

REFERENCES


