Proposed Guidelines for Hypertriglyceridemia in Japan with Non-HDL Cholesterol as the Second Target


The Research Committee for Primary Hyperlipidemia, Research on Measures for Intractable Diseases by the Ministry for Health, Labor, and Welfare in Japan.

The Japan Atherosclerosis Society (JAS) guidelines for the prevention of atherosclerotic diseases, proposing management for LDL cholesterol as the primary target, have successfully contributed to the prevention of cardiovascular events; however, recently, the impact of hypertriglyceridemia as an additional cardiovascular risk has become understood, especially in light of the rise in obesity, metabolic syndrome, and diabetes in the Japanese population. Rather than waiting to obtain conclusive domestic data confirming that hypertriglyceridemia is a cardiovascular risk factor and that its management is efficacious, we propose guidelines for hypertriglyceridemia using non-HDL cholesterol as a second target.


Key words: Hyperlipidemia, Dyslipidemia, Triglycerides, HDL cholesterol, LDL cholesterol

Introduction

Many prospective epidemiological studies have indicated a positive relationship between serum triglyceride (TG) levels and the incidence of coronary heart disease (CHD). TG-rich lipoproteins such as remnant lipoproteins and small dense LDL particles are increased in hypertriglyceridemia and have been established to be atherogenic by numerous clinical and experimental studies; however, classification of the plasma TG level as an independent risk factor for atherosclerosis has been controversial. This is partly because plasma TG levels are inversely intercorrelated by other well-established risk factors, such as low HDL cholesterol. To date, large scale trials for intervention targeting plasma TGs with TG reducing agents such as fibrates have not reached definitive conclusions about their effectiveness on primary endpoints, although fibrates have some impact on both primary and secondary prevention in small scale studies.

The precise estimation of plasma TGs as a cardiovascular risk is confounded by other risk factors, such as obesity, diabetes, hypertension and smoking. In addition, a cluster of metabolic risk factors, such as visceral obesity and insulin resistance with hypertriglyceridemia, referred to as metabolic syndrome, indicates that plasma TG concentrations are tightly linked to other strong risk factors for CHD. Thus, patients with elevated TGs are at increased risk for CHD, although greater risk cannot be independently explained by TGs. Meanwhile, recent meta-analyses suggested that plasma TGs could be an independent factor for CHD.

Supportively, many experimental studies indicated that triglyceride-rich lipoproteins as well as LDL are atherogenic. Taken together, these data suggest that hypertriglyceridemia should be regarded as a semi-independent risk factor and should be included as a clinical target for the prevention of CHD. Considering the increasing prevalence of obesity, metabolic syndrome, and diabetes in this country, guidelines specialized for patients with hypertriglyceridemia need to be immediately established. In this study, we propose new guidelines for Japanese patients with hypertriglyceridemia.
Table 1. Plasma lipid profile of severe and mild type IIb hyperlipidemic patients sub-grouped by non-HDL cholesterol level

<table>
<thead>
<tr>
<th></th>
<th>Male</th>
<th>Female</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>severe type IIb</td>
<td>mild type IIb</td>
</tr>
<tr>
<td></td>
<td>non-HDLc</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt;190 mg/dL</td>
<td>&lt;190 mg/dL</td>
</tr>
<tr>
<td>n</td>
<td>51</td>
<td>54</td>
</tr>
<tr>
<td>Total Cholesterol</td>
<td>270 ± 41.8</td>
<td>234 ± 40.3</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>347 ± 286</td>
<td>236 ± 110</td>
</tr>
<tr>
<td>HDL Cholesterol</td>
<td>42.4 ± 8.0</td>
<td>54.9 ± 15.2</td>
</tr>
<tr>
<td>LDL Cholesterol</td>
<td>159 ± 51.6</td>
<td>135 ± 38.1</td>
</tr>
<tr>
<td>non-HDL Cholesterol</td>
<td>228 ± 41.6</td>
<td>182 ± 39.1</td>
</tr>
</tbody>
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Subjects were patients who visited the outpatient clinic of the Endocrinology and Metabolism Unit of Tsukuba University Hospital on a regular basis (monthly or bimonthly) as described in Materials and Methods. Data are the means ± SD (mg/dL).

using non-HDL as a secondary target after the goal for LDL cholesterol as the primary target is achieved.

Materials and Methods

A total of 1,124 patients in Tsukuba University hospital in 2006 were consecutively included in the study (Table 1). Patients with severe illness were excluded. Plasma total cholesterol (TC), LDL-C, TG, HDL-C, glucose and HbA1c in either the fasted or fed state were determined enzymatically with the Hitachi 7070. Plasma HDL-C concentration was measured by a direct method using polyethylene-glycoso-pretreated enzymes. We calculated LDL-C concentration with Friedewald's formula (TC-TG/5-HDL-C) when TG was less than 400 mg/dL. Plasma non-HDL-C concentration was calculated as TC - HDL-C. One hundred and five male and 100 female patients were diagnosed with Type IIb hyperlipidemia (TC > 220 mg/dL and TG > 150 mg/dL). They were subcategorized into two groups according to their non-HDL cholesterol level (Table 1).

Results and Discussion

Advantage of Non-HDL Cholesterol as a Marker for Hypertriglyceridemia

LDL cholesterol has been established as the most potent predictor of CHD and is currently the primary target for treatment and prevention. Other risk factors, including TG, diabetes, obesity, and metabolic syndrome, do not directly elevate plasma LDL cholesterol, but could enhance the risk of LDL cholesterol by shifting up the curve, as depicted in Fig. 1. To evaluate and manage the risk of hypertriglyceridemia, the TG level must be interpolated into the risk of plasma cholesterol. In patients with high TGs, most VLDL cholesterol resides in the smaller (remnant) VLDL fraction. Cholesterol of remnant lipoproteins (VLDL and IDL), which is concomitantly increased by elevation of plasma TG is an appropriate surrogate marker of hypertriglyceridemia. TG-rich remnant lipoproteins have been established as atherogenic lipoproteins. Thus, RLPc, a commercially available laboratory test for remnant lipoprotein cholesterol, could be a suitable marker for the atherogenicity of hypertriglyceridemia; however, this test is expensive and is not practical for use as a routine parameter. In contrast, non-HDL cholesterol, defined as total cholesterol – HDL cholesterol, is easily calculated, and represents the sum-
mation of VLDL/IDL (remnant) cholesterol and LDL cholesterol. It reflects the risks for all apoB-containing lipoproteins and could be an excellent marker for atherogenic lipoproteins. Plasma TG itself is not an appropriate marker for CHD risk due to its internal and dietary variability. In contrast, non-HDL cholesterol is not affected by dietary states and has much less daily variability than TG.

**Predictive Power of Non-HDL Cholesterol**

Non-HDL cholesterol reflects the risks of both hypertriglyceridemia and LDL-cholesterol\(^{10,11}\). Several studies have indicated that non-HDL cholesterol is better than LDL cholesterol in its predictive power of cardiovascular diseases, indicating that VLDL cholesterol could contribute to CVD\(^{15}\). Non-HDL cholesterol is also a useful marker in a variety of subpopulations: men, the elderly, and patients with high-risk diseases such as diabetes and end-stage renal disease\(^{13-16}\). Our current clinical data from patients with type IIb hyperlipidemia also support the usefulness of non-HDL cholesterol (Table 1). In our outpatient clinic, 70% of patients had diabetes and roughly 10% were type IIb hyperlipidemia (cholesterol > 220 mg/dL and TG > 150 mg/dL). These type IIb hyperlipidemic patients were equally divided into two sub-groups: severe (non-HDL cholesterol levels ≥ 190 mg/dL for male patients and 180 mg/dL for female patients) and mild < 190 mg/dL for male patients and 180 mg/dL for female patients. When the severe and mild IIb groups were compared, total, LDL, HDL cholesterol, and TG levels were significantly different among these two groups for both genders, except for serum triglyceride in females (Table 1). These data indicate that non-HDL cholesterol is an excellent marker representing all the components of dyslipidemia. The usefulness of non-HDL cholesterol rather than low-density lipoprotein cholesterol as a tool for lipoprotein cholesterol screening and assessment of risk and therapy has been already recognized in the USA\(^{17,18}\). Another candidate marker for both remnant and LDL cholesterol is plasma apoB level\(^{19}\). ApoB is a direct marker for the particle number of apoB-containing lipoproteins and reflects risks of both remnants and LDL. Non-HDL cholesterol is highly correlated with apoB, and should replace this specialized and expensive laboratory test despite some reports indicating that apoB is better than non-HDL cholesterol for the predictive power of CHD\(^{13,20}\).

However, according to the Friedewald formula, the TG risk in non-HDL cholesterol represents only one fifth of TG levels as remnant cholesterol, and thus, the contribution of the risk is relatively weak compared to that of LDL cholesterol. Our previous data indicated that the correlation of non-HDL cholesterol to LDL cholesterol was much stronger than that to the TG level (Fig. 2)\(^{21}\). It should be noted that non-HDL cholesterol is not a specific marker for hypertriglyceridemia. Rather, non-HDL cholesterol should be regarded as a general single marker for both hypercholesterolemia and/or hypertriglyceridemia.

**Proposed Guidelines for Hypertriglyceridemia**

Based upon these considerations, we propose guidelines for hypertriglyceridemia in Japanese patients using non-HDL cholesterol as a secondary target, as shown in Table 2. This is an extended version of the 2007 edition of the Japan Atherosclerosis Society (JAS) guidelines for the prevention of atherosclerotic diseases in which LDL cholesterol is the primary marker and target. It is essentially similar to the AHA-ATPIII guidelines for hyperTG in USA\(^{22}\). ATPIII recommends using non-HDL cholesterol as a secondary target when plasma TG is greater than 200 mg/dL because VLDL cholesterol is not significantly accumulated if TG is less than 200 mg/dL\(^{23}\). We do not have enough clinical data for Japanese on the relationship between TG and VLDL cholesterol to provide the appropriate TG level where the use of a non-HDL marker should be considered. Currently, we recommend using non-HDL for patients with hypertriglyceridemia (TG > 150 mg/dL). Even for patients with hypertriglyceridemia, the primary target is still LDL cholesterol. In the 2007 JAS guidelines, goals of LDL for the secondary prevention group and the primary prevention group with category I, II, and III are 100, 120, 140, and 160 mg/
Table 2. Proposed Japanese Guidelines for Hypertriglyceridemia

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Categories</th>
<th>Goal for plasma lipids (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Coronary Risk Factors</td>
<td>Primary LDL-C</td>
</tr>
<tr>
<td></td>
<td>other than LDL-C</td>
<td>&lt;160</td>
</tr>
<tr>
<td>Primary Prevention</td>
<td>I (Low Risk Group)</td>
<td>0</td>
</tr>
<tr>
<td>Improving lifestyle as the first</td>
<td>II (Intermediate)</td>
<td>1~2</td>
</tr>
<tr>
<td>line, followed by medication</td>
<td>III (High)</td>
<td>≥3</td>
</tr>
<tr>
<td>Secondary Prevention</td>
<td>Past History of CHD</td>
<td>Past History of CHD</td>
</tr>
</tbody>
</table>

Goals for control depend upon categories of LDL cholesterol and non-HDL cholesterol. The primary target in hypertriglyceridemia is LDL-cholesterol. If the goal for LDL-cholesterol in the Japanese Guidelines for Atherosclerosis 2007 is already achieved, nonHDL-C is the secondary target. For the patients with TG >500 mg/dL, potential genetic disorders and the prevention of acute pancreatitis should be considered. Coronary risk factors other than LDL-cholesterol include low HDL cholesterol, aging, diabetes, hypertension, smoking, past history of CHD, and obesity (visceral obesity).

dL, respectively. Goals for non-HDL cholesterol in each group are those for LDL cholesterol plus 30 mg/dL. This is based upon our outpatient clinic data that non-HDL cholesterol was 30 mg/dL higher than LDL cholesterol (Fig. 2)\(^{21}\). ATPIII also recommends using LDL cholesterol goal + 30 mg/dL.\(^ {24}\) This also corresponds to the calculated VLDL cholesterol of the cut-off point of normal TGs (150/5 mg/dL). This goal is arbitrarily set and could be modified in the future, especially when the relative atherogenicity of remnants and LDL cholesterol are more precisely determined. In the case of TGs of greater than 500 mg/dL, the risk of pancreatitis should be carefully considered as a potential acute complication.

**Treatment of Hypertriglyceridemia Based upon Non-HDL Cholesterol Level**

Treatment of patients with hypertriglyceridemia for primary prevention should be initiated with lifestyle modifications, especially reducing weight and increasing physical activity. Lifestyle exacerbating hypertriglyceridemia, such as overweight, obesity, physical inactivity, cigarette smoking, excess alcohol intake, and very high carbohydrate diets, need to be improved. Other disorders and drugs that cause secondary hypertriglyceridemia, including diabetes, chronic renal failure, nephrotic syndrome, and steroid therapy, should also be treated first. In the event that lifestyle modification for at least three months is not effective to achieve the goal of non-HDL cholesterol, medication should be considered. Currently, due to lack of evidence to fully justify the use of fibrates for high TGs prior to statins, it is recommended to use a statin as the first line choice for high non-HDL cholesterol. If statin therapy is already used to control LDL cholesterol, management of non-HDL should be targeted by increasing the dose of the statin or switching to a stronger form. This is based upon the notion that remnant lipoproteins, as well as LDL, are taken up through LDL receptors that are up-regulated by statins. In the case of type III hyperlipidemia, or if high non-HDL cholesterol is much more prominent than LDL cholesterol because of hypertriglyceridemia, fibrates could be considered as they specifically reduce plasma TGs and are effective against type III hyperlipidemia. However, LDL cholesterol should be carefully monitored since fibrates occasionally raise LDL cholesterol following a decrease in TGs (VLDL cholesterol). In the case the goal for LDL cholesterol is not attainable, the addition of cholestimide and/or ezetimibe to statin could be considered, whereas EPA could be considered for hypertriglyceridemia. A positive result from a recent large scale Japanese study using both EPA and pravastatin to estimate the prevention of atherosclerotic events, justifies superimposing EPA on statin therapy, although the contribution of the plasma TG-lowering effect of EPA to the prevention of cardiovascular events is not yet determined.\(^ {25}\) The complexity of the choice of medication for high non-HDL cholesterol is currently inevitable because no agents specifically decrease non-HDL cholesterol. Drug information strongly warns against the use of both statins and fibrates because of increasing the risk of the life-threatening side effect of rhabdomyolysis. Joint use is justified only when the benefit exceeds the risk, which requires expertise in this field; however, considering the very few reports of rhabdomyolysis as a severe side effect in recent post-market studies in Japan, carefully prescribing both agents for high-risk patients such as those with type IIb hyperlipidemia could be re-considered. Joint use might be restricted in the elderly or renal compromised patients. In addition, monitoring mus-
cle symptoms and plasma creatine phosphokinase is necessary in patients prescribed either statins or fibrates.

Conclusions and Future Prospect of the Guidelines

Non-HDL cholesterol containing both LDL cholesterol and remnant cholesterol, is an excellent predictor of atherosclerotic risk, and should be a treatment target. Non-HDL cholesterol is simple, convenient, and free from dietary variations. These advantages are crucial for nation-wide use of the guidelines and health check activity. This simple measurement could also make it possible to re-evaluate previous clinical studies using this parameter to offer a good chance of estimating the usefulness and importance of this marker in a large meta-analytical scale.

In the current study, we propose that LDL cholesterol is the primary target and non-HDL cholesterol should be the secondary target for elevated TG. Considering that non-HDL and LDL cholesterol are partially redundant, non-HDL could replace LDL as the primary target and as a general marker for both elevated cholesterol and TG. As Table 1 shows, non-HDL cholesterol could be used as a general and convenient lipid marker for type IIb hyperlipidemia.

This proposal still faces the recent problem of selecting lipid markers for the initial assessment for dyslipidemia. The recent GL focus has been on LDL cholesterol rather than TC, while LDL cholesterol has a problem the lower reliability for direct measurement. In addition, a considerable portion of hypertriglyceridemia is not applicable to this equation. For subjects with hypertriglyceridemia, application of this new GL eventually requires all TC, TG, HDL, and LDL cholesterol measurements to assess both LDL and non-HDL cholesterol. Currently, however, the Japanese medical system covers only three out of four lipid measurements as healthcare services provided by health insurance. Further Japanese clinical studies and careful evaluation of the data, as well as technical improvements of reliable LDL cholesterol measurements, are required to determine the most efficient protocol to select lipid measurements as the initial assessment of dyslipidemia to prevent CVD in Japan. Furthermore, guidelines for HDL cholesterol should also be established, although the relative importance and positioning of non-HDL and HDL is yet to be determined.

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References

and apolipoprotein B in the prediction of coronary heart disease in men. Circulation, 2005; 112:3375-3383