Introduction

Many prospective epidemiological studies have indicated a positive relationship between serum triglyceride (TG) levels and incidence of coronary heart disease (CHD) (1,2). TG-rich lipoproteins such as remnant lipoproteins and resultant small dense LDL particles are increased in hypertriglyceridemia and have been established to be atherogenic by numerous clinical and experimental studies (3-6). However, classification of plasma TG level as an independent risk factor for atherosclerosis has been controversial. It 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 for their effectiveness on primary endpoints, although fibrates have some impact on both primary and secondary prevention in small scale studies (7-9).

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, clustering of metabolic risk factors such as visceral obesity and insulin resistance with

hypertriglyceridemia, referred to as metabolic syndrome, indicate 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 (1,2). 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 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 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 1124 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 were taken in either fasted or fed state 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. A hundred and five male and 100 female patients were diagnosed with TypeIIb hyperlipidemia (TC > 220 mg/dl and TG > 150 mg/dl). They were subcategorized into two groups according to 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 for 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 the LDL cholesterol by shifting up the curve as depicted in Figure 1. To evaluate and manage the risk of hypertriglyceridemia, TG level must be interpolated into the risk of plasma cholesterol. In patients with high TGs, most of VLDL cholesterol resides in smaller (remnant) VLDL fraction. Cholesterol of remnant lipoproteins (VLDL and IDL) that 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 (4,5). 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 summation of VLDL/ IDL (remnant) cholesterol and LDL cholesterol. It reflects 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 hypertrigyceridemia and LDL-cholesterol (10) (11). Several studies indicate that non-HDL cholesterol is better than LDL cholesterol for a predictive power of cardiovascular diseases, indicating that VLDL cholesterol could contribute to CVD(12). 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 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 female (Table 1). These data indicate that non-HDL cholesterol is an excellent marker representing all the components of dyslipidemia. 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 United States of America (17,18). Another candidate marker for both remnant and LDL cholesterol is plasma apoB level (19). ApoB is a direct marker for particle number of apoB-containing lipoproteins and reflects risks for both remnants and LDL. Non-HDL cholesterol is highly correlated with apoB, and should be its replacement for 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 equation, 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 as compared to that of LDL cholesterol. Our previous data indicated that correlation of non-HDL cholesterol to LDL cholesterol was much stronger than that to TG level (Figure 2 and (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 Fig. 3. It is an extended version of the 2007 edition of the Japan Atherosclerosis Society (JAS) guidelines for prevention of atherosclerotic diseases in which LDL cholesterol is the primary marker and target. It is essentially similar to the AHA-ATPIII guideline for hyperTG (22). ATPIII recommends to use non-HDL cholesterol as the 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 relationship between TG and VLDL cholesterol to provide the appropriate TG level where use of non-HDL marker should be considered. Currently we recommend to use non-HDL for the patients with hypertriglyceridemia (TG > than 150 mg/dl). Even for the patients with hypertriglyceridemia, the primary target is still LDL cholesterol. In the 2007 JAS guidelines, goals of LDL for secondary prevention group, primary prevention group with the category I, II, and III are 100, 120, 140, and 160 mg/dl, respectively. Goals for non-HDL cholesterol in each group are those for LDL cholesterol plus 30 mg/dl. It is based upon our outpatient clinic data that non-HDL cholesterol was 30 mg/dl higher than LDL cholesterol level (Figure 2 and (21)). ATPIII also recommends to use LDL cholesterol goal + 30 mg/dl (24). This also corresponds to calculated VLDL cholesterol of 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, 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 to exacerbate hypertrigylyceridemia 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 filure, nephrotic syndrome, and steroid therapy should also be treated first. In the event that lifestyle modification at least for three months is not effective to achieve the goal for 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 for control of 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 notion that remnant lipoproteins, as well as LDL, are taken up through LDL receptors that are up-regulated by statins. In 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 decrease in TGs (VLDL cholesterol). In case the goal for LDL cholesterol is not attainable, 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 estimating prevention of atherosclerotic events justifies superimposing EPA to statin therapy, although the contribution of plasma TG lowering effect of EPA to the prevention of cardiovascular events is not yet determined (25). The complexity for the choice of medication for high non-HDL cholesterol is currently inevitable because there are no agents to specifically decrease non-HDL cholesterol. Drug information strongly warns

against use of both statins and fibrates because of increasing risk of the life-threatening side effect rhabdomyolysis. The joint-use is justified only when the benefit exceeds the risk, which requires expertise of this field. However, considering very few number of reports of rhabdomyolysis as severe side effects in recent post-market studies in our country, it could be re-considered to carefully prescribe both agents for high risk patients such as those with type IIb hyperlipidemia. However, the joint-use might be restricted in cases of the elderly or renal compromised patients. In addition, monitoring of muscle symptoms and plasma creatine phosphokinase is necessary in the patients prescribed either statins or fibrates.

Conclusions and future prospect of the guidelines

Non-HDL cholesterol includes both LDL cholesterol and TG, is an excellent predictor of atherosclerotic risk, and should be the target for treatment. Non-HDL cholesterol is simple, convenient, and free from dietary variations. These advantages are crucial for nation-wide use of the guideline and health check activity. This simple measurement could also make it possible to re-evaluate previous clinical studies using this parameter

to provide a good chance to estimate of 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 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 both hypercholesterolemia and hypertriglyceridemia.

This proposal still encounters a recent problem of selection of lipid markers for initial assessment for dyslipidemia. The recent GL focus on LDL cholesterol rather than TC, while LDL cholesterol is recommended to be calculated by Firedewald equation using TC because of less liability of its direct measurement. In addition, a considerable portion of hypertriglyceridemia cannot be 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, Japanese medical system covers only three out of four lipid

measurements, as healthcare services provided by health insurance. Further Japanese clinical studies and careful estimation of the data, as well as technical improvement of reliable LDL cholesterol measurement, are required to determine the most efficient protocol of selection of lipid measurements as an initial assessment of dyslipidemia for prevention of CVD in Japan. Furthermore, guidelines for HDL cholesterol also need to be set up, although relative importance and positioning of non-HDL and HDL is yet to be determined.

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Table 1. Plasma lipid profile of severe and mild type IIb hyperlipidemic patients sub-grouped by non-HDL cholesterol level.

Male	severe typeIIb	mild typeIIb	
	non-HDLc		
	> 190 mg/dl	< 190 mg/dl	p
n	51	54	
Total Cholesterol	270 ± 41.8	234 ± 40.3	0.001
Triglycerides	347 ± 286	236 ± 110	0.031
HDL Cholesterol	42.4 ± 8.0	54.9 ± 15.2	0.000
LDL Cholesterol	159 ± 51.6	135 ± 38.1	0.029
non-HDL Cholesterol	228 ± 41.6	182 ± 39.1	0.000

Female	severe typeIIb	mild typeIIb	
	non-HDLc		
	> 180 mg/dl	< 180 mg/dl	p
n	52	48	
Total Cholesterol	265 ± 29.6	231 ± 20.2	0.000
Triglycerides	242 ± 120	218 ± 56	0.1
HDL Cholesterol	47.3 ± 14.1	63.2 ± 19.5	0.000
LDL Cholesterol	175 ± 40.4	125 ± 17.9	0.000
non-HDL Cholesterol	224 ± 30.2	168 ± 14.9	0.000

Subjects were patients who visited outpatient clinic of Endocrinology and Metabolism Unit of Tsukuba University Hospital on regular basis (monthly or bimonthly) as described in materials and methods. Data are means ± SD (mg/dl).

Figure Legends

Figure 1 Rationale for usage of non-HDL cholesterol: Impact of TG and other risk factors on LDL-cholesterol-CHD event relationship

nonHDL cholesterol = Total cholesterol – HDL cholesterol = VLDL cholesterol + IDL cholesterol + (remnant lipoprotein cholesterol) + LDL cholesterol (Friedewald equation).

VLDL cholesterol + IDL cholesterol (RLP cholesterol) ≈ TG / 5

The risk of hypertriglyceridemia is approximated to VLDL, IDL, and RLP cholesterol estimated as TG/5, and incorporated into non-HDLC. The difference between non-HDL cholesterol and LDL cholesterol was set up at 30 mg/dl based upon the data from Figure 2.

Figure 2. Distribution of non-HDL cholesterol vs. calculated LDL cholesterol in normolipidemic patients.

Non-HDL cholesterol and LDL cholesterol calculated from Friedewald formula were

highly correlated. Subjects were from outpatient clinic of Tsukuba University Hospital (21).

Figure 3 Proposed Japanese Guidelines for Hypertriglyceridemia

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