Prevention of Cardiovascular Disease in Diabetes Mellitus: by Stressing The CARDS Study

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ABSTRACT

Recently, diabetes mellitus has become a global epidemic disease. There is a study indicating that type 2 diabetes mellitus (DM) is frequently found in children and teenager. Furthermore, in some countries, it is more frequent than type 1 diabetes mellitus. WHO stated that in the year of 2000, there were 177 million diabetes mellitus patient in the world and it is predicted that in the year of 2030, it will be increased to 366 million. This is very problematical for some countries such as India, People’s Republic of China and Indonesia where the prevention and treatment facilities are still inadequate. To date, Indonesia has occupied the 4th rank, with predicted number of diabetes mellitus patient about 8.4 million and this number will be increased to 21.3 million in the year of 2030. There is no data about the number of patient with metabolic syndrome (MS) and insulin resistance syndrome (IR), but it should be higher than the number of diabetic patient. As we all have known, these conditions are the high-risk condition of diabetes mellitus development.

One of reasons concerning why prevalence and pre-diabetic condition are increased (including the increased MS) is rising obesity frequency. In the United States, over 60% of recent adult population are overweight, which is defined as “body mass index” (BMI) 25; and about 30% of them have obesity, which is defined as BMI 30%. If diabetes mellitus occurred, cardiovascular disease (CVD) including coronary heart disease (CHD) also may occur. It is important to prevent the diabetes mellitus as well as to prevent the complication risk of CVD in diabetic patient.

Key words: cardiovascular disease, coronary heart disease, diabetes mellitus.

INTRODUCTION

Cardiovascular diseases, including CHD, stroke and peripheral vascular disease, is the cause of death in about 80% diabetic patient and 75% hospitalization care of diabetes mellitus patient due to CVD. Besides that, since the new diabetes mellitus patient did not have any clinical symptoms for years, then there is 1 of 3 diabetes mellitus patient which is undetected, even in developed country such as United States. Therefore, it is not surprising if in one-third of diabetic patient, we found CVD along with the first diagnosis of diabetes mellitus is established.

The effect of diabetes mellitus on increased frequency of CVD has been studied in many epidemiologic studies. Framingham study demonstrated a study with 30 years follow-up period of increasing frequency of CVD such as CHD, heart failure, claudicatio intermittent and stroke in diabetes mellitus patient compared to the non-diabetic patient with the age range of 35-64 years. Female diabetes mellitus patient also has greater CHD risk than non-diabetic female.

Krolewski et al compared a long-term result at Joslin Diabetic Center with non-DM patient in Framingham study. They found a two-fold higher CVD mortality in male patients, and 4-5 folds higher in female diabetic patients. This is interesting, because the absolute frequency of CVD frequency in non-diabetic female usually is lower than non-diabetic male.

Data comparison of National Health and Nutrition Examination Survey (NHANES) between the year of 1982 and 1984, which was compared to the data between 1971 and 1975, indicated that there was a decrease of CHD from 37% to 27% in non-diabetic male and non-diabetic female patients. But the decreased CVD mortality rate in diabetes mellitus patient was not so high. In addition, there was increased mortality rate in female diabetic patients.

Hence, a question comes up: What are the factors that may increase the risk of CVD in diabetes mellitus patient? What can we do to prevent the increase of CVD in male and female diabetes mellitus patient?
An analysis of Multiple Risk Factor Intervention Trial (MRFIT) study, which involved more than 350,000 men, including 5000 diabetes mellitus patient, demonstrated that the mortality risk of diabetic patient caused by CVD is much higher if there is one or more of risk factors as follows: total cholesterol level over 200 mg/dl, smoking, systolic blood pressure over 120 mmHg. This result indicates that there should be more intensive management of risk factors in diabetic patient, because the blood vessel of diabetic patient is more vulnerable against deleterious effect of high cholesterol blood level, smoking, hypertension and other factors. Similar result has been reported by United Kingdom Prospective Diabetes Study (UKPDS) study, indicating a lower frequency of cardiovascular incidence in average pressure vessel of 144/82 compared to average blood pressure of 154/87 mmHg.

In seven years follow-up period, the non-diabetic patient has 3.5% incidence of myocardial infarction (MI). In diabetes mellitus patient, the risk of first MI is similar to the non-diabetic patient who has had a MI. In type 2 diabetes mellitus patient who has had chronic MI, the risk of new MI in seven years follow up period is 45%. From this study, we can conclude that diabetes mellitus is an equivalent cardiovascular risk factor, which means that diabetes mellitus patient is assumed to have CVD risk equivalent to the non-diabetic patient who has had a cardiovascular incident.

FACTORS CAUSING INCREASED CVD IN DIABETES MELLITUS

Many factors have an important role of hastening the atherogenesis process in diabetes mellitus patient. Dyslipidemia is the most important factor. In addition to the increased LDL cholesterol, which has a high frequency in general population, the diabetes mellitus patient has a specific lipid disorder, including: high triglyceride lipoprotein, low HDL cholesterol level, and alteration of LDL cholesterol composition, which has become smaller, more crowded, and more atherogenic. Other mechanisms include hyperglycemia, oxidative stress, endothelial dysfunction, hematological changes which lead to a pro-coagulant state (increased platelet aggregation, increased fibrinogen, decreased fibrinolysis, increased PAI-1), hypertension, and the IR condition.

Therefore, in Adult Treatment Panel III (ATP III) of the National Cholesterol Education Program (NCEP), diabetes mellitus as a risk factor of CVD is regarded equivalent to a patient who has experienced CVD. The 10-years risk of diabetes mellitus patient who has CVD is over than 20%, which is equivalent to the risk of patient who has experienced CVD.

METABOLIC SYNDROME (MS)

The MS term has undergone a lot of evolution. In 1988, Dr. Gerald Reaven was associated to the term of “X-Syndrome” (XS) consisting a group of symptoms or disorder, i.e. glucose intolerance, hyperinsulinemia, hypertriglyceride, low HDL cholesterol level and hypertension. Independently, these factors are a risk factor of CVD. Those factors will act synergistically in MS patient so that they will have a very high CVD risk.

Moreover, central obesity is also a risk factor that frequently presents with the X-syndrome, known as MS. Central obesity is characterized by an excess of fat accumulation in abdominal region. This condition is correlated to IR. Several studies indicate that the greater visceral adiposity, the lesser glucose usage occurs.

MS is frequently found in population and it frequently occurred prior to diabetes mellitus. In addition, it will cause CVD without an occurance of diabetes mellitus before.

Some clinical practice guidance of metabolic syndrome has been published. One of the most referred is the NCEP ATP III guidance. (Table 1) In this guidance, there are 5 evaluation measures: abdominal obesity (measured by the waist circumference), triglyceride level over 150 mg/dl, low HDL cholesterol level, high blood pressure i.e. over 130/85 mmHg, and blood glucose level over 110 mg/dl (in American Diabetes Association, the cut off point is 100 mg/dl). If there are 3 positive factors of these factors then it is adequate for MS diagnosis.

Table 1. Definition Metabolic Syndrome Based on ATP III

<table>
<thead>
<tr>
<th>Three of following items</th>
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<tbody>
<tr>
<td>1. Waist circumference:</td>
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<tr>
<td>- &gt;88 cm in female and &gt; 102 cm in male</td>
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<tr>
<td>- 94-102 cm in male who tend to have insulin resistance</td>
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<tr>
<td>2. Triglyceride &gt; 150 mg/dl</td>
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<tr>
<td>3. HDL: &lt; 50 mg/dl in female and &lt; 40 mg/dl in male</td>
</tr>
<tr>
<td>4. Blood pressure: &gt; 130/85 mmHg</td>
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<tr>
<td>5. Fasting blood glucose &gt; 110 mg/dl*</td>
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</tbody>
</table>

*In the new ADA guidance : 100 mg/dl

The definition of MS by WHO is quite different from ATP III. In the WHO’s definition there should be an impaired glucose tolerance, abnormal glucose-fasting level, diabetes, or IR signs. In addition, there should be 2 of 4 symptoms as follow: abdominal obesity (measured by BMI and not by the waist circumference),
dyslipidemia, blood pressure $\geq 140/90$ mmHg (different from the ATP III), and microalbuminuria (which is not included in the ATP III guidance).\(^1\)

Moreover, there is another different definition by The American Association of Clinical Endocrinologists (AACE). The criteria of AACE are based on whether the patient has any risk factors which indicate any insulin resistance (IR), such as high BMI, bad life-style, over 40 years of age, minority group, family history of diabetes mellitus, gestational diabetes mellitus. There are 2 measures similar to the ATP III criteria\(^1\), and combine further with post prandial glucose level $> 140$ mg/dL.

In spite of that, similarity of those three definitions is more important than their differences. The most important is that MS increases the risk of macrovascular complication. Hence, it should be managed well in order to lessen such vascular complication.

**THE PREVALENCE AND CVD RISK IN METABOLIC SYNDROME**

Twenty-five percent of adult people in United States about 20 – 79 year of age has the MS based on NCEP definition. While there are over than 40-45% people with MS in over 50 years of age.\(^1\)

MS frequently happens prior to diabetes mellitus and it is also a risk factor of CHD. In San Antonio Heart Study, patients who tend to have diabetes mellitus usually have more abdominal fat accumulation excess, higher triglyceride level, lower HDL cholesterol level and higher blood pressure. In addition, their blood glucose level are also higher statistically, and they also have insulin resistance (IR).\(^18\,19\)

This data is supported by a very large 20-years prospective study, the Nurses’ Health Study, which clearly demonstrates that the CVD risk is apparent even before the diabetes mellitus is clinically detected.\(^20\)

**DYSLIPIDEMIA IN DIABETES**

Dyslipidemia in diabetes mellitus usually is characterized by lipid metabolism disorder, which happened before diabetes mellitus occurred. Diabetes Mellitus, MS or IR patients tend to have a high triglyceride level, high VLDL level and low LDL level, highly-dense and or high LDL level, while HDL level usually is low.

The prevalence of dyslipidemia is higher in diabetic patient, especially in female. A data analysis of NHANES II indicates that diabetes mellitus women have a more frequent dyslipidemia about two times more frequent compared to non-diabetic women.\(^21\)

Moreover, in MRFIT study, the mortality rate of CVD after age correction increased although the cholesterol level slightly increased (example: $< 180$ mg/dl, equivalent to LDL level 100-110 mg/dl). There is also true for blood pressure. There is higher CVD mortality rate in both high blood pressure patient and patient with blood pressure ranging from 120-160 mmHg, who have about twice more frequent mortality rate.\(^1\) This indicates how vulnerable the blood vessels are in diabetic patient against dyslipidemia and hypertension. This also indicates that not only dyslipidemia but also all of risk factor should be managed together in order to suppress the frequent CVD in diabetes mellitus.

The Steno-2 study has supported this concept. Compared to the “conventional” therapy, an intensive control of multiple risk factors decreases the “combined endpoints” of CVD including CVD mortality, non-fatal myocardial infarction, coronary by-pass operation, non-fatal stroke, amputation and operation of peripheral vascular disease about 53%.\(^2\) Moreover, the frequency of nephropathy, retinopathy, and autonomic neuropathy are also decreased. Therefore, it demonstrates that the multiple-risk factors controlling is very beneficial.\(^2\)

The Steno-2 study has supported the recent-suggested recommendation, including:

- HbA1C level should be $\leq 7\%$
- Goal target of LDL level in diabetes mellitus patient $< 100$ mg/dL, and for patient with a very high risk (for example type 2 diabetes mellitus and CVD or other risk factors) the LDL target level is $< 70$ mg/dl
- Blood pressure should be $< 130/80$ mm Hg.
- Aspirin should be administered to all of adult patients, except there is any contraindication.
- ACE inhibitor or ARB is administered in diabetes mellitus patient with albuminuria or over than 55 years of age, and has one extra risk factor (based on Heart Outcomes Prevention Evaluation (HOPE) study).\(^2\)
- Beta-blocker is administered in diabetes mellitus patient with CHD. In decreasing mortality, this drug advantage more than its risk.\(^2\)

Although such therapy strategy has been proven beneficial, most of diabetes mellitus patient in the world (including the United States) has not achieved the suggested therapy goal. It should be emphasized that every decrease point of HbA1C level, lipid level, and blood pressure will be beneficial in diabetes mellitus patient, even though the target goal has not yet been achieved.\(^2\,2\)

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TARGET OF DYSLIPIDEMIA MANAGEMENT IN DIABETES MELLITUS

The important guidance of dyslipidemia management is the NCEP guidance and the ADA guidance. In both guidance, the most important objective is the management of LDL cholesterol, and the LDL cholesterol level should be < 100 mg/dl. In 2004, ADA revised the recommendation, and all of diabetes mellitus patient should be treated in order to achieve LDL cholesterol level < 100 mg/dl. American College of Physicians suggested that all of diabetes mellitus patient should be treated by statin.

In order to achieve this target, ADA has suggested life style changes and administration of statin (Table 3). Other related drugs may be used, including:

- Resin, which is rarely used because it has a lot of side effects and increases the triglyceride level.
- Hypolipidemic agents such as ezetimibe, but this drug is not as potent as statin in lowering the cholesterol level.
- Niacin, which may increase the LDL cholesterol level but worsen the glucose tolerance.
- Fenofibrate, the effect in lowering LDL cholesterol level is not potent (5-6%).

Increasing the HDL cholesterol level is more difficult and should be considered using niacin or fibrate acid.

For triglyceride, the ADA emphasized the importance of life-style changes such as decreased body-weight and exercise. In uncontrolled diabetes mellitus patient, a good management of blood glucose level occasionally may decrease the triglyceride level. Administration of fibrate acid derivative such as fenofibrate or gemfibrozil is also beneficial. It should be noted that gemfibrozil will increase the incidence of myositis in patient who had statin or niacin. If statin or niacin has been used, then the drug of choice is fenofibrate. High dose statin will also decrease the triglyceride blood level. There is no ADA recommendation, but it seems that liver cod oil is useful in lowering the triglyceride level.

Table 2. The Therapeutical Target for Diabetes Mellitus Patient (NCEP III and ADA)

<table>
<thead>
<tr>
<th>Therapeutical Consideration (mg/dl)</th>
<th>LDL Target (mg/dl)</th>
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<tbody>
<tr>
<td>NCEP ATP III</td>
<td></td>
</tr>
<tr>
<td>CVD or CVD equivalent risk</td>
<td>≥ 130</td>
</tr>
<tr>
<td>Chol non-HDL target</td>
<td>&lt; 130 mg/dl</td>
</tr>
<tr>
<td>ADA</td>
<td></td>
</tr>
<tr>
<td>CVD</td>
<td>&gt; 100</td>
</tr>
<tr>
<td>Non-CVD</td>
<td>&gt; 130</td>
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</tbody>
</table>

Table 3. Recommended Therapy of ADA

Lowering the LDL cholesterol
- Life-style modification
- Drug of choice: STATIN
- Other drugs: resin, inhibitors of cholesterol absorption, fenofibrate or niacin

Increasing HDL cholesterol
- Life-style modification
- Nicotinic acid or fibrate

Lowering triglyceride
- Life-style modification
- Blood glucose control
- Fibrate acid (gemfibrozil, fenofibrat)
- Niacin
- High-dose Statin (if there is high LDL cholesterol)

In NCEP guidance, the main target is also lowering LDL cholesterol and it also suggest statin administration as the first line agent, while “bile acid sequestrants” or nicotinic acid as the second line agent (this recommendation was established prior to ezetimibe). The secondary target is non-HDL cholesterol, which becomes a target if the triglyceride level > 200 mg/dl. In the past, NCEP recommended a high-carbohydrate and low-fat diet for patient with IR, but then it was modified and it suggested a fat intake 25-35% of total calorie. It also suggested decreased body weight for obese patient and almost all of diabetic patient principally has obesity and it also suggested a more frequent physical exercise.

THE CARDS STUDY

This study conducted only in type 2 diabetes mellitus patient and it is the first study which is exclusively conducted in diabetes mellitus patient. It is a primary prevention study, in patients who have no myocardial infarction history or CHD, and LDL cholesterol level less than 160 mg/dl. The median value of LDL cholesterol is 120mg/dl, which means lower than the normal value in general population. The patient should have at least 1 or more cardiovascular risk factor. 80% of them were assumed to have metabolic syndrome (SM).

An evaluation of 304 primary cardiovascular incidence and blinded double randomized therapy in 4 years period of 2830 patients has been achieved depend on which was occurred earlier. The study was ended 2 years earlier.
because there was a very significant result. In spite of that the average evaluation period reached about 3.9 years.28

At first, one third of patients were female and the mean age was 61 years old. Average BMI was 28.8. The study was conducted in United Kingdom.28 Based on this BMI, those patients were obese compared to the local population, although there were less obese compared to American typical population (The mean value American BMI with diabetes mellitus and non-Asian is about 31).

Initial LDL level ranged between 118 (placebo) and 119 (atorvastatin) mg/dl. In both groups, 25% had LDL cholesterol level < 1000, 25% was over than 137 mg/dl. The mean value of triglyceride level was 150 mg/dl in all of groups, which was not too high.28 Compared to similar population, in America there was not great disparity (triglyceride 160 mg/dl).29

In CARDS, the mean LDL cholesterol level alteration was 40%. HDL cholesterol changed only in 1% (different from other studies, which atorvastatin 10 mg caused a 4 – 5% increase relative to placebo), while triglyceride decreased about 21% compared to placebo. This is better than the usual result with atorvastatin 10mg, which has triglyceride level about 150 mg/dl.28

The Kaplan Meier curve indicated a decrease of relative risk by 37% of “primary endpoint” in atorvastatin group (Figure 1). The primary endpoint of this study is the incidence of fatal and non-fatal coronary incidence, stroke and coronary revascularization. The curve is clearly distinct after one year period and at the end of study there is 37% decrease of cardiovascular incidence (p=0.001).28 Another impressive result was 27% of all cause mortality in CARDS. It was not statistically significant (p=0.059), but it was nearly significant.28 In order to provide a better perspective, if it is compared to the 4S study result, there was only a 30% decrease (p < 0.01).31 In spite of that, it should be remembered that in CARDS, patient with CHD and a very high LDL cholesterol level was not included (similar to the 4 S study). Hence, the result of CARDS was very impressive compared to the 4 S study. If the study is continued, a statistic significance of decreased all cause mortality rate will possibly be achieved.

CONCLUSION

In CARDS, there is an administration of atorvastatin, 10 mg a day, safe and effective in decreasing the first CVD incidence in diabetes mellitus patient and normal cholesterol LDL level, which is statistically significant. Thus, there is no limit of certain LDL cholesterol level in diabetes mellitus, which become a reason not to use any statin.

In CARDS, there is 36% decrease of acute coronary incidence, including 31% fatal and nonfatal infarction 31% revascularization procedure, and 48% decrease of stroke in atorvastatin group compared to the
placebo group. All of them were statistically significant, with the exception for coronary revascularization procedure. This occurred regardless of initial LDL cholesterol level. In addition, it is interesting that the non-cardiovascular mortality (such as cancer and accident) was also slightly decrease. This is usually the common concerned factor which may be deleteriously affected because of statin administration. Moreover, there is no patient with rhabdomyolysis and the liver function of both group are similar (atorvastatin and placebo). 28

REFERENCES