Isolated Post-challenge Hyperglycemia: Concept and Clinical Significance

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ABSTRACT

The American Diabetes Association has strongly recommended that fasting plasma glucose should be sufficient for establishing diagnosis of diabetes mellitus; while World Health Organization supports to maintain the oral glucose tolerance test. Several epidemiological studies confirmed that postprandial hyperglycemia is a significant predictor for cardiovascular mortality and incidence. Post-challenge hyperglycemia following the oral glucose tolerance test is a condition similar to postprandial hyperglycemia. Isolated post-challenge hyperglycemia is a type of diabetes mellitus with a normal fasting plasma glucose level measured by oral glucose tolerance test. However, the glucose level following 2-hour post-challenge glucose test is ≥ 200 mg/dl. Several long-term studies on population have shown that subjects with isolated post-challenge hyperglycemia have higher risk for cardiovascular events and mortality. Moreover, they also have an equal risk as those who have previously had diabetes mellitus. Therefore, it is suggested that for screening of diabetes mellitus, especially in the elderly population, oral glucose tolerance test should be performed in addition to measuring fasting plasma glucose.

Key words: *IPH (Isolated Post-challenge Hyperglycemia), and impaired glucose tolerance (IGT)*

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INTRODUCTION

Diagnosis of diabetes mellitus can be established based on 3 methods, i.e.: a). for those who have specific symptoms of diabetes mellitus such as weight loss, polyuria, and polydipsia, a high plasma glucose level of ≥ 200 mg/dl, should be sufficient to establish diagnosis of diabetes mellitus, b). fasting plasma glucose level of ≥ 126 mg/dl, and c). Two hour post-prandial blood glucose level ≥ 200 mg/dl following 75 gram post-prandial glucose challenge test in oral glucose tolerance test (OGTT – 75 gram glucose).[1]

There are two different concepts between American Diabetes Association (ADA) and International Diabetes Federation (IDF) on diagnosis criteria of diabetes mellitus. The American Diabetes Association has recommended that single examination of a fasting plasma glucose level should be adequate for diagnosis of diabetes mellitus, which is easy to perform with lower cost.[2] In contrast, IDF has still strongly recommended to use the OGTT[3] based on rationale that normal fasting plasma glucose level is frequently found in elderly. Howeveer, on OGTT, the glucose level following 2-hour post-challenge glucose test is ≥ 200 mg/dl. In other words, diagnosis of diabetes mellitus is established only based on 2-hour post-challenge glucose level or post-OGTT.

By performing OGTT, the glucose level following 2-hour post-challenge glucose test will provide three results, i.e.: normal result if the plasma glucose level is <140 mg/dl, impaired glucose tolerance (IGT) ranged in 140-200 mg/dl, and diabetes mellitus if the plasma glucose level is ≥ 200 mg/dl. If the OGTT is performed following examination of fasting plasma glucose level, then the diagnosis of diabetes mellitus will be established based on fasting plasma glucose level of ≥ 126 mg/dl and 2-hour post-OGTT glucose level of ≥ 200 mg/dl. However, the fasting plasma glucose level can be < 126 mg/dl but the 2-hour post-OGTT glucose level ≥ 200 mg/dl. The last condition has become known as isolated post-challenge hyperglycemia (IPH). The IPH will be discussed further on this paper, particularly related to cardiovascular disease.

CLASSIFICATION OF DIABETES MELLITUS AND PLASMA GLUCOSE LEVELS

In 1979, The National Diabetes Data Group, Diagnosis and Classification of Diabetes and Other Categories of Glucose Intolerance[4] in USA introduced the new classification of diabetes mellitus for the first time. Afterward, it was widely brought in by the WHO Expert Committee on Diabetes Mellitus[5] in 1980. The classification introduced a category of hyperglycemia state which is not normal but it has not met the criteria of diabetes mellitus. Such category was known as impaired glucose tolerance or *toleransi glukosa terganggu (TGT)* when it is translated into Indonesian term. Impaired glucose tolerance is defined as 2-hours post-challenge plasma glucose level of 140-200 mg/dl on OGTT.

The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus[6] in USA made other new diagnosis criteria and classification on diabetes mellitus in 1997, which was also adopted by the WHO[7] in 1999. (Table 1) An important thing to distinguish it with a previous definition of normal glucose was a new concept on fasting plasma glucose level, i.e. the impaired fasting glucose (IFG), which has similarity with OGTT. Impaired fasting glucose is defined as fasting plasma glucose level of 110-126 mg/dl, which has been translated into Indonesian term as *glukosa puasa terganggu (GPT)* by the Consensus of Diabetes Mellitus Management on 2002.[8] As it progresses, the American Diabetes Association[2] changed the IFG definition again in 2003, from previously 110-125 mg/dl to 100-125 mg/dl. (Table 2) Both IFG and IGT have normal values in HbA1C measurement. This demonstrates that both conditions are not considered as diabetes mellitus.

Although both IFG and IGT have different etiology and pathogenesis, however, they become risk factors for potential diabetes mellitus in the future.[9] When an individual has both IFG and IGT detected at the same time, then the risk of diabetes mellitus will be higher compared to an individual who only has IFG or IGT. Some epidemiological studies demonstrate that the number of subjects with IGT is higher than IFG. Therefore, IGT developed more frequently to be diabetes mellitus than IFG.[1,10,11] Recently, both IFG and IGT are known as pre-diabetes, the general name used worldwide. In addition to their potential risk to the forthcoming diabetes mellitus, both have also been known as risk factors for cardiovascular disease. Nevertheless, IGT has stronger correlation to cardiovascular disease compared to IFG.[12]

Table 1. Diabetes mellitus classification

Type of DM	Causation of DM
Type 1 Diabetes Mellitus	Caused by beta pancreas cells destruction, leading to insulin deficiency
Type 2 Diabetes Mellitus	Caused by defect of insulin secretion with predominant insulin resistance
Other types of Diabetes mellitus	It depends on various etiologies such as drug-induced, endocrinopathies, chronic pancreatitis, etc.
Gestational Diabetes Mellitus	

Source: Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Diabetes Care 2003; 20: 1183-1197.[2]

Table 2. Classification of fasting plasma glucose and 2-hours post-OGTT

Fasting plasma glucose level	
- Normal fasting plasma glucose	<100 mg/dl (6.1 mmol/L)
- Impaired fasting plasma glucose	≥100 mg/dl (6.1 mmol/L), and < 126 mg/dl (7.0 mmol/L)
- Diabetes mellitus	≥ 126 mg/dl (7.0 mmol/L)
Plasma glucose level following 2-hours 75 gram glucose post-challenge test (OGTT)	
- Normal	< 140 mg/dl (7.8 mmol/L)
- Impaired glucose tolerance	≥ 140 mg/dl (7.8 mmol/L), and < 200 mg/dl (11.1 mmol/L)
- Diabetes mellitus	≥ 200 mg/dl (11.1 mmol/L)

Source: Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Diabetes Care 2003; 26: 3160-3176.[3]

THE PREVALENCE OF ISOLATED POST-CHALLENGE HYPERGLYCEMIA

When the fasting plasma glucose test and OGTT are performed, most of patients with diabetes mellitus will be diagnosed by fasting plasma glucose level of ≥126 mg/dL and OGTT ≥ 200 mg/dL. The DECODE study (Diabetes Epidemiology: Collaborative Analysis of Diagnostic Criteria in Europe) conducted in Europe, involving 7680 male and 9251 female subjects aged between 30 – 89 years-old, has classified diabetes mellitus based on 3 criteria: a). There was only 28.0% subjects with fasting plasma glucose and OGTT criteria, b). while there were 40.0% subjects who merely met the criteria of fasting plasma glucose, c). while in 31.0% of subjects, they were detected with merely OGTT criteria or IPH criteria.[13] (Figure 1)

A similar study in Asia known as The Diabetes Epidemiology Collaborative Analysis of Diagnostic Criteria in Asia (DECODA)[14] involving 6817 subjects found that 43% patients with diabetes mellitus were newly detected. Of such number, 43% subjects were diagnosed as IPH. The NHANES (National Health and Nutrition Examination Survey) III study in the USA found that among the newly diagnosed patients with diabetes mellitus aged 40 – 74 years-old, 44.0% diagnoses were established based on fasting plasma glucose and OGTT criteria, only 14% were diagnosed based on fasting plasma glucose criteria and the remained 41.0% were based on 2-hours OGTT criteria.[15] Barret-Connor reported that from 1858 male and female participants aged 50-89 years-old in the The Rancho Bernardo Study, they found 258 (13.88%) subjects of new diabetic patients and 154 (59.7%) of them were IPH.[16]

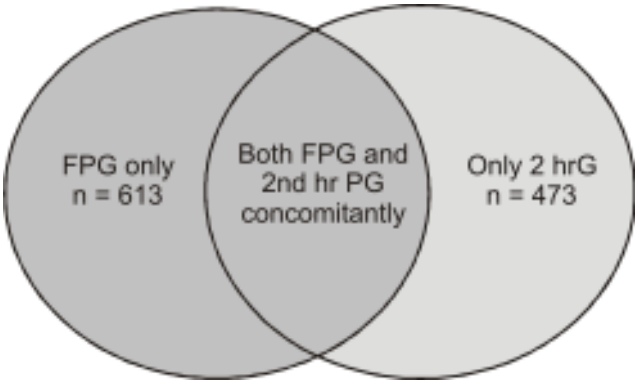

Figure 1. Different diagnosis of DM in asymptomatic subjects. FPG = fasting plasma glucose; 2 hr PG = 2 hr post-challenge glucose.

Sourced: The DECODE Study Group. Will new diagnostic criteria for diabetes mellitus change phenotype of patients with diabetes? Reanalysis of European epidemiological data.[14]

CLINICAL IMPLICATION OF ISOLATED POST-CHALLENGE HYPERGLYCEMIA

It has been known since earlier that the main cause of death in patients with diabetes mellitus is due to cardiovascular disease, and approximately 80% cases are caused by coronary artery disease. Compared to the normal population, some studies have demonstrated that patients with diabetes mellitus have two to three time higher risks of coronary artery disease.[17] The major cause of high cardiovascular mortality in patients with diabetes mellitus, particularly in DM type 2, is hyperglycemia, in addition to other risk factors such as obesity, hypertension, and dyslipidemia. Frequently these factors are detected earlier before the diagnosis of diabetes mellitus itself. A study by Haffner et al[18] in 1998 has demonstrated that diabetic patients without coronary artery disease have an equal risk of developing acute myocardium infarction in the future compared to patients who have had coronary artery disease previously. Therefore, today, in the context of preventing coronary artery disease, patients with diabetes mellitus are treated equally as those with history of myocardial infarction. (Figure 2)

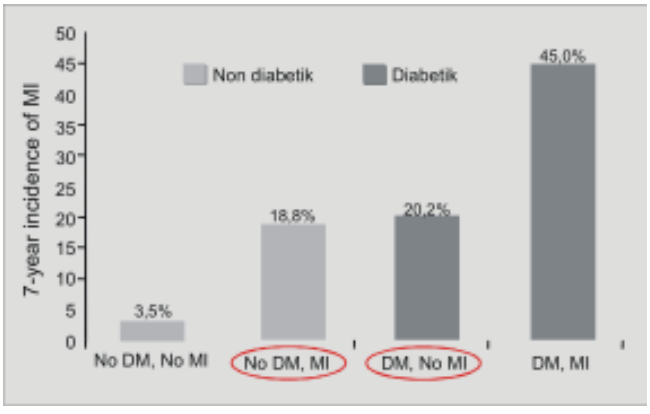

Figure 2. Type 2 diabetes mellitus (DM) and coronary artery disease (CAD). The 7 year incidence of fatal or nonfatal myocardial infarction (MI) is essentially the same in patients who have diabetes without a history of CAD and in patients with CAD who are not diabetic. P < 0,001 for the difference between patients with and without MI in both group. Haffner SM, et al.[18]

Several studies have confirmed that IPH is a significant predictor for developing cardiovascular events in the future. In Honolulu Heart Program, which involved 8006 male participants aged 45-70 years old; found that post-challenge glucose level was strongly associated with cardiovascular events.[19] Hence, in Funagata Study that compared IFG and IGT subjects, concluded that IGT has the role as a risk factor for cardiovascular events rather than IFG.[20] The Rancho

Bernardo Study in the USA that has monitored patients with IPH for 7 years, found that the risk of cardiovascular disease is significantly higher than non-diabetic patients. Cardiovascular disease obviously has independent correlation with age, hypertension, central obesity, smoking, HDL cholesterol, and triglycerides.[9] Similar findings have been reported by the DECODE study in Europe, which indicated that 2 hour post-challenge glucose level in OGTT has strongly been correlated to morbidity and mortality of cardiovascular disease. The study has also shown that mortality risk of patients with high level of fasting plasma glucose will only be apparent if it is accompanied by an increase of 2-hour post-OGTT glucose level. [13]

MANAGEMENT

Management of IPH is similar to the management of patients with the type 2 diabetes mellitus. The consensus of American Diabetes Association and European Association for the Study of Diabetes in 2006[21] has confirmed that life style modification and metformin as the first step for management of the type 2 diabetes mellitus. Metformin was recommended as the first-line drug because it decreases plasma glucose level, either in fasting or after meal condition. Moreover, it does not cause hypoglycemia or obesity, and it also has anti-aterogemic effect.

Some precautions in taking metformin treatment:

1. Considering that most of IPH patients are elderly, the kidney and liver functions should be concerned before commencing metformin treatment
2. Since most of IPH patients only have mild hyperglycemia, metformin dose should be adjusted; starting with a low dose, such as 500 mg/day
3. The IPH patients are mostly elderly and consequently, the risk of cardiovascular events is more common, such hypertension and dyslipidemia. Management for both risk factors is similar to other diabetic patients
4. Aspirin should be given, except it is contraindicated
5. It is possible that IPH patients have already had history of cardiovascular disease such as post-ischemic stroke or coronary artery disease, which means more intensive treatment for hypertension or dyslipidemia is necessary.

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