Impaired Glucose Tolerance, Impaired Fasting Glycaemia and Cardiovascular Risk

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ABSTRACT

Type 2 Diabetes Mellitus tends to increase year by year and it has high morbidity and mortality, especially among those who have macro-vascular complication(s) as cardio-vascular disease.

There are many prevention efforts that have been done, especially primary prevention i.e. prevention of Type 2 Diabetes Mellitus development. Impaired Glucose Tolerance (IGT) and Impaired Fasting Glycaemia (IFG) is regarded as a phase between individual with normal blood glucose and type 2 diabetes mellitus.

Individual with Impaired Glucose Tolerance (IGT) has higher possibility to develop Diabetes Mellitus compared to Impaired Fasting Glycaemia (IFG). Likewise, it also has more important role to cause Cardio-Vascular Disease. IGT may develop Cardiovascular Disease similar to Diabetes Mellitus, hence either IGT or Type 2 Diabetes Mellitus is categorized as independent risk factor of Cardio-Vascular Disease development.

If compared to IFG then frequency of IGT is more excessive in the population, so that 2 hrs blood glucose after 75 gram glucose load test should be done in blood glucose testing.

***Keywords**: Impaired Glucose Tolerance (IGT), Impaired Fasting Glycaemia (IFG), Cardio-Vascular Disease (CVD), Metabolic Syndrome.*

INTRODUCTION

The term of Impaired Glucose Tolerance (IGT) or *Toleransi Glukosa Terganggu (TGT)* is firstly presented by "American Diabetes Association" (ADA) replacing the former term i.e. pre diabetes, chemical diabetes, borderline diabetes and latent diabetes. TGT is an intermediate group that is a group between normal individual and Diabetes Mellitus patient(s).

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Furthermore WHO on the year of 1980 in Diabetes Mellitus classification incorporate IGT as specific group apart from DM and gestational diabetes.

Several studies showed that IGT will develop Diabetes Mellitus range from 1,5 – 4.0 % per year and tends to develop cardiovascular disease in the future.[1]

Impaired Fasting Glycaemia (IFG) or *"Glukosa darah Puasa Terganggu (GDPT)"* was newly introduced on 1997 by ADA. It is regarded as has hyperglycemia tendency, has A_{1c} that tends to elevate above the normal value as compared to IGT.[2] ADA also regards the IFG group as intermediate group that is between normal individual and Diabetes Mellitus, who tends to have Diabetes Mellitus and Cardio Vascular Disease.[1,2]

Another study (Alexander, et al, 2000) showed that the increment of blood glucose level has high risk to increase morbidity and mortality of Cardio Vascular Disease. [2]

International Diabetes Federation (IDF) has review the relationship between IGT, IFG with Diabetes and Cardio Vascular Disease.

The prognosis of Cardio Vascular Disease in Diabetic patient is worse than non-diabetic patient(s). It is obvious on fatal cases of myocardium infarct, most of them is caused by Diabetes Mellitus i.e. 45% male, 39% female diabetic, while in non-diabetic patient(s) there was only 38% found on male and 25% female.[2] This data shows the importance of primary and secondary prevention of Diabetes Mellitus .

Diabetes mellitus is a metabolic disease characterized by hyperglicemia because of defect on insulin secretion and function or both. Usually, at the first stage, it has not any sign(s) or symptom(s) yet. It is called asymptomatic so that this disease is left undiagnosed for years. [4,5,6,7]

Recent studies shows that not less than 120 million people around the world have Type 2 Diabetes Mellitus and it is predicted that on the year of 2010 the amount of

Diabetes Mellitus patient will increase up to 220 million and this increment is especially found in developing country. The data of mortality rate statistically may be less then the true condition because the death that resulted from Diabetes Mellitus is frequently unreported.[4]

Diabetes mellitus may cause social economy impact, chronic complication and lost of work productivity.[4] Generally, Diabetic patient has impaired of defect on insulin secretion and insulin resistance. As long as the beta cells could still compensate insulin secretion then the DM will not happened. IGT start to turn up if insulin secretion has not compensated anymore to insulin resistance, which cause post-prandial hyperglicemia.[5] While ADA regards IGT equal to IFG.

Acknowledging the higher incidence of DM and considering the negative effect that resulted from it, then we should prevent DM as it is one of major risk factor of cardio vascular disease that could be fatal. [5]

By the alteration of DM diagnostic procedure(s) while IGT and IFG are the marker of DM presence in the future and prediction of cardio vascular of risk factor then it is very important to detect IGT and IFG in keeping with diagnostic criteria as determined by ADA (1997) and WHO (1999).

Diagnosis Criteria of Diabetes Mellitus

If we follow the procedures of diagnosis criteria of Diabetes Mellitus then the criteria diagnosis Diabetes Mellitus that currently used has been revised several times. The diagnosis which was used on 1979 and 1980 was based on criteria of U.S. National Diabetes Data Group and WHO i.e. if there is classic clinical symptom(s) and sign(s) plus direct blood glucose level of $\geq$ 200 mg/dl, then we could establish the diagnosis of Diabetes Mellitus. For those who have no symptom then we should perform fasting blood glucose (FBG) test and 2 hrs blood glucose after 75 gram glucose load test (Oral Glucose Tolerance Test abbreviated as OGTT). If the result of FBG $\geq$ 140 mg/dl and or 2 hrs blood glucose after glucose load $\geq$ 200 mg/dl then we could establish the diagnosis of Diabetes Mellitus. If the 2 hrs blood glucose after 75 gram glucose load test (OGTT) is within 140-199 mg/dl then it is called as IGT. The diagnosis criteria of Diabetes Mellitus that based on OGTT test is the "Gold Standard" that still used up to now. [4]

For 2 decades this diagnosis criteria of Diabetes Mellitus is still remained, but during that time data of epidemiology study showed many patients who have FBG level <140 mg/dl had already have chronic complication as diabetic retinopathy which is a specific chronic complication of Diabetes Mellitus. While frequently patient who has 2 hrs blood glucose after glucose load $\geq$ 200 mg/dl also has FBG level of <140 mg/dl. [4]

Based on it then on 1997 ADA revised the diagnosis procedure of Diabetes Mellitus by lowering the abnormal value of FBG from 140 mg/dl to 126 mg/dl and only examine the FBG i.e. if $\geq$ 126 mg/dl, then we already could establish the diagnosis of Diabetes Mellitus. Examination of 2 hrs blood glucose level after glucose loading or OGTT is not necessary done anymore. For those who have fasting blood glucose level within 110-125 mg/dl, they are called as IFG.[2,4,5]

The examination of 2 hrs blood glucose level after glucose loading is not necessarily done by the assumption that IGT and IFG are analog as intermediate phase before Diabetes Mellitus is developed. Besides, by examining FBG only, the examination is more simple, acceptable and lower cost. [1,2,6] In longer period, IFG similar to IGT in developing complication of diabetic retinopathy.

The revision that has been issued by ADA, turned out to get criticism from various epidemiology study, that showed many subject with normal FBG examination, but then by examination of 2 hrs blood glucose after glucose load apparently showed $\geq$ 200 mg/dl (Isolated postchallenge hyperglicaemia).[1,3,4,5,]

The study of "Diabetes Epidemiology: Collaborative Analysis of Diagnostic Criteria in Europe (DECODE Study) 1999 has studied and evaluated the Diabetes Mellitus prevalence on European elders community within 60-79 years. By using the criteria of ADA, which only examine the FBG, apparently 1/3 of them have Diabetes Mellitus, if they examine in keeping with WHO criteria. If the examination of 2 hrs blood glucose level after glucose loading is performed in the same manner of WHO criteria on those who had IFG, then the amount of IFG patients were decrease in half.

The Diabetes Mellitus patient who is not diagnosed by ADA criteria is found to have equal mortality rate as other diabetics. Apparently those who have IFG with examination of blood glucose level after glucose loading, then there will be half decrease of IFG frequency. The conclusion of this study is fasting blood glucose level itself is not enough to diagnose Diabetes Mellitus or in other word the examination of OGTT is need to be performed to diagnose and screen more diabetic patient. [8,9]Acknowledging of those various studies then WHO on 1999 recommended diagnosis procedure of Diabetes Mellitus by still using ADA criteria 1997, but the OGTT examination is still should be done. The diagnosis criteria of Diabetes Mellitus which is recommended by

WHO (1999) are as follow: Those who have classic symptoms of Diabetes Mellitus i.e. polydipsy, polyuria, polyphagy and unexplainable loss of weight plus direct blood glucose level of ≥ 200 mg/dl are enough to establish the diagnosis of Diabetes Mellitus. Besides that, for those who has no classic symptoms then the diagnosis is established by OGTT examination i.e. fasting blood glucose level of ≥126 mg/dl and or 2 hrs blood glucose level after glucose loading of ≥ 200 mg/dl (Table 1).[1,6,8,9]

Table 1. Diagnosis Criteria of Diabetes

Normoglycemia	IFG or IGT	Diabetes*
FBG <110 mg/dl	IFG≥ 110 mg/dl and < 126 mg/dl (IFG)	FBG ≥126 mg/dl
2 hrs† <140 mg/dl	2 hrs ≥† 140 and < 200 mg/dl (IGT)	2 hrs ≥ 200 mg/dl Diabetic symptoms and GDS≥ 200 mg/dl

Main difference between diagnosis criteria of WHO and ADA 1997 is diagnosis criteria of ADA 1997 suggests Diabetes Mellitus diagnosis, especially for population, simply by single FBG examination, contrary WHO 1999 decides besides FBG, the 2 hrs examination after glucose loading on OGTT should be done.[11]

If the diagnosis criteria of Diabetes Mellitus of ADA 1997 and WHO 1999 version were combined, then there are several possibility i.e. : If FBG < 110 mg/dl, it is called normal FBG, FBG within 110-125 mg/dl is called IFG and if FBG ≥ 126 mg/dl is called diabetes mellitus. If OGTT is performed pursuant to WHO 1999 then we said normal glucose tolerance if the 2 hrs blood glucose level after glucose loading (OGTT) < 140 mg/dl. It is called IGT if within 140-199 mg/dl and diabetes mellitus if blood glucose ≥ 200 mg/dl. Both IFG and IGT are risk factor of type 2 diabetes mellitus and cardiovascular disease, but data of DECODE group showed that IGT has higher risk as compared to IFG.[8,9]

Table 2. Impaired Fasting Glucose (IFG) and Impaired Glucose Tolerance (IGT) and Diabetes mellitus

Fasting plasma Glucose	Score
Normal	< 110 mg/dl
IFG	110 – 125 mg/dl
Diabetes mellitus	≥ 126 mg/dl
Plasma Glucose post load 75 gram Glucose :	
Normal	<140 mg/dl
IGT	140 – 199 mg/dl
Diabetes mellitus	≥ 200 mg/dl

- The diagnosis of Diabetes Mellitus is established on the next day by examining FBG, 2 hrs blood glucose after glucose load or direct blood glucose examination (if there is any symptom). FBG is blood glucose level after 8 hrs fasting.

† This test need 75 gram anhydrous glucose solved in water. 2 hrs , means 2 hrs after 75 gram glucose loading

Recently the adult population in United States who have IGT are 13.4 million (6.9%), 5.4 million (2.7%) of IFG and 10.2 million (5.2%) have diabetes mellitus diagnosis and the rest of 85% are normal.[2] This number shows that IGT is more excessive as compared to diabetes mellitus.[2]

Both IFG and IGT are regarded as couple of intermediate phase which are assumed as serial of carbohydrate metabolism disorder[4]

The two diagnosis criteria of diabetes mellitus of ADA (1997) version and WHO (1999) version caused various epidemiology studies which compare the diagnosis criteria based on ADA and WHO, with objective to find which is the better criteria.[10]

DECODE studies on European community conclude that by using diagnosis criteria of ADA version which only use fasting blood glucose examination, the diagnosis of diabetes mellitus on obese patient is more sensitive as compared to the non-obese. Contrary, on non-obese patient the examination of 2 hrs blood glucose after glucose loading is more sensitive. We conclude from this study, the ethnic factor has a very important role in establishing the diagnosis of Diabetes Mellitus[4,11,12]

Furthermore, "Third National Health and Nutrition Examination Survey "(NHANES III) shows that on the Diabetes Mellitus group that have been diagnosed by using FBG (≥126 mg/dl) apparently they have higher A_{1c} as compared to the group that have been diagnosed by WHO 1985 criteria, that is by using the OGTT.[12] Hence, the diagnosis based on ADA criteria, which only examine FBG is less sensitive than IGT that using the WHO 1999 criteria.

IFG and IGT

To confirm whether someone is in group of IFG or IGT, it depends on FBG examination only or and 2 hrs blood glucose examination after glucose loading. For example an individual who is in IFG category may also have IFG or diabetes mellitus if we examine his 2 hrs blood glucose level. So, an individual may have 2 different category.[3]

Most of the IGT subject, have normal FBG level if we examine their fasting blood glucose level, in contrary others are IFG if we examine their 2 hrs blood glucose level and it is still normal. This condition is called as isolated IGT or isolated IFG.[3]

Comparing IGT and IFG, then the IGT incidence is more than IFG. From 9 studies, most of them showed

that IGT was frequently found then IFG. This difference is assumed because of gender, age distribution and phenotype factor.[3,11]

Peak prevalence of IFG is in middle age (40-50 years) with an exception in European women, which increase up to 70 years, while the prevalence of IGT increase by age. The epidemiology study result shows that IFG is frequently found on male of all age group except on 70-79 years group in Europe and 80-89 years group in Asia. In the contrary, female IGT is frequently found in all age group except in European group with an exception in 80-89 years age group.[3]

The Asian in every age group both male and female have more IGT as compared to IFG, contrary IFG is commonly in European especially males over 60 years old. Based on those facts, it is apparent that the prevalence of IGT and IFG depend on gender, ethnic, and age.

Shaw et al (1999) compared IGT and IFG by epidemiology to predict future diabetes mellitus on 3229 population subject in Mauritus by examining FBG and 2 hrs blood glucose levels after glucose loading. They found 609 of IGT subject and only 267 of IFG subject. Both of group are evaluated for 5 years and they found 297 subject have develop diabetes mellitus, 148 patients come from IGT and only 77 patient come from IFG group. (figure 1).

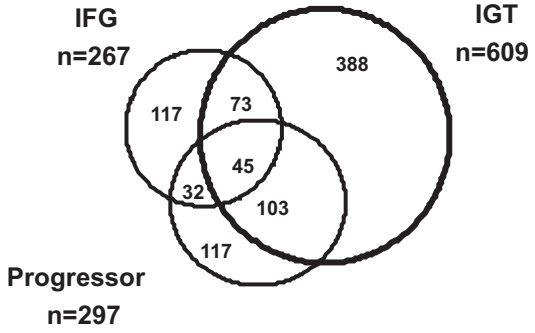

Figure 1. Progression to Diabetes Over 5 Years in Maurtius According to Baseline Glucose Tolerance Status

Based on this data, it is clear that IFG capacity and sensitivity caused less future diabetes mellitus compared to IGT, which has been supported by other studies. Highest Diabetes Mellitus risk is on IGT patient together with IFG (combination).[3,4,6,11-14]

Risk Factor of Cardiovascular Disease

It has been reported that type 2 diabetes mellitus has twice tendency to develop cardiovascular disease and worse prognosis as compared to non-diabetes mellitus patient. [2] This is because type 2 diabetes mellitus tends to increase triglyceride level and decrease HDL-cholesterol level and increase blood pressure, which will cause more aterogenic condition.[2]

Nowadays both IGT and IFG especially the isolated are related to cardiovascular risk factor and is clustered together as a part of metabolic sydrome together with hypertension, obesity, dyslipidemia and type 2 diabetes mellitus. Some data showed that IGT itself has bigger relationship with hypertension and dyslipidemia compared to IFG.[3]

In various studies, it is found that IGT is more sensitive in developing cardiovascular disease as compared to IFG. This could be seen from various epidemiology studies result such as Honolulu Heart Program (1999) study that examined 8006 Japanese males on 45-68 years old, live in Honolulu, and has been followed up for 23 years. All of them have 1 hrs blood glucose level after 50 grams glucose loading examination. The result was divided into 4 groups that was low-normal group i.e. they who have blood glucose level of <151 mg/dl, high-normal group i.e. within 151-224 mg/dl, asymptomatic hyperglicemia group with >225 mg/dl and known diabetes group with blood glucose level of ≥ 225 mg/dl. Patients with coronary heart disease and stroke were excluded from the research. Final result after 23 years showed 2166 person died, 384 death was caused by cardiovascular disease or sudden death, 864 of them got cardiovascular disease.[13]

Table 3. Age- adjusted Rates of Total Mortality and CHD Incidence and CHD Mortality

	Low normal	High normal	Asymptomatic hyperglicemia	Known diabetes
Total mortality	13.0	14.5	20.4	24.8
CHD incidence	5.0	5.9	8.8	14.1
CHD mortality	1.7	2.0	3.7	6.3

Data are rates per 1,000 person-years

If we correlate it to glucose intolerance in keeping with those 4 groups then we found significant correlation within cardiovascular disease and blood glucose level increase (table 3). Likewise the death amount because of cardiovascular disease. It is concluded that the higher blood glucose level after loading, the higher cardiovascular disease incidence.[13]

Former study that is Hysayama study on 2427 Hysayama citizen in Japan for 5 years showed the same result i.e. IGT and type 2 diabetes mellitus are independent risk factor of cardiovascular disease.[13]

The study which compare IGT and IFG in developing Cardio Vascular Disease has been performed by "Funagata Diabetes Study" on 1999 that examine 2534 Funagata citizen on 40-49 age group. The OGTT with 75 gram glucose loading was done and the result was divided into 2016 people of normal glucose tolerance group, 382 people of IGT, 253 diabetic patients. Then all of them were observed for 7 years about their cause of death either by Cardiovascular Disease or Stroke. The result showed significant lower Cardio Vascular Disease and stroke survival rate on IGT and Diabetes Mellitus group as compared to normal glucose tolerance group (figure 2A) [16]

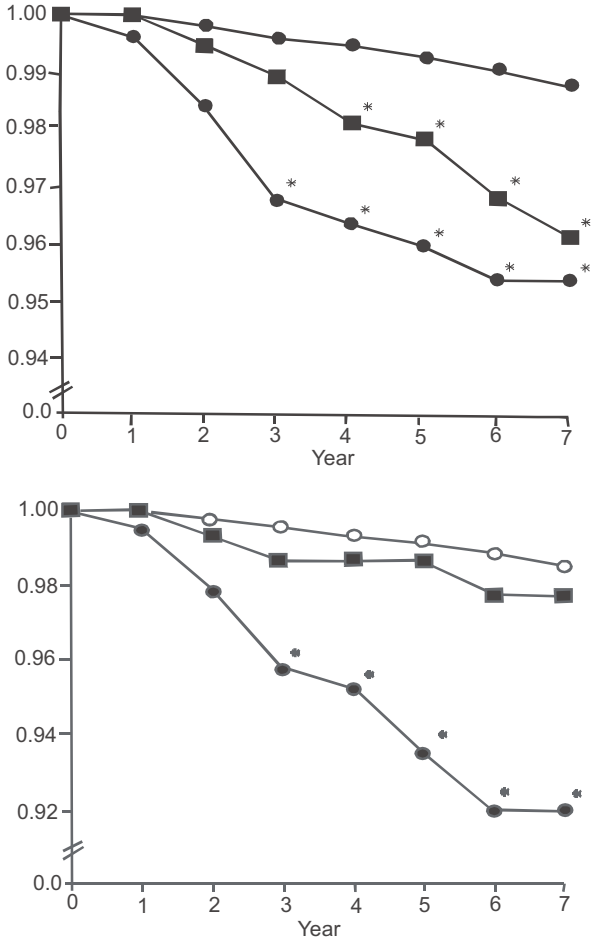

Figure 2 : **A.** Cummulative Survival Rate on Normal Glucose Tolerance (o) compare to IGT (■)and DM (●). There is significant difference of cardio vasular survival rate between normal glucose tolerance with IGT and DM**. B.** Survival rate of fasting blood glucose (o) has no significant difference as compared to IFG ( ), while compare to the DM (●) both of them has significant difference (* p <0,05).[16]

Furthermore the Funagata study compared average survival rate of normal blood glucose level patient to the IFG and Diabetes Mellitus patients. The result showed that cardiovascular and stroke survival rate on IFG group has no significant difference from those who had normal blood glucose. While compared to Diabetes Mellitus, then both IFG or normal FBG group have significant difference. (figure 2B).[16]

Cumulative Survival Rate

We conclude that IGT could be the risk factor of cardio vascular disease and stroke and IFG can not be assumed to replace the IGT concept as risk marker to aggravating situation to develop diabetes or cardio vascular disease. [16,17]

In the same year, they reported cross sectional study by prospective analysis on 4515 participant on " Cardiovascular Health Study" for 8 years on 65 years old people and then they performed the study of incidence and prevalence of Cardio Vascular Disease pursuant to ADA and WHO criteria. [16] The conclusion of this study showed that by ADA criteria which only examine FBG level, it seemed less predictive compare to WHO criteria that examine 2 hrs blood glucose level after glucose loading in order to cause Diabetes Mellitus and Cardio Vascular Disease. [18]

This is supported by "Framingham offspring study" that examined fasting hyperglycemia and 2 hrs after glucose loading hyperglycemia. They concluded that the examination of 2 hrs after glucose loading is an independent risk factor of Cardio Vascular Disease. [19]

Clinical implication of those studies is that IGT could be regarded as independent risk factor of causing Diabetes Mellitus and Cardio Vascular Disease, while IFG could not. Based on that we should examine the 2 hrs blood glucose level after glucose loading in every blood glucose examination.

CONCLUSION

Diabetes Mellitus prevention is a very important factor to treat Cardiovascular Disease (CVD) that could be fatal. Therefore we need early detection of impaired glucose tolerance (IGT) and Impaired fasting glycemia (IFG) as intermediate group and marker or risk factor about Diabetes Mellitus in the future.

It is proved that IGT and IFG have a tendency to develop Diabetes Mellitus. Nevertheless, IGT has greater possibility to develop Diabetes Mellitus compare to IFG. Besides, both IGT and Diabetes Mellitus have greater possibility to develop Cardio Vascular Disease while IFG has not. The IGT prevalence is higher than IFG, this

caused difference of gender and phenotype distribution within both of them.

Both of diabetes mellitus and IGT are included to metabolic syndrome which is the main factor cause of cardiovascular disease.

Based on that, then the examination of 2 hrs blood glucose after glucose loading (WHO) need to be performed, not only to diagnose DM but also to determine the presence of IGT.

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