

## COMPARISON OF PANCREATIC INSULIN RESPONSE TO HYPERGLYCEMIA AMONG FILIPINO SUBJECTS OF VARIOUS GLYCEMIC STATUS

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### ABSTRACT

**Objective:** To determine the demographic profile of patients who consulted for assessment of glycemic status and classify them based on the American Diabetes Association (ADA) guidelines in the diagnosis of DM type 2 after oral glucose tolerance test (OGTT) and identify the insulin response of different glycemic status.

**Research design and methods:** This is a descriptive, case control study done from April 2002 to January 2003. Fifty (50) consecutive DM patients were seen and assessed after 75 grams OGTT based on demographic data: age, sex, family history and body mass index (BMI). Patients were divided: group 1-DM, group 2-impaired glucose tolerance (IGT), group 3-hyperinsulinemia only (insulin levels of more than 20 U/ml) and group 4-normal

**Results:** There is significant difference in the insulin secretion among the groups compared with the normal subjects. ( $p < 0.025$ ) Multiple comparison between groups showed there is a significant high insulin level ( $p = 0.05$ ) in groups 1, 2 and 3 when compared to normal subjects (group 4).

**Conclusion:** The mean insulin concentration after 2 hours of 75 grams glucose showed significant difference among the group and higher than the normal subjects. The mean insulin of the paired groups (diabetics, IGT, hyperinsulinemia) was not different except those mean insulin compared with group 4(normal). Insulin weight during OGTT 2nd hour will determine pre-diabetic state.

**Keywords:** hyperinsulinemia, prediabetes, impaired glucose tolerance

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### INTRODUCTION

Diabetes mellitus type 2 is a metabolic disorder characterized by hyperglycemia, which may be due to a predominantly insulin resistant state with relative insulin deficiency, or to a predominantly secretory defect with insulin resistance. The detection or screening test for diabetes mellitus is by means of a fasting plasma glucose (FPG) test or 2-hour oral glucose tolerance test (OGTT), the former being more convenient, more reproducible, less costly and easier to administer. However, some individuals with normal FPG will have impaired glucose tolerance (IGT) or diabetes if a 2 hour OGTT is performed, but fewer people with normal 2 hour OGTT will have impaired fasting glycemia (IFG) or diabetes if an FPG test alone is done,<sup>1</sup> thus OGTT appears to identify more people who have impaired glucose homeostasis.

There is increasing evidence that by the time glucose tolerance or fasting glucose levels become impaired, appreciable pancreatic Beta cell destruction may have already occurred.<sup>2</sup> Likewise, patients who may be glucose tolerant or those with completely normal OGTT findings may have compensated hyperinsulinemia to maintain glucose levels at normal.<sup>3</sup>

This state of compensated hyperinsulinemia may be equated to decreasing insulin sensitivity. A schematic description of the natural history or progression to type 2 diabetes (Appendix) was proposed by Olefsky and Kruszynska.<sup>4</sup> A host of methods have been developed to assess insulinsensitivity and insulin resistance in vivo<sup>5</sup> including the use of insulin at 2 hours post 75 grams glucose loading.<sup>6</sup> Normal immunoreactive insulin range from 5-20  $\mu\text{U}/\text{mL}$  (35.5-142 pmol/L) in the fasting state, reach 50-130  $\mu\text{U}/\text{mL}$  at 1 hour and usually return to levels below 30  $\mu\text{U}/\text{mL}$  by 2 hours.<sup>7</sup> The objectives of this study are to determine the demographic profile of patients who underwent 75 grams OGTT and to identify the insulin sensitivity of patients of different glycemic status using the paired second hour glucose-insulin levels in the OGTT.

## MATERIALS AND METHODS

### Subjects

Patients who consulted and/or were referred to an endocrine referral clinic for the evaluation of glycemic status from April 2002 to January 2003 were included in this study. Fifty consecutive patients were evaluated with a standard 75 grams OGTT and enzyme-linked insulin immunoassay 2 hours after glucose loading. Patients were defined based on demographic data such as age, sex, presence of diabetes in a first-degree relative and body mass index. Majority of these patients did not present with the classic symptoms of diabetes including polyuria, polydipsia, polyphagia and unexplained weight loss. Glucose and insulin levels taken 2 hours after 75 grams glucose loading were determined and compared between groups depending on their blood glucose levels.

Patients were divided to 4 groups based on their glucose and insulin levels after a standard 75 grams OGTT<sup>8</sup> set by the American Diabetes Association. Groups were identified as follows--  
 - 1) diabetes mellitus (DM), 2) impaired glucose tolerance (IGT), 3) normal glucose with compensated hyperinsulinemia (COMP HYPER) 4) normal glucose and insulin (NORMAL-NORMAL). (Table I) Level of insulin of more than the upper limit of normal--- 142 pmol/L (20µU/mL) was considered hyperinsulinemic. Descriptive statistics was used to determine measures of central tendencies. Analysis of variance (ANOVA) was used to analyze differences between groups while non-parametric studies using Kruskal-Wallis test were done to test difference of %S. Post-hoc analysis and multiple comparisons using Scheffe's and Tukey-Kramer tests were likewise done, if applicable. Statistical analyses were made using the statistical software package NCSS 2000/PASS 2000.

## RESULTS

Clinical and metabolic descriptors of the study population are shown in Table II. Fifty patients were included in the study with a mean age of 38.52±14.43 years and mean BMI of 26.58 ± 4.32 kg/m<sup>2</sup>. Two-thirds of the total patient population was females and 68 percent had diabetes in the family. Patients were grouped based on their glucose/insulin results—13 (26 percent) had diabetes mellitus, 10 (20 percent) had impaired glucose tolerance (IGT), 21 (42 percent) had compensated hyperinsulinemia and 6 (12 percent) were normal-normal.

Analysis of variance between means showed significant difference for height (Figure 3) at p value of 0.5, but no significant difference in weight (Figure 2) and BMI (Figure 4). Analysis of variance of age between the 4 groups showed significant difference at p value of 0.015 with post hoc analysis showing difference between means of age of diabetics from patients with compensated hyperinsulinemia, whereby diabetics were noted to be older. Analysis of variance of absolute insulin levels (Figure 7) showed significant difference at p value of <0.001. Multiple comparisons showed that insulin levels of patients with compensated hyperinsulinemia is not different from DM, IGT and normal-normal but patients with normal insulin and glucose (Normal-normal) is different to DM and IGT only. Multiple comparisons of the four groups revealed that there is a lower mean absolute insulin level in normal-normal groups that is different from DM, IGT and compensated hyperinsulinemia.

Table I. Criteria for the Diagnosis of Diabetes Using 75 grams OGTT.\*

	Fasting plasma glucose	2 hour postload glucose
Normoglycemia	< 110 mg/dL**	< 140 mg/dL
Impaired fasting glycemia	≥ 110 mg/dL and < 126 mg/dL	----
Impaired glucose tolerance	-----	≥ 140 mg/dL and < 200 mg/dL
Diabetes mellitus	≥ 126 mg/dL	≥ 200 mg/dL

\*This test requires the use of a glucose load containing the equivalent of 75 grams anhydrous glucose dissolved in water. Blood glucose is determined at zero hour (after fasting at least 8 hours) and 2 hours post glucose load.

\*\*To convert mg/dL to mmol/L, divide value by 18.1

Table II. Clinical and Metabolic Descriptors of the Study Population

Diabetics	Groups				Anova	
	IGT n=13	Comp n=10	Normal- hyper n=21	F normal n=6	P (dl=3.46)	
Sex male	6	1	2	4	-	-
female	7	9	19	2	-	-
Age in years	48.62 ± 12.92	35.50 ± 16.15	33.14 ± 12.87	40.50 ± 9.97	3.85	0.015
DM in the family	9	5	17	3	-	-
Weight (kg)	67.38 ± 11.85	59.50 ± 10.61	64.90 ± 14.29	75.75 ± 16.93	1.94	N8
Height (m)	1.59 ± 0.08	1.54 ± 0.07	1.54 ± 0.10	1.68 ± 0.09	4.18	0.01
BMI (kg/m <sup>2</sup> )	26.82 ± 4.75	25.09 ± 3.39	27.09 ± 4.72	26.71 ± 3.67	0.49	N8
FPG (mmol/L)	7.87 ± 1.59	5.62 ± 0.94	5.20 ± 0.70	5.40 ± 0.74	18.84	<0.0001
2° glucose	14.26 ± 3.03	9.12 ± 1.18	6.03 ± 1.27	5.50 ± 1.06	58.63	<0.0001
2° insulin (pmol/L)**	546.66 ± 266.77	589.00 ± 418.56	338.33 ± 150.49	89.91 ± 34.18	6.53	<0.001

Critical F = 260

\*NS = not significant

\*\*to convert pmol/L to uU/mL, divide value by 7.1

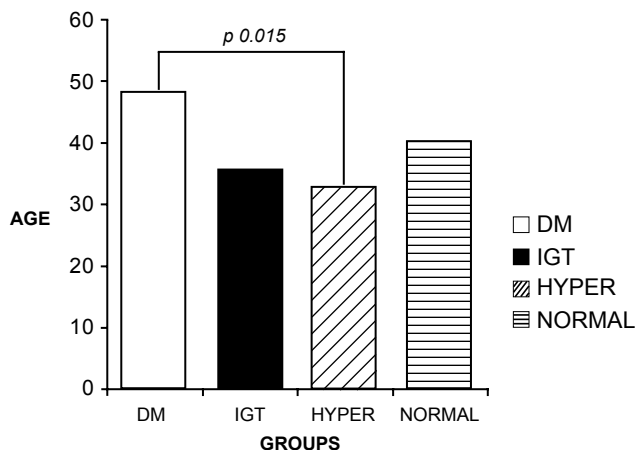


Fig. 1. Multiple Comparison of Age Between Groups

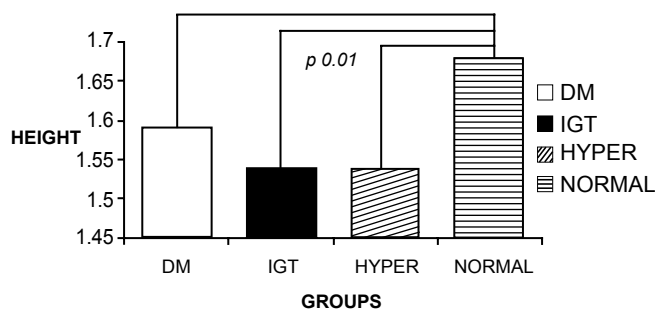


Fig. 3. Multiple Comparison of Height Between Groups

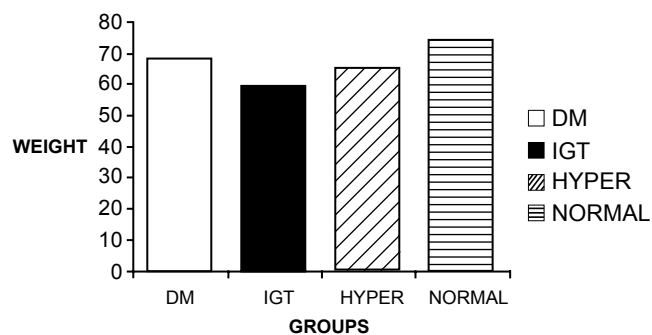


Fig. 2. Multiple Comparison of Weight Between Groups

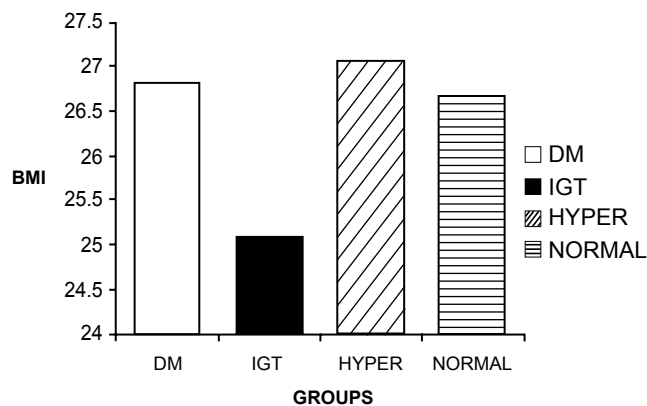


Fig. 4. Multiple Comparison of BMI Between Groups

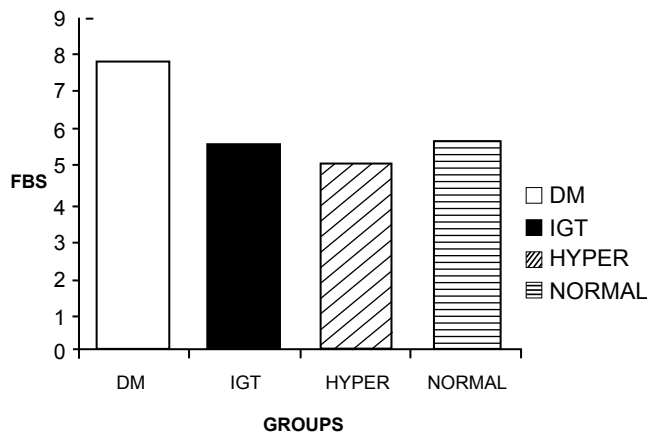


Fig. 5. Multiple Comparison of FBS Between Groups

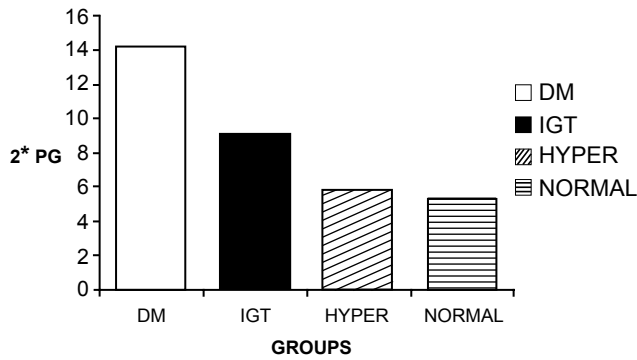


Fig. 6. Multiple Comparison of 2 Hours Post Glucose Load Between Groups

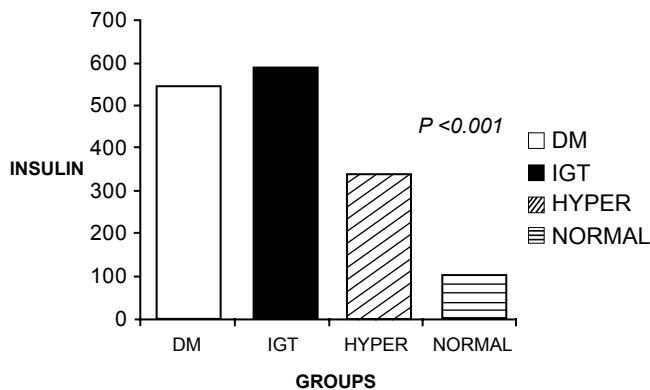


Fig. 7. Multiple Comparison of Insulin Between Groups

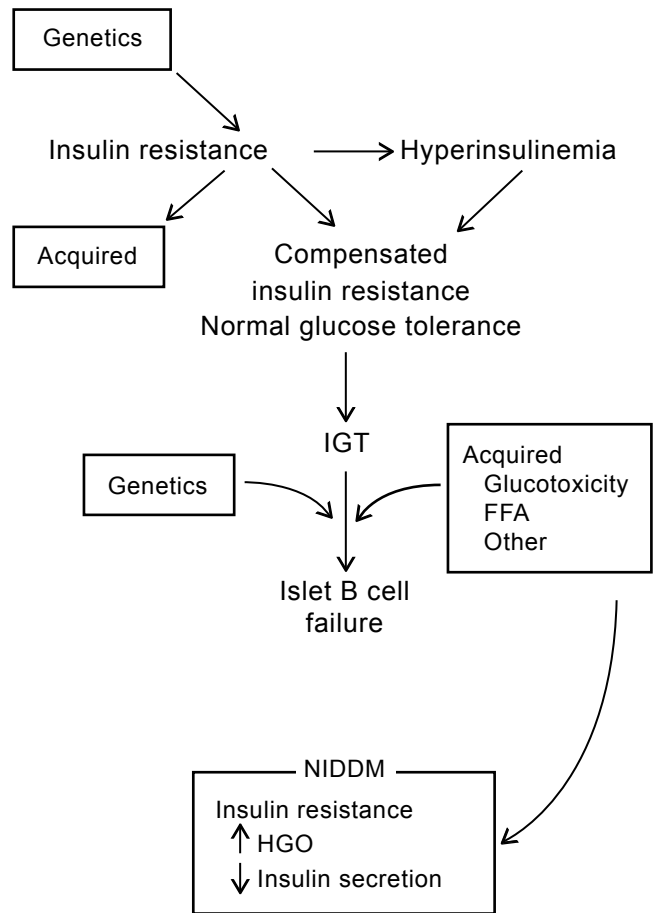


Fig. 8. Proposed Etiology for the Development of Type 2 Diabetes (From Olefsky J. Kruszynska Y. Type 2 Diabetes Mellitus Etiology. Pathogenesis and Natural History. In DeGroot L. Jameson JL (eds): Endocrinology 4th ed. W.B. Saunders. Philadelphia. Pennsylvania. 777-798, 2001)

## DISCUSSION

Patients diagnosed with diabetes were noted to be older which is consistent with well established risk factor of advancing age as a common finding in insulin resistance and diabetes. Based on the US National Health and Nutrition Examination Survey (NHANES) 1999-2000, the combined unadjusted prevalence of total diabetes and impaired fasting glycemia in adults aged = 20 was 14.4 %, and this increased with age, reaching 33.6 % by age = 60 years.<sup>9</sup> A number of large epidemiologic studies showed that the risk for diabetes, and presumably insulin resistance, rises as body fat content increases from the very lean to the very obese as determined by the body mass index.<sup>3</sup> In our study, patients who had compensated hyperinsulinemia have a greater mean BMI but was

not statistically significant from those with diabetes, IGT and normal glucose-insulin. In other studies, insulin resistance was also noted in normoglycemic, first-degree relatives of type 2 diabetics even at a time when they are non-obese, implying a strong genetic component in the development of insulin resistance.<sup>3</sup> In our study 34 (68 percent) of patients had family history of diabetes. Among the different groups 80 percent of patients who had compensated hyperinsulinemia have a family history of diabetes versus 69 percent among diabetics and 50 percent among IGT and normal to patients.

Strumvoll *et al*<sup>6</sup> used the plasma glucose and insulin responses during an OGTT to predict  $\beta$  cell function and insulin sensitivity. They found out a good correlation between the insulin sensitivity index (ISI) using a hyperglycemic and euglycemic-hyperinsulinemic clamp studies and insulin at 120 minutes taken from an OGTT. This parameter holds true in individuals with normal glucose tolerance as well as in individuals with IGT. In contrast, fasting glucose and insulin ratio may be an inappropriate physiologic index of insulin sensitivity especially if the fasting glucose is elevated.<sup>5</sup> Similar to diabetics, patient with IGT have significantly lower insulin sensitivity indexes compared with normal glucose tolerance subjects, suggesting that IGT subjects have a relative defect in the ability to secrete insulin to adequately compensate for their insulin resistance.<sup>10</sup> Furthermore, it has been noted that there is reduced glucose clearance among glucose tolerant offspring's of diabetic parents. This reduced clearance is accompanied by compensatory hyperinsulinemia, not hypoinsulinemia, suggesting that the primary defect is in the peripheral tissue response to insulin and glucose, not in the pancreatic beta cell.<sup>11</sup> In our study, it showed that there is some degree of preserved insulin sensitivity in patients with normoglycemia compared to those with altered glucose homeostasis. Multiple comparisons of the absolute insulin levels 2 hours post glucose loading showed that there was no significant difference between the 3 groups except for those with normal blood glucose and insulin, highlighting compensated hyperinsulinemia in patients with normal glucose levels. Findings in our study confirmed previous study that there is increasing evidence that by the time glucose tolerance or fasting glucose levels become impaired, appreciable  $\beta$ - cell hypersecretion is present.

## RECOMMENDATIONS

There are five basic criteria to justify initiating a program to prevent a disease like diabetes mellitus, most especially its disease related morbidity and mortality. Important to this is that the early development and natural history of the disease should be understood sufficiently well to identify parameters that measure its progression to disease.<sup>12</sup> To date, prevention trials for type 2 diabetes mellitus target the "pre-diabetes" stage of impaired glucose tolerance. With previous work on compensated hyperinsulinemia in patients with normal OGTT, it seems likely that attempts to prevent type 2 diabetes will be more successful if intervention is commenced when blood glucose levels are still in the normal range. This compensated hyperinsulinemic phase, "pre-pre-diabetes", should be identified among patients at risk to develop diabetes mellitus. However, to date, a bedside/office and physician-patient friendly assessment of this has not been done.

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