Correlation of Glycosylated Hemoglobin And Oral Glucose Tolerance Test Results In Hyperinsulinemic Pre-Impaired Glucose Tolerance State Versus Normoinsulinemic-Normal OGTT

Pilar D. Torres-Salvador, M.D.[1],
Gelinemae G. Malaza, M.D.[1],
Leilani B. Mercado-Asis, M.D., Ph.D., MPH[1,2]

ABSTRACT

Background Prediabetes is an intermediate stage prior to development of diabetes mellitus. Pre-impaired glucose tolerance state represents an early stage in the pathogenesis of diabetes wherein the normal glucose is attained by compensated hyperinsulinemia. Glycosylated hemoglobin is used in diagnosis and monitoring of diabetes but has not been explored in pre-IGT state. The objective of this study is to compare the 2-hour blood glucose, 2-hour insulin level, and HbA1c between normoinsulinemic-normal OGTT and pre-IGT groups.

Methods Conducted at University of Santo Tomas Hospital, this was a retrospective analytical study of high-risk individuals for evaluation of type 2 diabetes from 2000-2011 and underwent 75-gm OGTT with 2-hour blood sugar and insulin determinations. The 2-hour glucose, insulin level and HbA1c in normoinsulinemic-normal OGTT were compared with the pre-IGT group using t-test. Correlation between the 2-hour blood glucose and insulin level with the HbA1c was done using Pearson correlation analysis. Statistical significance was considered for p-value of <0.05.

Results Second-hour blood glucose and insulin levels were significantly higher in the pre-IGT group as compared to the normoinsulinemic-normal OGTT group (128.60±18 and 89.29±68.82 vs. 90.68±26 and 17.40±8.15). The HbA1c of the pre-IGT group was significantly higher than the normoinsulinemic-normal OGTT group (6.09±0.55 vs. 5.15±0.25, p-value <0.001). There was weak positive correlation between the HbA1c and 2-hour blood glucose levels between the two groups but not with the insulin levels.

Conclusion The pre-IGT groups have significantly higher 2nd hour blood sugar, insulin and HbA1c

✉ Prof. Leilani B. Mercado-Asis
lanibmasis@gmail.com

[1] Section of Endocrinology, Department of Internal Medicine, University of Santo Tomas Hospital, Manila, Philippines

[2] Faculty of Medicine and Surgery, University of Santo Tomas, Manila, Philippines

levels. This suggests that indeed the metabolic abnormality must be addressed as early as the pre-IGT stage.

Keywords prediabetes, HbA1C, hyperinsulinemia, normoinsulinemic

INTRODUCTION

Diabetes mellitus type 2 is a disorder characterized by inability to normalize blood glucose due to insulin resistance with relative insulin deficiency from progressive ß-cell destruction. It is therefore detected with elevation of fasting glucose or impaired glucose tolerance.

Compensated hyperinsulinemia producing normal glucose is a state that preludes diabetes (1). The basal immunoreactive insulin is 10µIU/ml in fasting level and reaches peak concentration by 30 minutes, rapidly declining to baseline after second hour (2). In a study by Matawaran and Mercado-Asis (3), it was shown that high-risk individuals may present with normal 2-hour glucose (<140mg/dl) but with increased insulin levels (> 30uIU/ml). This state of compensated hyperinsulinemia which may reflect decreasing insulin sensitivity is thence termed pre-impaired glucose tolerance state or pre-IGT. This supports the proposed schematic description by Olefsky and Kuzynska on the natural history of type 2 diabetes wherein insulin resistance is initially addressed by increase in β cell insulin secretion to maintain normoglycemia (1**).**

Glycosylated hemoglobin (HbA1c) is a convenient and reliable parameter used in diagnosis and monitoring of Type 2 DM but has not been explored in pre-IGT state. The objective of this study is to compare the 2-hour blood glucose, 2-hour insulin level, and HbA1c among normoinsulinemic-normal OGTT group and pre-IGT group.

METHODS

Study Design and Subjects

This was a retrospective cross-sectional study of high-risk individuals who consulted in the outpatient clinic at the University of Santo Tomas Hospital (USTH) for evaluation of type 2 diabetes from 2000-2011. Demographic profile of patients such as age, height and weight were recorded. Subjects underwent 75-gm OGTT with 2-hour blood sugar and insulin determination. HbA1c was also measured.

Data Handling

Patients were categorized based on the results of 2-hour glucose level after 75-gm OGTT as having normal glucose tolerance wherein the 2-hour plasma glucose is <140mg/dL, impaired glucose tolerance (IGT) if the 2-hour plasma glucose is 140-199mg/dL, and type 2 diabetes mellitus if the 2-hour plasma glucose is ≥200mg/dL (4).

Patients with normal glucose tolerance were further subdivided into normoinsulinemic-normal OGTT if the 2-hour plasma glucose and insulin levels were normal, and pre-impaired glucose tolerance (pre-IGT) if the 2-hour plasma glucose was normal but insulin level was elevated (3).

Statistical Analysis

The 2-hour glucose with insulin level and HbA1c of patients with normoinsulinemic-normal OGTT were compared with the pre-IGT group using t-test. Correlation between the 2-hour blood glucose and insulin level with the HbA1c was done using Pearson correlation analysis. Statistical significance was considered for p-value of less than 0.05.

RESULTS

There were a total of 174 patient records reviewed from USTH Outpatient department. One hundred twenty-five (71.8%) had normal glucose tolerance, 25 (14.4%) had impaired glucose tolerance, and 24 (13.8%) with type 2 diabetes mellitus. Of those with normal glucose tolerance test, 85 (68%) had elevated 2-hour insulin level whereas 40 (32%) had normal insulin level. Among these, only 65 had HbA1c result thence included in the analysis. Therefore, the prevalence of pre-IGT in this subject population is 68%.

Thirty-three patients (51%) had normoinsulinemic-normal OGTT and 32 (49%) with hyperinsulinemic-normal OGTT (pre-IGT). The pre-IGT group was significantly older than the normoinsulinemic-normal OGTT group (Table 1).

Plasma glucose levels were within normal range at 90.68±26 mg/dL for normoinsulinemic-normal OGTT group and 128.60±18 mg/dL for pre-IGT group (Table 2) based on American Diabetes Association classification (4). However, the 2-hour blood glucose and insulin level were significantly higher in the pre-IGT group as compared to the normoinsulinemic-normal OGTT group (128.60±18 mg/dL and

Table 1. Demographic Profile Of Patients With Normoinsulinemic-Normal OGTT[a] And Pre-IGT[b].

Parameters	Normoinsulinzemic-Normal OGTT[a]	Pre-IGT[b]	p-value[c]
	N1=33	N2=32	
Gender			
Female	26 (79%)	21 (66%)	0.2360
Male	7 (21%)	11 (24%)	
Age (years)	34.3±12.3	42.3±14.2	0.0181
BMI (kg/m^2)	27.1±5.6	28.9±5.7	0.1479

[a]Oral Glucose Tolerance Test
[b]Pre-Impaired Glucose Tolerance Test
[c]p<0.05 as statistically significant

Table 2. Correlation Of The HbA1c[a] And 2-Hour Glucose Level Between Normoinsulinemic-Normal OGTT[b] and Pre-IGT[c].

Group	HbA1c (%)	2-Hour Glucose (mg/dL)	Correlation
Normoinsulinemic-Normal OGTT[b]	5.15±0.25	90.68±26	p=0.0109 r=0.4373
Pre-IGT[c]	6.09±0.55	128.60±18	p=0.0173 r=0.4178

[a]Glycosylated Hemoglobin
[b]Oral Glucose Tolerance Test
[c]Pre-Impaired Glucose Tolerance Test

Table 3. Correlation Of The HbA1c[a] And 2-Hour Plasma Insulin Between Normoinsulinemic-Normal OGTT[b] And Pre-IGT[c].

Group	HbA1c (%)	2-Hour Insulin (μIU/mL)	Correlation
Normoinsulinemic-Normal OGTT[b]	5.15±0.25	17.40±8.15	p=0.1660 r= -0.2469
Pre-IGT[c]	6.09±0.55	89.29±68.82	p=0.6290 r= -0.0888

[a]Glycosylated Hemoglobin
[b]Oral Glucose Tolerance Test
[c]Pre-Impaired Glucose Tolerance Test

89.29±68.82 μIU/mL versus 90.68±26 mg/dL and 17.40±8.15 μIU/mL, respectively) (Figure 1, Figure 2). There was weak positive correlation between the HbA1c and 2-hour blood glucose level between the 2 groups (r=0.4178) (Table 2). However, such correlation was not observed with insulin level.

Interestingly, the HbA1c of the pre-IGT group was significantly higher than those in the normoinsulinemic-normal OGTT group (6.09±0.55 % vs. 5.15±0.25 %, p-value <0.001) (Figure 3).

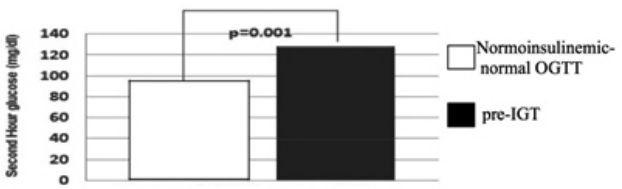

Figure 1. Comparison of 2-hour plasa glucose between normoinsulinemic normal OGTT and pre-IGT showing statistically significant difference between groups

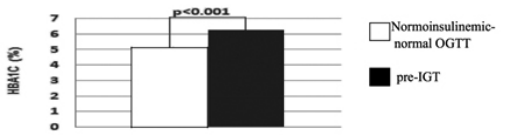

Figure 2. Comparison of 2-hour insulin between normoinsulinemic-normal OGTT and pre-IGT showing statistically significant difference between groups

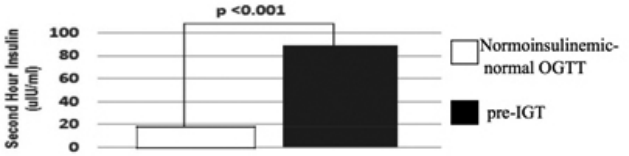

Figure 3. Comparison of HbA1c between normoinsulinemic-normal OGTT and pre-IGT showing statistically significant difference between groups

DISCUSSION

Pre-diabetes is an intermediate stage prior to the development of diabetes mellitus and encompasses impaired fasting glucose (IFG) and impaired glucose tolerance (IGT). American Diabetes Association defines this as fasting plasma glucose of at least 100mg/dL but less than 126 mg/dL and/or a 2-h 75-g OGTT of at least 140 mg/dL and less than 200 mg/dL and/or A1C of 5.7-6.4% (4). The progression of pre-diabetes (IFG, IGT) to diabetes occurs over several years with an annual risk of 5-10% (5).

Pre-impaired glucose tolerance (pre-IGT) state represents an earlier stage in the pathogenesis of diabetes wherein the normoglycemia is attained by compensated hyperinsulinemia (3). Based on this study, normoinsulinemic-normal OGTT patients have glycosylated hemoglobin of 5%, and pre-IGT patients have significantly higher HbA1c at a mean of 6%. Following the ADA classification (4), a large number of high-risk individuals in the pre-IGT stage of metabolic derangement will definitely be missed. The HbA1c correlating with blood sugar in this study in both normoinsulinemic-normal OGTT and pre-IGT groups is another point of contention. This finding could influence re-stratification of individuals at high risk to develop diabetes mellitus by setting lower cut-off values.

The start of hyperinsulinemia at the pre-IGT stage is an important and critical issue for early clinical care and prevention of long-term complication of type 2 diabetes mellitus. C-peptide, a structure cleaved from proinsulin, is equimolar with insulin and can bind to different cell receptors activating signaling pathways (6). It can deposit in the vascular walls of diabetic individuals and bring about pro-inflammatory effect leading to atherogenesis (7). Vascular smooth muscle cell proliferation and neointima formation are contributed upon by C-peptide as shown in in vitro studies (8). This is probably the reason why in the study by Bahar et al (9), the risk of microalbuminuria which is a marker for atherosclerosis and coronary artery disease, is already high in IFG and IGT subjects. Similarly, retinopathy is found in 20.91% of IGT patients (10). Since insulin determination is not routinely done in the workup of high-risk individuals, beginning impairment of metabolic activity as evidenced by elevated insulin level would likely be missed out. Therefore, at the level of IFG and IGT, complications common in established diabetes are already seen (9, 10).

Medical intervention with lifestyle change and insulin sensitizing agent has been shown to decrease the risk of progression to diabetes mellitus by 52% (11) whereas 58% risk reduction in IGT group can be achieved with diet and exercise (12). Therefore, it could be predicted that intervention at the level of pre-IGT could prevent early development of macrovascular complications in a large number of high-risk individuals.

CONCLUSION

This present study has shown that individuals with pre-IGT have significantly higher 2-hour blood glucose and insulin levels, and higher HbA1c as compared to the normoinsulinemic-normal OGTT individuals. Furthermore, the HbA1c in both groups correlated with the 2-hour glucose but not with insulin levels. Our results have placed another challenge on what stage of the metabolic derangement must treatment be initiated.

CONFLICT OF INTEREST

There is no potential conflict of interest of authors relevant to this article.

REFERENCES

1. De Groot L, Jameson JL. Endocrinology. 6th ed. W.B. Saunders, Philadelphia, Pennsylvania. 2010. Chapter 41, Type 2 Diabetes Mellitus: Etiology, Pathogenesis and Natural History; p. 767.
2. Gardner D, Shoback D. Greenspan's Basic and Clinical Endocrinology. 9th ed. McGraw Companies, Inc, USA. 2007. Chapter 17, Pancreatic hormones and Diabetes Mellitus; p. 577.
3. Matawaran B, Mercado-Asis L. Comparison of pancreatic insulin response to hyperglycemia among filipino subjects of various glycemic status. Phil J Int Med. 2009; 47: 25-30.
4. American Diabetes Association. Standards of medical care in diabetes-2016. Diabetes Care 2016; 39 (Supplement 1): S13-S22.
5. Gerstein HC, Santaguida P, Raina P, Morrison KM, Balion C, Hunt D, et al. Annual incidence and relative risk of diabetes in people with various categories of dysglycemia: a systematic overview and meta-analysis of prospective studies. Diabetes Res Clin Pract 2007; 78: 305–312.
6. Vasic D, Walcher D. Proinflammatory effects of C-peptide in different tissues. Int J Inflam. 2012; 2012:932725.
7. Marx N, Walcher D, Raichle C, Aleksic M, Bach H, Grub M, et al. C-peptide colocalizes with macrophages in early arteriosclerotic lesions of diabetic subjects and induces monocyte chemotaxis in vitro. Arterioscler Thromb Vasc Biol. 2004; 24: 540–545.
8. Walcher D, Babiak C, Poletek P, Rosenkranz S, Bach H, Betz S, et al. C-peptide induces vascular smooth muscle cell proliferation: involvement of Src-kinase, phosphatidylinositol 3-kinase, and extracellular signal regulated kinase ½. Circ Res 2006; 99: 1181–1187.
9. Bahar A, Makhlough A, Yousefi A, et al. Correlation between prediabetes conditions and microalbuminuria. Nephrourol Mon. 2013; 5(2): 741-744.
10. Chen X, Zhao Y, Zhou Z, eZhang X, Li Q, Bai L, et al. Prevalence and risk factors of diabetic retinopathy in Chongqing pre-diabetes patients. Eye (Lond). 2012; 26(6): 816-820.
11. Kernan WN, Viscoli CM, Furie KL, Young LH, Inzucchi SE, Gorman M, et al. Pioglitazone after ischemic stroke or transient ischemic attack. N Engl J Med 2016; 374(14): 1321-1331.
12. Diabetes Prevention Program Research Group. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N Engl J Med 2002; 346: 393-403.