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Early postprandial Insulin secretion: its relation to Insulin sensitivity

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ABSTRACT

Background: Lack of first phase insulin secretion during oral glucose tolerance test [OGTT] in Type 2 Diabetes Mellitus (DM) is attributed to glucose toxicity. Alternatively, the role of insulin resistance in impaired insulin release secondary to lack of glucose entry into β cells may be responsible, but is not examined. Aim: The role of insulin sensitivity in 1st phase insulin secretion was assessed. Material and Methods: Plasma glucose (G) and insulin (I) concentrations were determined after an overnight fast (F) and upto 60 minutes during OGTT with glucose 75g in 12 normal (N), 14 with impaired glucose tolerance (IGT) and 41 subjects with Type 2 DM. First phase insulin secretion (Δ Insulin) was determined as a percentage rise from baseline 100x (Peak-Basal)/Basal. Insulin sensitivity was determined as FI x FG (mUxmM/L). Results: FG were normal (≤ 5.5 mM/L) in both N and IGT; and ≥7.0 mM/L in Type 2 DM. FI x FG and Δ insulin were 35 ± 4 and 389 ± 89% in N; 77 ± 5 and 254 ± 65% in IGT; and 235 ± 19 and 95 ± 15% in Type 2 DM. Significant negative correlations were noted between Δ insulin one hand and FI x FG on the other amongst all subjects [p < 0.0001 for all correlations]. Conclusion: Decline of 1st phase insulin secretion in IGT and Type 2 DM may be attributed to inhibited release of depleted insulin stores in the β Cells induced by impaired glucose entry due to insulin resistance, and is unlikely to be caused by glucose toxicity in IGT in presence of fasting euglycemia.

Keywords: Insulin Secretion; Insulin Resistance; Impaired Glucose Tolerance; Type 2 Diabetes Mellitus

1. INTRODUCTION

The presence of post prandial hyperglycemia as well as impaired glucose tolerance [IGT] is well documented to be earlier stages in evolution of Type 2 Diabetes Mellitus [1-4]. Moreover, the role of first phase post prandial insulin secretion in controlling post prandial glycemia is well established [4-6]. Finally, inhibition of first phase post prandial insulin secretion in onset of post prandial hyperglycemia or IGT in early stages of evolution of Type 2 DM is well defined [4-7]. This decline in first phase post prandial insulin secretion in subjects with Type 2 DM is often attributed to 'glucose toxicity' in presence of fasting hyperglycemia [8,9]. However, the decline in first phase insulin secretion in presence of fasting euglycemia and post prandial hyperglycemia or IGT can not be explained by 'glucose toxicity'. Moreover, raising plasma glucose in normal subjects during a hyperglycemic clamp study failed to inhibit first phase post prandial insulin rise in normal subjects [10]. Thus, the concept of 'glucose toxicity' may neither be totally accurate nor adequate in explaining the inhibition of first phase post prandial insulin secretion, in IGT or Type 2 DM. Therefore, alternative mechanisms need to be explored for the decline in 1st phase insulin secretion in presence of fasting euglycemia and postprandial hyperglycemia in Type 2 DM or in IGT. Insulin resistance at the level of ß cells themselves may be such an alternative mechanism which is likely to inhibit glucose entry and in turn decrease either the synthesis or release of the stored insulin resulting in decreased insulin secretion in response to oral or IV administration of glucose or a meal. Therefore, this study assessed the influence of insulin sensitivity on the magnitude of the first phase insulin secretion.

2. SUBJECTS & METHODS

The study was approved by the Research and Development Committee and the Human Studies Subcommittee at the medical center. 12 lean [BMI, 24 ± 2 kg/m^2] male employees, (mean age 46 ± 4 yrs) with normal glucose tolerance [NGT], 14 obese [BMI 35 ± 3 kg/m^2]

male employees (mean age 48 ± 3 yrs) with impaired glucose tolerance [IGT] and 41 men [BMI, 35 ± 4 kg/m^2] newly diagnosed with Type 2 Diabetes (mean age 49 ± 5 yrs) were randomly selected to participate in a study following signing informed consent documents. The diagnosis of NGT, IGT and Type 2 DM was documented by previous OGTT according to criteria established by ADA [11]. Subjects with hospitalization in previous 6 months, elevated liver enzymes greater than twice normal values and serum creatinine > 1.5 mg/dl were excluded. None of the subjects were consuming any medications at the time of the study. They were advised to abstain from alcohol for at least a period of two weeks. Subjects presented at the laboratory between 0800-0900 hours after an overnight fast. 3 ml blood samples were drawn prior to and at 15,30, 45 and 60 minutes after oral ingestion of glucose 75 g. Blood samples were immediately centrifuged at 4˚C and serum was extracted and stored at -20ºC for later determination of glucose and insulin concentrations. Serum glucose and insulin were determined by well established commercial kits. Interassay and intraassay coefficients of variation for these determinations ranged between 4-10% in our laboratory.

First phase insulin secretion was determined as a percentage rise (Δ% insulin 0-30) from baseline [100xPeak insulin level at 30 minutes-basal level/Basal Level.], as well as by insulinogenic index calculated as (Δ% insulin 0-30/Δ% glucose 0-30) as described previously (**Table 1**) [12]. Insulin sensitivity was determined as a Product, Fasting Insulin x Fasting Glucose (FI x FG) used in HOMA method as well as its modifications, as described previously (**Table 1**). [13-16]. Moreover, it has been documented recently to be a reliable index of insulin sensitivity [16]. Finally, insulin secretion/insulin resistance index [IS/IR] was determined by a calculation [(Δ%I 0-30/Δ % G 0-30)/ FIxFG] as determined previously [17] because this index also expresses relationship between first phase insulin secretion and insulin sensitivity (**Table 1**). Statistical analysis was conducted by analysis of variance and by students' 't' test for comparisons between individual groups. Simultaneously, a relationship between first phase insulin secretion and insulin sensitivity was assessed, by a linear regression method with calculation of a correlation coefficients between Δ% insulin and insulinogenic index on one hand and FI x FG as well as IS/IR on the other. Finally, correlations were also determined between indices of 1st phase insulin secretion on one aspect and both fasting plasma glucose and insulin concentrations on the other.

3. RESULTS

Fasting plasma glucose levels were ≤ 5.5 mM/L in both normal subjects and subjects with IGT whereas HbA1c concentrations were < 5.7% in normal subjects and 5.7-6.4% in subjects with IGT. In comparison, fasting plasma glucose levels and HbA1c concentrations were >8.0 mM/L and > 7.5% in subjects with Type 2 DM. As expressed by both the % rise [Δ%Insulin] as well as insulinogenic index, 1st phase insulin rise was lowest in subjects with Type 2 DM with highest FI x FG, whereas maximum insulin rise was noted in subjects with NGT with lowest FI x FG and intermediate values were observed in subjects with IGT [**Table 2**]. Moreover, insulin secretion/insulin resistance indices were markedly reduced in subjects with IGT with even further lowering in subjects with Type 2 DM in comparison to values noted in subjects with NGT [**Table 2**]. A significant negative correlation was noted between % insulin rise on one hand and FI x FG on the other amongst all subjects (**Figure 1**). Similar significant negative correlation was also noted between insulinogenic index on one hand and index of insulin sensitivity [FPxFG] on the other [**Table 2**]. Finally, significant positive correlations were also noted between % insulin rise [ΔI] and insulinogenic indices on one aspect and IS/IR indices on the other [**Table 3**]. However, no significant correlations were noted between Δ % Insulin and insulinogenic indices on one hand and either fasting glucose or fasting insulin concentration on the other. [P > 0.05 for all comparisons].

4. DISCUSSION

Lack of early or first phase insulin secretion during oral glucose tolerance test [OGTT] or following a meal in Type 2 Diabetes Mellitus (DM) is attributed to fasting hyperglycemia, a concept of glucose toxicity [8,9]. However, raising fasting glucose concentration failed to

Table 1. Indices of 1st phase insulin secretion and insulin sensitivity.

1st Phase Insulin Secretion	
Δ % Insulin 0-30 min	100 x (Peak Insulin level at 30 min-Basal level /Basal level)
Insulinogenic Index	Δ % Insulin 0-30 min/ Δ % Glucose 0-30 min
Insulin Sensitivity Index	Fasting Insulin x Fasting Glucose (FI x FG)
Insulin Secretion/Insulin resistance Index (IS/IR)	(Δ % Insulin 0-30/Δ % Glucose 0-30)/(FI x FG)

Table 2. Fasting serum insulin x fasting serum glucose (FI x FG), % rise (Δ) of insulin at 30 minutes from fasting level, insulinogenic index [$\Delta I\%_{0-30}/\Delta\%$ $Glucose_{0-30}$] and insulin secretion [IS]/insulin resistance [IR] index [$(\Delta I_{0-30}/\Delta G_{0-30})/(FIxFG)$] in participating subjects.

Subjects	FI x FG mU×mM/L	ΔInsulin (%)	Insulinogenic Index	IS/IR Index
NGT	35 ± 4	389 ± 89	6.2 ± 0.9	0.17 ± 0.1
IGT	77 ± 5*	254 ± 65*	3.4 ± 0.5*	0.04 ± 0.006*
DM2	235 ± 19†‡	95 ± 15†‡	1.3 ± 0.2†‡	0.006 ± 0.0004†‡

* → $p < 0.01$ vs NGT; † → $p < 0.0001$ vs NGT; ‡ → $p < 0.001$ vs IGT

Table 3. Correlations between parameters of insulin secretion [IS] and insulin resistance [IR].

Correlation	r Value	p Value
Δ I vs FI x FG	- 0.50	< 0.0001
Δ I vs IS/IR Index	0.54	< 0.0001
Insulinogenic Index vs FI x FG	- 0.62	< 0.0001
Insulinogenic Index vs IS/IR Index	0.63	< 0.0001

***** See Table 1 for definitions

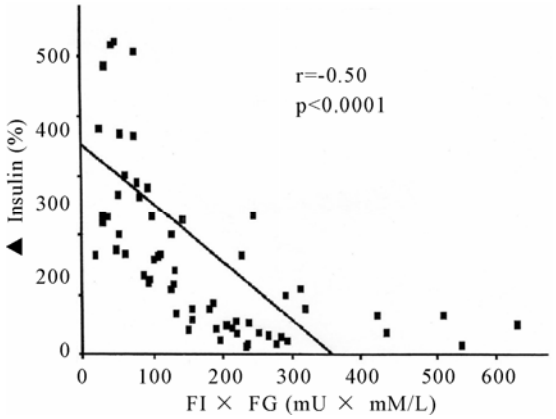

Figure 1. Correlation between1st Phase Insulin Secretion (▲ Insulin) and Index of Insulin Sensitivity (FIxFG).

inhibit first phase insulin secretion in normal subjects [9].

Moreover, the concept of glucose toxicity can not explain the decline in 1st phase insulin secretion in subjects with impaired glucose tolerance (IGT) because of presence of fasting euglycemia. This study demonstrates that first phase or early insulin response to oral glucose load is distinctly dependent on the degree of insulin resistance as expressed by markedly significant correlations between the indices of insulin secretion and insulin resistance [**Table 2**]. This finding is consistent with previous studies conducted in subjects with varying degrees of glucose tolerance ranging from normal glucose tolerance to Type 2 diabetes [1,17-25]. Some of these reports used glucose clamps technique whereas others have utilized HOMA or its modifications to quantify insulin resistance, but with identical conclusions that in subjects with IGT, first phase or early insulin secretion is related to insulin resistance [17-25]. It is plausible that the decline in 1st phase insulin secretion during the stages of IGT, and postprandial hyperglycemia with fasting euglycemia or the decrease in both the 1st and 2nd phase insulin rise with both fasting and postprandial hyperglycemia in Type 2 DM may be caused by worsening insulin resistance at the level of pancreatic β cell itself [4-7,21,24, 26-29]. However, normal glucose tolerance in some obese subjects despite presence of insulin resistance as documented in our previous study [16] is attributed to a prompt and a brisk response to ingestion of glucose or a meal [1,17-25]. In this population of obese subjects with normal glucose tolerance, mild insulin resistance with an intermediate values of FI x FG between normal lean subjects and obese subjects with IGT have been documented [16]. Therefore, it is apparent that a critical degree of severity of insulin resistance may be required for inhibition of glucose entry into pancreatic beta cells causing decline in 1st phase insulin secretion. Furthermore, progressively increased inhibition of entry of glucose secondary to a progressive rise in insulin resistance appears to be responsible for a progressive decline in 1st phase insulin secretion with progression from normal glucose tolerance to type 2 Diabetes as documented in several studies [1,17-25].

The major stimulus for both the insulin synthesis and release by the pancreatic β cells is the entry of glucose. This phenomenon is recently described as 'β cell glucose sensitivity' [24]. This study [24] attributed worsening glucose tolerance to progressive β cell dysfunction induced by declining β cell glucose sensitivity. This finding is almost identical to our observation of declining 1st phase insulin secretion with rising insulin resistance with progressive worsening of glucose tolerance. Furthermore, the role of insulin sensitivity in insulin secretion is fur-

ther evident by studies demonstrating the presence of glucose transporters on β cell membranes with their enhancement by circulatory insulin [30-36]. Finally, it is likely that inhibited entry of glucose into β cells caused by declining β cell glucose sensitivity and insulin resistance decreases insulin synthesis and storage in β cell granule pool leading to a fall in 1st phase postprandial rise as documented in another study [37].

Therefore, the maximum 1st phase insulin secretion in subjects with NGT may be attributed to prompt facilitation of glucose entry into β cells secondary to normal insulin sensitivity to circulating insulin concentration. Alternatively, the least 1st phase insulin rise in subjects with Type 2 DM may be explained by markedly inhibited glucose entry into β cell caused by extreme insulin. Finally, the intermediate 1st phase insulin rise in subjects with IGT is likely to be secondary to subnormal β cell insulin sensitivity but not lowered to the extent noted in subjects with Type 2 DM.

In conclusion, the decline of 1st phase insulin secretion in subjects with IGT, as well as postprandial hypoglycemia in Type 2 DM may be a manifestation of decreased insulin sensitivity at the level of pancreatic β cell itself and not caused by "glucose toxicity" alone.

5. ACKNOWLEDGMENT

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