CORRELATION BETWEENINSULIN SECRETION AND VARYING QUANTITY OF FOOD

Shraddha Badgujar*, J V Dixit**

*Junior Resident Doctor, **Associate Professor and Head, Department of Community Medicine, Government Medical College, Aurangabad-431001

Abstract:

Background & objectives: Diabetes mellitus is a lifestyle disease, the solution to which should be a lifestyle modification. The co-investigator of this study, Dr Dixit, has initiated "World free of Obesity and Diabetes campaign"; which proposes the 'two meal a day diet plan' for patients with Type-2 diabetes and obesity. The worldwide accepted idea of frequent meals for diabetes patients is being challenged by the campaign based on the concept that similar amount of insulin is secreted during every episode of food intake. Multiple times insulin secretion consequent to multiple meals, results in hyperinsulinemia, obesity, insulin resistance and type 2 diabetes. The main objective of this study was to determine the insulin levels in Phase I (10 min) and Phase II (60 min) of insulin secretion in response to varying quantity of food and study the correlation between them.

Methodology: Longitudinal study design was used to follow the blood glucose and insulin levels of 18 volunteers for three consecutive days. A meal with fixed food items but with increasing quantities everyday was given to the eligible volunteers by the coordinators of 'World free of Obesity and Diabetes' campaign. The blood glucose and corresponding insulin levels were recorded at 0 min (baseline), 10 min, and 60 min. Statistical analysis was done to study the correlation between insulin levels in response to varying quantities of food. The blood samples were tested in NABL accredited laboratories.

Results: Among the 18 volunteers, according to HbA1c status and history of taking medicines, 27.8% (5/18) belonged to non-diabetic, 27.8% (5/18) to pre-diabetic and 44.4% (8/18) to diabetic category. The results of our study show that there was no linear correlation between increase in food quantity and insulin level in all these categories as evident after applying Pearson's correlation co-efficient with 2-tailed significance test. After performing one-way ANOVA test, no significant variation in the insulin level was observed in response to varying food quantities.

Interpretation & conclusion: There was no significant linear correlation between Increasing food quantities and insulin level. The Blood glucose levels increased with increased quantities of food. It suggests that insulin index and glycaemic index do not go hand in hand. Our study shows that the 'Food quantity' does not play a deciding role for insulin levels. Study emphasises the need of larger studies to compare insulin secretion in response to two meals versus multiple meals. It can be concluded that to reduce insulin level it is a better option to take two meals in a day compared to multiple meals.

Key Words: Insulin Secretion, Diabetes Mellitus, Food quantity

Author for correspondence: Dr Shraddha Badgujar, Department of Community Medicine, Government Medical, College, Aurangabad-431005; e- mail:shraddhabadgujar94@gmail.com

Introduction:

Diabetes is a group of metabolic diseasescharacterized by hyperglycaemia resulting from defects in insulin secretion, insulin action, or both. The chronic hyperglycaemia of diabetes is associated with long-term damage, dysfunction, and failure of different organs, especially the eyes, kidneys, nerves, heart, and blood vessels. Deficient insulin action results from inadequate insulin secretion and/or diminished tissue responses to insulin at one or more points in the complex pathways of hormone action. [1]Secreting insulin at the right moment and in appropriate

amounts is the vital function of pancreatic beta cells. Therefore, any alteration of their functioning perturbs glucose homeostasis. It is therefore not surprising that beta cells are under the tight control of an array of stimulatory and inhibitory factors, among which glucose plays the leading role [2-4]. It is well established that glucose-stimulated insulin secretion follows a characteristic biphasic time course. Phase I insulin secretion begins within 2 minutes of ingestion of food and continues for 10 to 15 minutes. The Phase II of prandial insulin secretion follows, and is sustained until normoglycemia is restored (pseudo-steady state), which varies from 60 to 120 minutes.[5]The prevalence of diabetes in India and world is on rise in last few decades. Same is true for obesity. There have been attempts to find out ways by which the possibility of diabetes mellitus can be delayed or prevented by lifestyle modifications or by medicines. The aim of therapy for patients with insulin-dependent diabetes mellitus is normoglycemia. Elevated basal and stimulated insulin levels are intimately related to the occurrence of obesity.[6] Obesity per se is accompanied by increased basal insulin levels and decreased oral glucose tolerance. Insulin is a saving hormone and stores energy in the form of fats in the body. In its presence the body uses carbohydrates for getting energy. If the level of insulin decreases as generally happens in the state of fasting, the body uses fats as a source of energy.[5]The insulin-treated patient receives a fixed dose of an insulin and must match the food intake to the inherent peaks of the insulin's activity. Hence, the diabetic patient matches the foodto insulin intake, in contrast to the normal person who matches the insulin to food intake. The co-investigator of this study, Dr Dixit, has initiated “World free of Obesity and Diabetes campaign”; which proposes the ‘two meal a day diet plan’ for patients with Type-2 diabetes and obesity. The worldwide accepted idea of frequent meals of low quantity for diabetes patients is being challenged by the campaign based on the concept that insulin is secreted during every episode of food intake, thus aiding in hyperinsulinemia and obesity in Type-2 diabetes patients. This study was done in view of verifying this idea. The main objective of this study was to determine the insulin levels in Phase I (10 min) and Phase II (60 min) of insulin secretion in response to varying quantity of food and study the correlation between them. This study was done with an attempt to address the knowledge gap of insulin levels in response to varying quantity of food. Diabetes mellitus is a lifestyle disease, thus, the role of a lifestyle modification in the form of dietary regulation, needs to be studied for diabetes reversal and prevention of its complications.

Material and Methods:

Longitudinal study design was used.The study was approved by the Institutional Ethics Committee of Government Medical College, Aurangabad in August 2020. A call for voluntary participation in the study was put forth via WhatsApp messenger group of “World free of Obesity and Diabetes” campaign in the month of September 2020. Any participant of thecampaign, voluntarily willing to meticulously follow the meal plan provided in the studyandreport the test results, were included after obtaining a written informed consent. Any volunteer who did not give consent or had very high or very low baseline blood glucose and/or insulin levels, were excluded from the study. The volunteers were categorized as non-diabetic, pre-diabetic or diabetic on the basis of pretested HbA1c levels through the campaign. The status of diabetes was assessed to note any extreme variations in readings due to any pre-existing condition; thus, aiding in ruling out the outliers

during data analysis.Eligible volunteers were given a patient instruction sheet in English/ Hindi/ Marathi and asked to visit the NABL (National Accreditation Board for Testing and Calibration Laboratories)accredited laboratories, informed by the campaign coordinators near the place of their residence.The volunteers visited the laboratory every morning for three consecutive days with 10-hour gap from the last meal (fasting state). The doctor coordinators of the campaign in the respective areasprescribed the investigations in writing after explaining the instructions to the volunteers and acquiring informed consent in English/ Hindi/ Marathi from every eligible volunteer every day. Blood glucose was estimated by standard biochemical glucose oxidase method. Insulin levels was investigated by CLIA (Chemiluminescence Immunoassay) /CMIA(Chemiluminescent Microparticle Immuno-Assay) tests. Three readings were taken every day, that is, at 0 minutes (fasting state), 10 minutes (prandial state), and at 60 minutes (post prandial state). All subjects were provided a meal at the testing center by the campaign coordinators with an increasing amount every day for three consecutive days. The meal plan was-'Day 1- 'x'; Day 2- '2x'; Day 3- '3x' quantity of food. The quality and content of the diet was same every day except for the increase in the quantity. For example: Day 1- '½ roti ½ bowl vegetable'; Day 2- '1 roti 1 bowl vegetable'; Day 3- '1 ½ roti 1½ bowl vegetable'. The readings were recorded systematically in a Case Report Form by the campaign coordinators and submitted to the principal investigator. All the readings were entered systematically in Microsoft Excel 2019 for data analysis. Statistical analysis to study the correlation between increasing food quantity and corresponding blood glucose and insulin level was done by IBM SPSS v.26 software (Statistical Product and Service Solutions).

Results:

The results of Blood Glucose levels and Insulin levels were used to study the correlation between insulin level in phase I and phase II with varying quantities of food. Fig. 1 shows that increase blood glucose level in response to varying quantities of food did not increase the insulin levels linearly, as maximum observations were plotted below the reference line in an overlay scatterplot.

Fig. 1: Overlay Scatter-plot showing Insulin secretion to corresponding Blood Glucose level at varying quantities of food

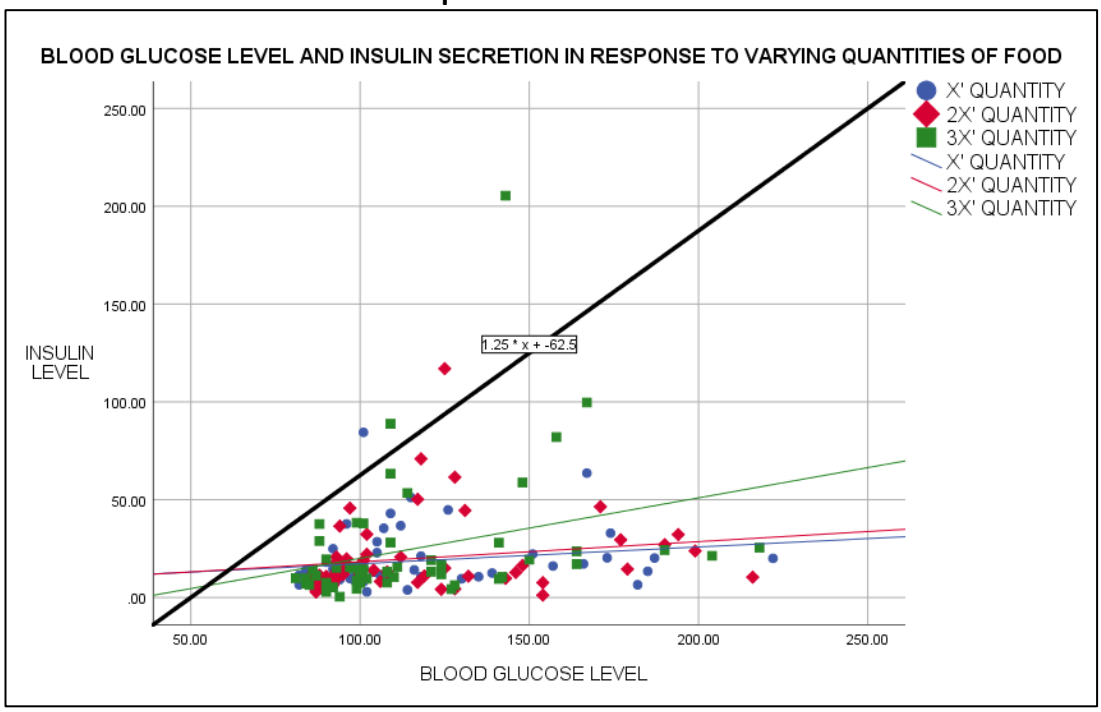

Fig.2: Insulin Level with corressponding Blood Glucose level in Prandial state (Phase I) in response to varying food quantities

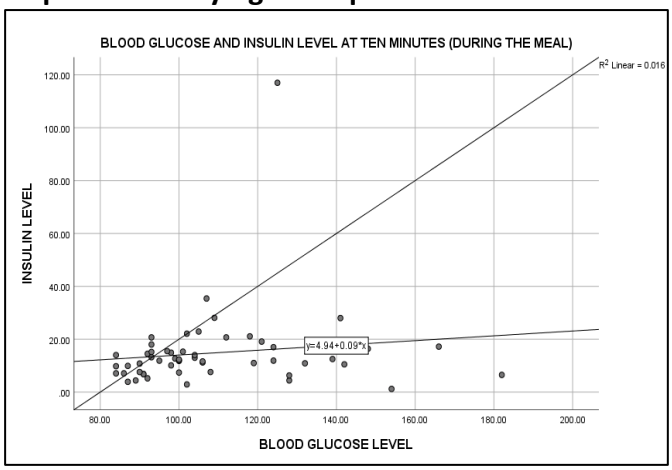

Table 1: Pearson's Correlation co-efficient for Phase I of insulin secretion in response to varying food quantities

		INSULIN	GLUCOSE
INSULIN	**Pearson Correlation**	1	**0.127**
	Sig. (2-tailed)		**0.360**
	N	54	54
GLUCOSE	**Pearson Correlation**	**0.127**	1
	Sig. (2-tailed)	**0.360**	
	N	54	54

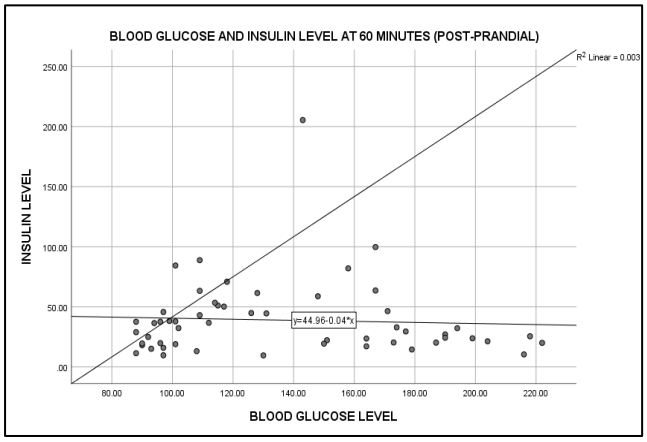

Fig.3: Insulin Level with corressponding Blood Glucose level in Post-prandial state (Phase II) in response to varying food quantities

Table 2: Pearson's Correlation co-efficient for Phase II of insulin secretion in resposne to varying food quantities

		INSULIN	GLUCOSE
INSULIN	**Pearson Correlation**	1	**-0.057**
	Sig. (2-tailed)		**0.680**
	N	54	54
GLUCOSE	**Pearson Correlation**	**-0.057**	1
	Sig. (2-tailed)	**0.680**	
	N	54	54

A Pearson's correlation co-efficient was used to study whether a linear correlation existed between blood glucose levels and insulin secretion in Phase I and Phase II in response to increase in food quantity. Pearson's correlation co-efficient was 0.127 and -0.057 (Table 1 & 2) for Phase I and Phase II of insulin secretion respectively. A 2-tailed significance test (Table 1 & 2) shows that the 'p' value was 0.360 and 0.680 for Phase I and Phase II of insulin secretion respectively. The value of p>0.05, reveals that the linear correlation between insulin levels and varying quantities of foodwas not significant. A simple scatter plot graph (Fig.2 & 3) was drawn to establish the same (R^2 Linear= 0.016 for Phase I and 0.003 for Phase II). Descriptive statistics (Table 3 & 7) for mean, standard deviation, standard error of mean and 95% confidence interval were calculated to spot the outliers or missing values before applying one-way ANOVA. There was no statistically significant difference between groups, as determined by one-way ANOVA (Table 4-Phase I: F=0.567, p=0.571; Table 8-Phase II: F=2.634, p=0.082). A Tukey post hoc test revealed that there was no statistical difference between the insulin levels in Phase I and Phase II, when compared between the observations after intake of 'x', '2x' or '3x' quantities of food.

Table 3: Descrtiptive Statistics of Phase I of insulin secretion in response to varying quantities of food

FOOD QUANTITY	N	Mean	Std. Deviation	Std. Error	95% Confidence Interval for Mean		Minimum	Maximum
					Lower Bound	Upper Bound		
X	18	13.2889	7.65229	1.80366	9.4835	17.0943	2.90	35.40
2X	18	18.0383	25.38880	5.98420	5.4128	30.6639	1.20	117.00
3X	18	13.0833	6.73099	1.58651	9.7361	16.4306	5.20	28.10
Total	54	14.8035	15.66551	2.13181	10.5277	19.0794	1.20	117.00

Table 4: One-way ANOVA test for Phase I of insulin secretion to varying quantities of food

Category	Sum of Squares	df	Mean Square	F	Sig.
Between Groups	282.909	2	141.455	**0.567**	**0.571**
Within Groups	12723.728	51	249.485		
Total	13006.637	53			

Table 5: Intergroup comparison by Tukey HSD test in Phase I level of Insulin secretion

Dependent Variable: PHASE I INSLUIN LEVEL							
	Comparison Groups		Mean Difference (I-J)	Standard Error	Significance	95% Confidence Interval	
						Lower Bound	Upper Bound
Tukey HSD	X	2X	-4.74944	5.26503	0.641	-17.4591	7.9602
		3X	0.20556	5.26503	0.999	-12.5041	12.9152
	2X	X	4.74944	5.26503	0.641	-7.9602	17.4591
		3X	4.95500	5.26503	0.617	-7.7547	17.6647
	3X	X	-0.20556	5.26503	0.999	-12.9152	12.5041
		2X	-4.95500	5.26503	0.617	-17.6647	7.7547

Table 6: Descrtiptive Statistics of Phase II of insulin secretion in response to varying quantities of food

FOOD QUANTITY	N	Mean	Std. Deviation	Std. Error	95% Confidence Interval for Mean		Minimum	Maximum
					Lower Bound	Upper Bound		
X	18	31.6722	19.92627	4.69667	21.7631	41.5813	9.60	84.40
2X	18	32.7000	17.57485	4.14243	23.9602	41.4398	10.40	70.90
3X	18	52.4789	45.96854	10.83489	29.6193	75.3385	17.10	205.40
Total	54	38.9504	31.58538	4.29823	30.3292	47.5715	9.60	205.40

Table 7: One-way ANOVA test for Phase I of insulin secretion to varying quantities of food

Category	Sum of Squares	df	Mean Square	F	Sig.
Between Groups	4951.069	2	2475.534	**2.634**	**0.082**
Within Groups	47923.645	51	939.679		
Total	52874.714	53			

Table 8: Intergroup comparison by Tukey HSD test in Phase I level of Insulin secretion

Dependent Variable: PHASE II INSLUIN LEVEL							
	Comparison Groups		Mean Difference (I-J)	Standard Error	Significance	95% Confidence Interval	
						Lower Bound	Upper Bound
Tukey HSD	X	2X	-1.02778	10.21806	0.994	-25.6940	23.6384
		3X	-20.80667	10.21806	0.114	-45.4729	3.8595
	2X	X	1.02778	10.21806	0.994	-23.6384	25.6940
		3X	-19.77889	10.21806	0.139	-44.4451	4.8873
	3X	X	20.80667	10.21806	0.114	-3.8595	45.4729
		2X	19.77889	10.21806	0.139	-4.8873	44.4451

Discussion:

In our study, 18 participants volunteered to comply to the proposed meal plan and report the results of Blood glucose and insulin levels at 0 (Baseline), 10 (Phase I/ Prandial) and 60 min (Phase II/ Post-prandial) of meal after a fasting period of 10 hours for three consecutive days. Among the 18 volunteers, according to HbA1c status, 27.8% (5/18) belonged to Non-diabetic, 27.8% (5/18) to Pre-diabetic and 44.4% (8/18) to Diabetic category. The results of our study show that there was no linear correlation between insulin level and increase in food quantity in all these categories. After performing one-way ANOVA test, no significant variation in the insulin level was observed in Phase I and II in response to varying food quantities. These findings are congruent with the study by Dixit et al, which reports, one cannot control the basal insulin secretion, but the insulin secretion occurring as a result of eating episodes can be controlled. Due to eating many times in the day the insulin levels always remain very high.Due to eating many times in the day the insulin levels always remain very high. In some studies, subjects consumed 20% of calories with breakfast and 40% with lunch and dinner respectively.However, the amount of insulin secreted after each meal did not differ significantly. [7,10]Del Prato et al reports that both animal and human studies support the critical physiologic role of the first-phase of insulin secretion in the maintenance of post-meal glucose homeostasis. If the primary goal of diabetes therapy is control of post-meal glucose excursion, then the regulation of glucose absorption from the gut and entry into the circulation is an important mechanism to consider.[8]Steiner et al reports in his literature on current concepts of diabetes mellitus that, first phase of insulin may be the first defect in the development of diabetes, thus no matter how insulin is injected, one will never achieve perfect glycaemic control in the diabetes. Thus, the first phase may be very important in determining the way in which the body handles a load of carbohydrate. If the peak concentration is high enough it appears to "open the doors of the cell" allowing glucose to enter and lead to glucose intolerance.[9]Following the same individuals was the strength and recording their insulin levels in response to increase in food quantity was a novel idea of our study. Thus, 'Food quantity' does not play key role in deciding

insulin levels in all individuals irrespective of their diabetic status. Diabetes is a heterogeneous group of metabolic disorder characterized by defects in insulin secretion and action. Insulin resistance is a key feature of Type-2 diabetes. However, insulin resistance alone does not appear to be sufficient to cause diabetes. Hallberg et al quotes that, Despite the growing evidence that reversal is possible, achieving reversal is not commonly encouraged by our healthcare system. In fact, reversal is not a goal in diabetes guidelines. Specific interventions aimed at reversal all have one thing in common: they are not first-line standard of care. This is important, because there is evidence suggesting that standard of care does not lead to diabetes reversal. This raises the question of whether standard of care is really the best practice.[11]Hence dietary modification in a pre-diabetic and diabetic patient might be the key todiabetes reversal and prevent its complications.

Conclusion:

There was no significant linear correlation between Increasing food quantities and insulin level, although the Blood glucose levels increased with increasing quantities of food. Our study emphasises the fact that the 'Food quantity' does not play a deciding role for insulin levels in non-diabetic, pre-diabetic or diabetic individuals. This study was done with an attempt, in brief, to verify the ideaof 'Insulin is secreted in response to every episode of food consumption, hence the frequency should be altered and not the quantity, for diabetes reversal and prevention of its complications'; as proposed by 'World free of diabetes and obesity campaign.'Diabetes reversal by lifestyle modification is a cost-effective mode of overcoming obesity and other complications associated with Type-2 diabetes.This study calls for an interventional program of combined regimen of dietary modifications for diabetes reversal along with therapeutic management for diabetes control.This study was done with an attempt to add to the existing knowledge of this type of intervention.

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Statement of Conflict of Interest:

This study received funding from 'ADORE' Trust. The co-investigator of this study, Dr J V Dixit, is the chairman of 'ADORE' trust, who was responsible for logistics, financial support, coordination of testing centers from different areas, and to monitor the study. The principal investigator of this study is student of Dr J V Dixit. The principal investigator assures that this relationship did not influence the outcome of the study.

Limitations of the study:

The insulin levels were measured at three points- '0', '10' and '60' min which is used in studies where 'insulin index' is calculated; and not in a continuous manner as done with a pancreatic clamp.

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Conflict of Interest: None