ORIGINAL RESEARCH PAPER

Internal Medicine

STUDY OF SIGNIFICANCE OF INSULIN AND GLUCAGON RATIO IN NEWLY DIAGNOSED DIABETES MELLITUS

KEY WORDS: Insulin to Glucagon ratio, hyperglycemia, hyperglucagonemia

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ABSTRACT

Diabetes refers to the group of common metabolic disorders that share the phenotype of hyperglycemia. It is the most common metabolic disorder responsible for most of the disease-causing mortalities among the people. Along with insulin various other factors affect glucose regulation with pancreatic alpha cell dysfunction being one of the factor. The data on alpha cell dysfunction is scarce and its importance has reemerged recently. Therefore, the present study was conducted to determine the significance of insulin-to-glucagon ratio in the newly diagnosed diabetic patients. **Objectives:** To investigate the association between Insulin to Glucagon ratio and Diabetes and To study the correlation of the Insulin to Glucagon ratio with Fasting and post prandial glucose levels and HbA1c. **Methods:** It is an hospital based cross sectional study involving 30 newly diagnosed diabetic patients, who were subjected to detailed examination and were evaluated with blood investigations like Fasting and post prandial blood sugars, serum HbA1c, fasting serum insulin, serum glucagon and lipid profile values. **Conclusion:** Fasting blood glucose, post prandial blood glucose and HbA1c levels were found to be negatively correlated (r=-0.939, -0.913, r=-0.919; p<0.001 respectively) with Insulin to Glucagon Ratio.Hyperglucagonemia relative to insulin may cause uncontrolled hyperglycemia with Insulin to Glucagon ratio being a better indicator than individual lab values of insulin and glucagon alone.

INTRODUCTION

- Diabetes refers to the group of common metabolic disorders that share the phenotype of hyperglycemia [1] leading to serious damage to the heart, blood vessels, eyes, kidneys and nerves [2].Diabetes affects more than half a billion people globally today. As per the International Diabetes Federation (IDF), worldwide there are 537 million adults aged 20-79 years who are living with diabetes and it is projected that by 2030, the number of cases will increase to 643 million and 783 million by 2045, if appropriate measures are not taken to control this disease.
- In India, more than half of patients have poor glycemic control and have vascular complications. Therefore, to prevent the development and progression of complications there is an urgent need to develop novel therapeutic agents of diabetes [3].
- The alpha and beta cells of the pancreas control endogenous glucose production, triacylglycerol deposition, and protein synthesis by modulating relative concentrations of glucagon and insulin [4].Defects in insulin secretion and aggravation of insulin resistance are considered the primary factors affecting diabetes development and progression. However, apart from insulin itself, various other factors like dysregulation of glucagon upon pancreatic α-cell dysfunction can also affect glucose regulation in diabetes [1,3,4,5,6].
- The secretory mechanism of glucagon from α-cells has been proposed to be regulated by insulin concentrations from β-cells, which are located closely to α-cells. When insulin secretion increases after meals, glucagon secretion must be suppressed [7,8,9].
- This pathway, however, appears to be dysregulated in diabetic individuals, who have greater postprandial glucagon levels than healthy people [10,11].This suggests that α-cell resistance or dysfunction may be present in patients with diabetes [4,5,6,12]
- In this aspect, Unger RH suggested the 'bihormonal-abnormality' hypothesis in regards to the development of diabetes, stating that both relative or absolute hyperglucagonemia and insulin deficiency may be present in diabetic subjects [4].
- Relative hyperglucagonemia is seen in all types of diabetes, and has been implicated in its pathogenesis as described above. As a result, medicines that limit glucagon activity are being tested in clinical studies to treat type 2 diabetes.
- Some glucose-lowering drugs, such as dipeptidyl peptidase-4 inhibitors (DPP-4i), Glucagon-like peptide-1 receptor agonist (GLP-1 A) and the amylin agonist pramlintide, reduce glucagon production, resulting in a reduction in the excessively high glucagon levels seen in type 2 diabetes and an improvement in the insulin-to glucagon ratio.
- Therefore, in this study we aim at determining the significance of insulin and glucagon ratio in the newly diagnosed diabetic patients and assess its contribution on blood glucose level and various other metabolic parameters.

MATERIALS AND METHODS

Aim And Objective:

To estimate the importance of Insulin and Glucagon ratio in newly diagnosed patients with diabetes mellitus.

Study Design:

This study is an analytical study with a cross-sectional design.

Place Of Research:

Rajarajeswari medical college and hospital, Bangalore.

Study Duration: 18 MONTHS

Sample Size: 30

Inclusion Criteria: Patients recently diagnosed with diabetes mellitus as per the WHO/ADA 2007 guidelines for diabetes.

Exclusion Criteria :

1. Patients who were on treatment for type 1 and type 2 diabetes mellitus.

2. Patients who presented with serious infections, DKA, etc. at the time of diagnosis.

METHODOLOGY:

Patients, newly diagnosed with diabetes mellitus, attending the General medicine Department's OPD at RajaRajeswari Medical College and Hospital, Bangalore were included.

After obtaining informed consent from the patients' detailed medical history was obtained and patients were further guided for various biochemical tests based on the defined inclusion-exclusion criteria.Fasting and postprandial blood sugars, fasting serum insulin, fasting serum glucagon, HbA1c levels and various other biochemical tests were included.

RESULTS:

TABLE 1- Clinical parameters of the patients

	Mean ± SD	Min-Max	Median(Q1-Q3)
FBS (mg/dl)	217.97 ± 55.012	133 - 311	217.5(166.25-265.25)
PPBS (mg/dl)	275.3 ± 61.494	201 - 411	275.5(219.5-304)
HBA1C (%)	7.83 ± 0.882	6.5 - 9.5	7.6(7.1-8.75)
Insulin(microU/ml)	19.43 ± 5.809	11.64 - 29.38	18.06(14.4225-25.3875)
Glucagon(pg/ml)	76.74 ± 18.543	51.2 - 109.36	72.025(60.41-88.73)
Insulin/Glucagon Ratio (microU/pg))	0.255 ± 0.057	0.16 – 0.37	0.246 (0.209 – 0.308)

TABLE 2- Clinical parameters of patients on the basis of

	Ratio < 0.246			Ratio >= 0.246			p value
	Mean ± SD	Min-Max	Median (Q1-Q3)	Mean ± SD	Min-Max	Median (Q1-Q3)	
	262.93						
FBS		216 -	266	173 ±		163(149 -	
	±				133 - 249		<0.001 **
(mg/dl)		311	(243-285)	32.737		188.5)	
	29.397						
	323.6		305				
PPBS		275 -		227 ±		219(212 -	
	±		(289-		201 - 301		<0.001 **
(mg/dl)		411		26.249		235)	
	46.315		351.5)				
HBA1C	8.5 ±	7.6 -	8.6	7.16 ±		7.1(6.8-	
					6.5 - 8.9		<0.001 **
(%)	0.564	9.5	(8.05-8.9)	0.577		7.35)	
Insulin	15.21		14.43				
		11.64 -		23.64 ±	14.42 -	25.41(20.3	
(microU/m	±		(13.265 -				<0.001 **
		20.06		4.986	29.38	1-26.97)	
l)	2.635		16.745)				
			68.9				
Glucagon	75.3 ±	51.2 -		78.19 ±	55.21 -	82.55(62.7	
			(60.22-				0.535
(pg/ml)	21.605	109.36		15.526	102.17	95-88.48)	
			90.61)				

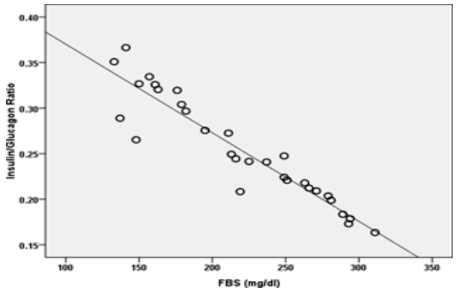

Figure 1- Graph showing the correlation between Insulin/Glucagon Ratio (microU/pg) and FBS

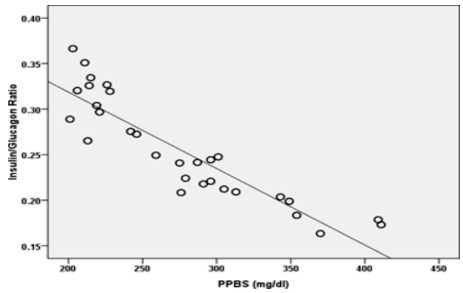

Figure 2- Graph showing the correlation between Insulin/Glucagon Ratio (microU/pg) and PPBS

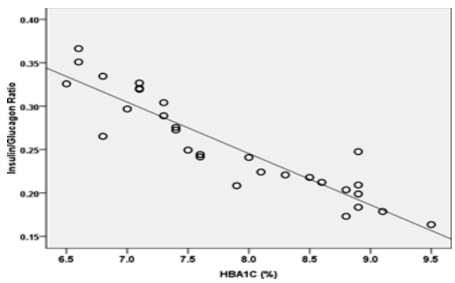

Figure 3- Graph showing the correlation between Insulin/Glucagon Ratio (microU/pg) and HbA1c

DISCUSSION:

- Defects in insulin secretion and aggravation of insulin resistance are considered the primary factors affecting diabetes development and progression. However, apart from insulin itself, various other factors also affect glucose regulation with pancreatic alpha cell dysfunction being one of the factor. The significance of alpha cell malfunction has lately resurfaced (8).
- A total of 30 newly diagnosed diabetic cases, from both the genders with mean age 34.5 ± 2.764 years were included in the study on the basis of pre-defined inclusion and exclusion criteria.
- In the present study, Fasting blood sugar (FBS) i.e. the glucose level with an overnight fasting and Post Prandial blood sugar (PPBS) i.e. the glucose level after the meals was measured. Mean FBS was found to be 217.97 ± 55.012 mg/dl and mean PPBS was found to be 275.3 ± 61.494 mg/dl. Mean HbA1c was found to be 7.83 ± 0.882.
- Mean Insulin in the present study was 19.43 ± 5.809 (microU/ml) and mean Glucagon was 76.74 ± 18.543 (pg/ml). Mean Insulin to Glucagon ratio was 0.255 ± 0.057 (microU/pg) and median (IQR) was 0.246 (0.209 – 0.308) microU/pg. The enrolled subjects were further distributed based on the Insulin and Glucagon ratio (I/G).
- Non-significant association of mean height (160.53 ± 4.086 vs 160.73 ± 4.148), weight (62.4 ± 8.822 vs 58.27 ± 9.308) and BMI (24.6 ± 3.795 vs 23.13 ± 3.758) was observed in the two groups (p=0.660, 0.184 and 0.230, respectively).
- In our study a significantly higher levels of mean FBS (262.93 ± 29.397 vs 173 ± 32.737), PPBS (323.6 ± 46.315 vs 227 ± 26.249) and HbA1c (8.5 ± 0.564 vs 7.16 ± 0.577) was

observed in patients with I/G ratio ≤ 0.246 (p=<0.001 each).
- The Insulin:Glucagon ratio is inversely correlated with increased glucose production of the liver. A high ratio indicates glucose storage and increased protein synthesis, whereas a low one is a sign of increased gluconeogenesis from amino acids (99).
- FBS, PPBS and HbA1c showed a significantly negative correlation with the insulin to glucagon ratio (r=-0.939, -0.913 and -0.919, respectively) suggestive of uncontrolled hyperglycemia with a decrease in ratio.
- Non-significant correlation was observed with age, height and HDL with the insulin to glucagon ratio.

CONCLUSION:

- Measurement of Insulin to Glucagon ratio reflects a better indicator of uncontrolled hyperglycemia across the whole DM population.
- In our study the patients were divided based on Insulin/Glucagon ratio into two groups- group 1, I/G ≤ 0.246 and group 2, I/G ≥ 0.246.
- The present study concludes that levels of Fasting blood sugar and Post Prandial blood sugar (mean FBS of 262.93 in group 1 and 173 in group 2, mean PPBS of 323.6 in group 1 and 227 in group 2) are significantly negatively correlated (r=-0.939, and -0.913, p<0.001, respectively) with Insulin to Glucagon ratio in diabetic patients. This suggests that with increase in the I/G ratio there is a decrease in blood sugar and with decrease in the I/G ratio there is increase in the blood sugar levels.
- Levels of HbA1c (mean HbA1c of 8.5 in group 1 and 7.16 in group 2) is also found to be negatively correlated with Insulin and glucagon ratio (r=-0.919; p<0.001) in our present study, suggesting a worse glycemic control with a decrease in I/G ratio.
- This study suggests that Insulin to Glucagon ratio is better than abrupt cut-off value of insulin or glucagon individually to reflect blood glucose control. Thus a treatment strategy to suppress glucagon along with increasing insulin concentration may be an option for a better blood sugar control and to prevent further diabetes related complications.

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