Original Article

Insulin Resistance as a Prognostic Indicator in Severe Sepsis, Septic Shock and Multiorgan Dysfunction Syndrome

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ABSTRACT

Background: Insulin resistance can be broadly defined as subnormal biological response to normal insulin concentration. Insulin resistance (IR) is one of the major factors in the pathogenesis of sepsis. **Aim:** To study the Insulin Resistance as Prognostic Indicator in Severe Sepsis, Septic Shock and Multiorgan Dysfunction syndrome (MODS). **Materials and Methods:** A prospective observational study done at Intensive care unit of Department of Medicine, at the tertiary care health centre of Northern India, it was done between June 2016-to May 2017. Patients with age between 14 to 75 years and satisfying the criteria for severe sepsis, septic shock, MODS according to third international consensus 2016 guidelines was included in the study. Patients on statins and insulin, those who had chronic disease and who had CPR were excluded. **Results:** A total of 81 patients were enrolled. Mean of fasting blood glucose (FBG), fasting insulin level and insulin resistance of both groups were calculated and compared on Day 1 and Day of outcome. Out of 81 patients 42 were euglycemic (RBS<140 mg/dl) and 39 were hyperglycemic (RBS>140 mg/dl). Mean fasting insulin (13.36+4.95v/s 9.83+4.54) and insulin resistance (6.65+3.84v/s2.41+1.11) of hyperglycemic was found to be significantly (p<.01) higher than euglycemic group of patients. Of 39 hyperglycemic patients 30% (n=13) expired while out of 42 euglycemic patients 28.5% expired (n=12) showing mortality was higher in hyperglycaemic patients and the value was found to be non-significant. **Conclusion:** In patients of severe sepsis, septic shock and MODS stress induced hyperglycemia and insulin resistance are associated with increased mortality. IR is a good and easily estimated method for assessing, but it is not the appropriate indicator of mortality in patients with severe sepsis and organ failure as there are many other factors which come into interplay leading to poor prognosis.
Key words: Insulin resistance, Severity, Sepsis, Septic shock, MODS.

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INTRODUCTION

Sepsis is the host response to infection which involves a series of clinical, haematological, inflammatory and metabolic responses that can ultimately lead to organ failure.[1] Sepsis is associated with poor patient outcomes and high financial costs. It is estimated that 750,000 cases of sepsis occur each year and the mortality rate from severe sepsis remains high at approximately 28% despite recent advances in management and therapy.[2] Hyperglycemia occurs frequently in critically ill patients. Mechanisms include insulin resistance, absolute or relative insulin deficiency, impaired glucose metabolism and the effect of medications such as corticosteroids and densely caloric enteral and parenteral nutritional supplements.[3] Hyperglycemia is also associated with poor outcome in both diabetic and non-diabetic patients after stroke.[4-7] Sepsis is an insulin resistance state and degree of insulin resistance is directly proportional to the severity of stress response.[8] Insulin resistance generally refers to resistance to the metabolic effects of insulin, including the suppressive effects of insulin on endogenous glucose production, the stimulatory effects of insulin on peripheral (predominantly skel-

etal muscle) glucose uptake and glycogen synthesis and the inhibitory effects of insulin on adipose tissue lipolysis.[9]

The metabolic response to critical illness includes stimulation of the hypothalamic-pituitary-adrenal axis, resulting in increased growth hormone, prolactin and Cortisol levels and these endocrine changes result in hyperglycemia. Catecholamines, both endogenous and exogenous, also contribute to the hyperglycemia of critical illness. Mediators of systemic inflammatory response, such as interleukin-1 (IL-1) and tumor necrosis factor alpha (TNF-α), cause hyperglycaemia and peripheral insulin resistance by inducing the release of stress hormones. They also alter insulin receptor signalling and create insulin resistance.[10-12] Mild hyperglycemia in critically ill patients can also be harmful since it acts as procoagulant, induces apoptosis, impairs neutrophil function, increases risk of infection, impairs wound healing and is associated with increased mortality even after adjusting for severity of illness.[13,14] Whereas previous practice was to treat only marked hyperglycemia (e.g., >200 mg/dL), more re-

cent evidence suggests that control should be much more rigorous. Recent scientific experiments have clearly shown that strict blood glucose control in the range of 80-140 mg/dl significantly improves morbidity and mortality among critically ill patients. In the landmark prospective randomized, controlled clinical trial conducted by Van den Berg *et al.* involving adults admitted to surgical intensive care unit (ICU) who were on mechanized ventilation, intensive insulin therapy reduced overall in-hospital mortality by 34%, blood stream infections by 46%, acute renal failure requiring dialysis by 41%, the median number of red blood cell transfusions by 50% and critical care neuropathy by 44% and reduced length of mechanical ventilation and ICU care.[15]

Insulin resistance (IR) is one of the major factors in the pathogenesis of sepsis. The metabolic response to sepsis entails rapid breakdown of the body's reserves of protein, carbohydrate and fat. There is a shift in the balance between insulin and its counter-regulatory hormones favouring the latter in patients with MODS. This leads to prominent metabolic derangements composed of high release and low use of glucose, amino acids and free fatty acids (FFA), resulting in increased blood levels of these substrates. Circulating, proinflammatory mediators further enhance this state of global catabolism. Insulin has the inherent capability to counteract the metabolic changes observed in septic patients.

This prospective observational study was designed with an objective to study the insulin resistance as prognostic indicator in severe sepsis, septic shock and multiorgan dysfunction syndrome.

MATERIALS AND METHODS

We conduct a prospective observational study at the Intensive care unit of Department of Medicine, at the tertiary care health centre of Northern India from June 2016 to May 2017. Patients with age between 14 to 75 years and satisfying the criteria for severe sepsis septic shock, MODS according to third international consensus 2016 guidelines was included in the study. Patients on treatment with statins, insulin or with chronic liver disease, chronic kidney disease, thyroid dysfunction, diabetes, severe anaemia, chronic inflammatory condition and malignancy and post CPR patients were excluded from the study.

Methodology

After approval from institutional ethical committee the present study was conducted in 81 patients with sepsis and MODS of either sex aged 14-75 years admitted in MICU between periods of June 2016 to June 2017. APACHE 2 score was calculated for all the patients admitted in MICU on day 1 to estimate the risk of death. Hyperglycemia, defined as a blood glucose greater than 140 mg/dl (7.8 mmol/l), is reported in 22-46% of non-critically ill hospitalized patients.

Among the Patients of sepsis Insulin resistance was calculated on Day 1 and Day of outcome (death/discharge) by using Homeostasis model assessment.[16]

$$\text{HOMA IR} = \frac{\text{(fasting blood glucose (mg/dl) x fasting insulin)}}{405}$$

Severe sepsis septic shock and MODS patient enrolled as diagnosed by 2016 international consensus (SOFA SCORE).

Statistical Analysis

The statistical analysis was done using SPSS (Statistical Package for Social Sciences) Version 15.0 statistical Analysis Software. The descriptive data are presented as the number and percentage for categorical data and continuous variables were expressed as mean ± standard deviation (SD) or median with a minimum and a maximum dependent on the distribution of data and discrete variables that were expressed in percentages. The differences of clinical characteristics were compared by student's

t-test and Chi-square test, as appropriate. '*P* < 0.05 was defined as statistically significant'.

RESULTS

Out of 81 patients enrolled in the study 35 (43.21%) had HOMA IR ≥3.70 i.e. insulin resistant 2 was classified as Group I while rest 46 (56.79%) had HOMA IR <3.70 i.e. insulin controlled were classified as Group II. (Table 1)

Fasting blood glucose, fasting insulin level and HOMA-IR of hyperglycemic patients were also found to be higher than that of patients with euglycemia and statistically significant differences were found. (Table 2)

Of 39 hyperglycemic patients 30% (*n*=13) expired while out of 42 euglycemic patients 28.5% expired (*n*=12) showing mortality was higher in hyperglycemic patients though the difference was not found to be significant. (Table 3)

Mean fasting blood glucose, fasting insulin level, insulin resistant, of remaining 26 hyperglycaemic patients were significantly lower (*P*<.01) than their corresponding day 1 value but beta cell function increased at the time of discharge. (Table 3)

Fasting insulin level, insulin resistance (HOMAIR) levels of expired patients were found to be significantly higher than that of patients who survived. Fasting blood glucose was also high in expired patients, but difference was not found to be significant. (Table 4)

DISCUSSION

Out of 81 patients fasting blood glucose of 42 patients were found to be less than 140 mg/d, rest 39 patients had RBG ≥ 140 mg/dl. On com-

Table 1a: Distribution of Patients of Sepsis according to Insulin Resistance at admission (*n*=81).

Group	Insulin	No.	%
Group I	Insulin resistant HOMA IR ≥3.70	35	43.21
Group II	Insulin controlled HOMA IR <3.70	46	56.79
	Total	81	100.00

Table 1b: Association of Age and Insulin Resistance.

	Group I (*n*=35)		Group II (*n*=46)		Total (*n*=81)	
	No.	%	No.	%	No.	%
31-40	14	40	16	34.7	30	37
41-50	13	37.1	17	36.9	30	37
51-60	08	22.8	13	28.2	21	26
χ^2=4.179(df=6); 0.652						

Table 2: Comparison of (Day 1) Fasting Blood sugar, Fasting Insulin and HOMA IR among Hyperglycemic and Euglycemic patients.

	Euglycemic (RBS <140 mg/dl)			Hyperglycaemic (RBS >140 mg/dl)			'*p*'
	n	Mean	SD	*n*	Mean	SD	
Fasting Blood sugar	42	98.677714	6.6592107	39	198.02051	59.15052	<0.001
Fasting Insulin	42	9.837381	4.5422703	39	13.364872	4.955923	<0.001
HOMA IR	42	2.4123501	1.1178132	39	6.6566989	3.849214	<0.001

Table 3: Comparison of Change in Fasting Blood sugar, Fasting Insulin and Insulin resistance (HOMA IR) among Hyperglycemic patients (*n*=26) at Day 1 v/s Day of Outcome (discharged).

	Day 1		Day of Outcome		Statistical significance (Paired '*t*' test)
	Mean	SD	Mean	SD	'*p*'
Fasting blood glucose	198.3385	56.94249	110.6192	23.56455	<0.001
Fasting Insulin	10.77385	2.818693	9.006346	2.7952183	0.0275
HOMA IR	5.20953	1.864327	2.521054	1.2375129	<0.001

Table 4: Association between Severity Scores and Outcome.

	Survived			Expired			Student '*t*' test '*p*' value
	n	Mean	SD	*n*	Mean	SD	
Fasting Blood sugar	56	145.36	62.98	25	149.08	69.51	0.82
Fasting Insulin	56	10.31	3.83	25	14.29	6.29	0.0061
HOMA IR	56	3.73	2.05	25	6.09	5.21	0.0365
APACHE II	56	16.42	6.02	25	16.70	6.34	0.072
SOFA SCORE	56	5.72	3.63	25	6.01	3.87	0.83
SAP 2 SCORE	56	33.01	13.22	25	34.32	13.30	0.038
GCS SCORE	56	11.26	4.57	25	11.24	4.58	0.933

parison on Day1 mean fasting blood glucose of hyperglycaemic group of patients (198.02±59.15 v/s 98.67±6.65) was higher than euglycemic patients and difference was found to be significant (*p*< .01). Mean fasting insulin (13.36±4.95v/s 9.83±4.54) and insulin resistance (6.65±3.84v/s 2.41±1.11) of hyperglycemic was also found to be significantly (*p*<.01) higher than euglycemic group of patients. This result of my study was found to be correlating with study of Das S *et al.* which also show significant difference between FBG, fasting insulin and insulin resistance in euglycemic and hyperglycaemic group of patients on Day 1.[17]

Of 39 hyperglycemic patients 30% (*n*=13) expired while out of 42 euglycemic patients 28.5% expired (*n*=12) showing mortality was higher in hyperglycaemic patients (insulin resistant, stress reduced hyperglycemia) than in euglycemic patients. Though the difference was not found to be significant (*P*>.05) due to small sample size. This observation of my study also correlates well with VanVught *et al.* study who conducted a prospective observational cohort study on 987 patients of critical illness admitted in 100 patient and found that severe admission hyperglycaemia was associated with increased 30 days mortality (adjusted hazard ratio 1.6 95% CI) in patient without diabetes and with diabetes (adjusted hazard ratio (1.91 95% CI).[18] James Stephen Kinsley *et al.* reviewed data of 1826 patients of intensive care unit and found that mean and maximum

glucose values were significantly higher among non survivors and mortality increased progressively to 42.5% among hyperglycaemic patients showing modest degree of hyperglycemia is associated with increased mortality in patients with wide range of medical and surgical illness.[19] Mean fasting blood glucose, fasting insulin level, insulin resistant and beta cell function of remaining 26 hyperglycaemic patients who got discharged were calculated at the day of discharge and compared to Day1 means value. It was found that fasting mean glucose level (110.61 ± 23.56 v/s 198.33 ± 56.94) fasting insulin level (9.0 ± 2.79 v/s 10.7±2.81) and insulin resistance (2.52±1.23 v/s 5.20±1.86) were significantly lower (*P*<.01) than their corresponding Day 1 value showing that as patient improves there was significant reduction in glucose level and insulin level leading to decrease in insulin resistance. This result was in correlation with study of Das *et al.* who also observed in their study that in patients of sepsis and MODS having hyperglycaemia at the time of admission have significant reduction in the mean for study FBG, fasting insulin and insulin resistance as they recovered from their illness. Of those who died the first day mean insulin level (14.29±6.29) and insulin resistance (6.09±5.21) were significantly high (*p*<.05), when compared with fasting insulin (10.31±3.83) and insulin resistance (3.73± 2.05)of the patients who survived (hyperglycemic+englycemic) fasting blood glucose (149.08±69.51) but difference was not found to be significant. This result also correlates with study of Das *et al.* in which the first day Insulin level of expired patient and insulin resistance were higher abut have low beta cell function as compared to those who survived.

CONCLUSION

In conclusion it can be said that in patients of severe sepsis, septic shock and MODS stress induced hyperglycemia and insulin resistance are associated with increased short term mortality. IR is a good and easily estimated method for assessing, but it is not the appropriate indicator of mortality in patients with severe sepsis and organ failure as there are many other factors which come into interplay leading to poor prognosis.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

ABBREVIATIONS

IR: Insulin resistance; **MODS:** Multiorgan Dysfunction syndrome; **FBG:** Fasting blood glucose; **IL-1:** Interleukin-1; **TNF-α:** Tumor necrosis factor alpha; **ICU:** Intensive care unit; **FFA:** free fatty acids; **HOMA IR:** Homeostasis model assessment; **SOFA:** Sequential Organ Failure Assessment Score; **SPSS:** Statistical Package for Social Sciences; **APACHE II:** Acute Physiology And Chronic Health Evaluation II; **SAPS:** Simplified Acute Physiology Score II; **GCS:** Glasgow Coma Scale.

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