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Case control study of insulin resistance and β cell function as prognostic indicator of septicemia patients admitted to tertiary care teaching hospital

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Abstract

The study was aimed to evaluate insulin resistance and β cell function as prognostic indicator in multi organ dysfunction in septicemia. A case control follow up study consisting of 50 non diabetic patients of septicemia with multi organ dysfunction (MODS) and 50 control participants were enrolled by simple random sampling, excluding the ones not met inclusion criteria. The eligible individuals were evaluated for haematological investigation, renal function tests, serum bicarbonate, fasting blood glucose and serum insulin levels at the point of entry, 3rd day and 7th day of admission. Homa IR and Homaβ cell function were computed using fasting blood glucose and insulin levels. These prognostic dependent variables were compared with independent variables by the student t-test and odds ratio for assessing the mortality and severity among study participants. Study cases had a statistically significant ($p<0.001$) high mean values of Homa IR at the time of entry, on Day 3rd and 7thwhereas Homaβ cell function had statistically($p<0.001$) low values, compared to control group. In sepsis patients mortality (6 cases) was higher in study groups where patients had more insulin resistance (IR) (6.55±1.44) and less β cell dysfunction (37.17±25.59) compared to control group (with 2 mortality cases) which had less IR (2.77±0.33) and more β cell dysfunction (152.37±5.06) in study and control group respectively, ($p<0.05$).Both insulin resistance and β cell dysfunction are reliable indicators of the state of severity and mortality in critically ill patients with multi-organ dysfunction syndrome (MODS).

Keywords: Septicemia, MODS, Insulin resistance, β cell function, Prognosis.

Introduction

Sepsis involves a series of clinical, hematological, inflammatory and metabolic responses that can ultimately lead to organ failure.(1) It is associated with insulin resistance (IR) and was observed as early as 1989.(2)IR with acute hyperglycemia, profound negative nitrogen balance and diversion of protein from skeletal muscle to splanchnic tissue are prominent features of sepsis.(3) Hyperglycemia and the risk of death remain significantly higher even after adjusting for the severity of illness.(4)Mild hyperglycemia is potentially harmful because it acts as procoagulant, induces apoptosis, impairs neutrophil function, increases risk of infection, impairs wound healing and is associated with increased risk of death.(5-7) Patients with renal dysfunction also have high levels of IR.(8) The degree of hyperlactatemia parallels the severity of hypermetabolism and is accompanied by a concomitant increase in oxygen consumption, IR, and urea nitrogen excretion.

Very limited studies have evaluated the state of the beta cells of the islet of Langerhans in non-diabetic critically ill patients who either survived or died during this acute illness.(9) These subjects were supposed to have normal beta cell function as well as good beta cell reserves to overcome this stress hyperglycemia. IR in these patients with normal beta cell function is supposed to enhance beta cell activity. Therefore, we decided to study the beta cell function and insulin resistance by applying the homeostasis model of assessment B (HOMA-B) and HOMA-IR in these non-diabetic subjects during critical illness which can serve as prognostic indicators.

Material and Methods

The hospital based follow up case control study was conducted at Sardar Patel Medical College and Associated Group of Hospitals in Bikaner, India. This district has a population of around twelve lakh and has this only tertiary care teaching hospital. Diabetes Care Research Center is attached to this college where this proposed study was planned out for the period of one year.The Non Diabetic septicemic patients with multiple organ dysfunction syndrome who were admitted (IPD) and met the inclusion criteria were enrolled by the simple random sampling in the study. These constituted the study cases and accounted as 50 subjects. To compare these cases, other 50 non diabetic individuals without septicemia and multiple organ dysfunction syndromes were enrolled and labeled as controls. The inclusion criteria had the criteria of sepsis which is defined by presence of at least two of the four signs of the systemic inflammatory response syndrome (SIRS):(10) (1) fever (>38°C) or hypothermia (<36°C); (2) tachycardia (>90 beats per minute); (3) tachypnea (>20 breaths per minute), hypocapnia (partial pressure of carbon dioxide <32 mm Hg), or the need for mechanical ventilatory assistance and (4) leukocytosis (>12,000 cells/mm^3), leukopenia (<4000 cells/mm^3), >10% band cells in the white cell differential and suspected or proven infection. The exclusion criteria consisted of patients with type 2 diabetes mellitus

(HbA_1c >6.5%), past history of glucose intolerance, pancreatitis, corticosteroid therapies, cirrhosis, malignancies and chronic renal failure.

All the study participants (n=100) were evaluated for the glycosylated hemoglobin (investigated by DS-5 HbA_1c Analyzer[11] based on Ion exchange chromatography) to declare them non diabetic. The independent variables used in the study were Glassgow coma scale, temperature, total leucocyte count, blood urea, serum creatinine, bicarbonate (HCO_3) and pH. All blood samples were taken early in the morning with 8 hours of fasting before administration of any medication, from the other limb of intravenous infusion with aseptic technique. These values of the diagnostic tests were estimated at the time of admission to hospital, at 3rd and 7th day. The dependant variables constituted the HOMA-IR and Homa-β cell function. Each participant was given 75gm of glucose to measure blood sugar level (glucose oxidase method) and plasma insulin levels (fully automated chemiluminescence analyzer - CLIA test,[12] Immulite, DPC, USA) at 0, 60 and 120 minutes. Insulin resistance and β-cell function was assessed by homeostasis model assessment.

Statistical analysis: Data were entered into a spreadsheet and analyzed using SYSTAT statistical software. Missing data were excluded. Mean and standard deviations were calculated for the dependent and independent variables. The association between the variables among study cases and controls were evaluated by the student t test. Crude odds ratio with 95%CI were calculated to estimate the risk with care of eliminating confounding variables.

Results

It is evident from Table 1 that the mean values of total leukocyte count, blood urea, serum creatinine and fasting blood sugar were comparatively higher for the study cases compared to the control group. Study cases had a statistically significant high mean values of Homa IR at the time of entry, on day 3rd and 7th in respect to the study control with application of unpaired t test ($p<0.001$). On the contrary the Homa β cell mean values were lower among cases in comparison to controls ($p<0.001$) during the said follow up days. The only non-significant association was observed for the Glass gow coma scale on the 7th day among both the groups.

Table 1: Association of study variables among study group (n=50) and control group (n=50)

Variables	Study Group		Control Group		t	p
	Mean	SD	Mean	SD		
TLC (10^3/µl)						
Day 1	26719.62	6319.35	8067.38	1809.56	20.065	<0.001
Day 3	23432.94	4525.80	8092.98	1822.58	22.232	<0.001
Day7	18099.30	4091.64	8308.76	1839.27	15.432	<0.001
Blood Urea (mmol/L)						
Day 1	130.12	34.63	37.18	7.45	18.553	<0.001
Day 3	113.94	19.36	41.74	20.50	18.108	<0.001
Day7	56.34	12.78	39.89	6.65	8.071	<0.001
Serum Creatinine (µmol/L)						
Day 1	5.60	1.73	1.09	0.33	18.030	<0.001
Day 3	4.05	1.41	1.07	0.33	14.518	<0.001
Day7	2.66	1.01	1.12	0.35	10.218	<0.001
pH						
Day 1	7.34	0.04	7.40	0.04	7.53	<0.001
Day 3	7.32	0.03	7.42	0.04	13.39	<0.001
Day7	7.36	0.03	7.42	0.03	8.38	<0.001
HOMA IR						
Day 1	3.72	2.06	2.11	0.98	4.98	<0.001
Day 3	5.32	2.66	2.82	1.38	5.88	<0.001
Day7	4.37	2.57	2.00	1.37	5.75	<0.001
Homa β cell function						
Day 1	23.75	18.95	172.92	139.67	7.48	<0.001
Day 3	17.66	10.05	94.44	53.72	9.93	<0.001
Day7	13.12	8.23	290.42	23.55	8.76	<0.001
Glasgow Coma Scale						
Day 1	13.18	2.26	14.40	1.47	3.20	<0.01
Day 3	13.35	1.80	14.26	1.41	2.77	<0.01
Day7	14.11	1.51	14.52	1.20	1.46	>0.05

Fasting Blood Sugar (mmol/L)						
Day 1	13.60	1.60	6.46	0.87	27.71	<0.001
Day 3	15.77	1.37	7.38	0.89	36.44	<0.001
Day7	15.98	2.30	5.57	0.85	30.00	<0.001
Serum HCO_3 (mmol/L)						
Day 1	18.97	4.20	25.25	2.19	9.38	<0.001
Day 3	18.43	2.71	25.00	2.02	13.74	<0.001
Day7	22.64	2.09	25.19	1.99	6.25	<0.001

In this analytical study all the independent variables were compared with the dependent ones for estimating the risk with application of odds ratio (Table 2). It is evident that individuals with increased leukocytes (criteria of sepsis) had 6.5 times chances of increased risk of insulin resistance on day 1(odd ratio 6.50, 95% CI2.58-16.36) in comparison to controls (without leucocytosis). Day 3 and day 7 also presented the increased risk of insulin resistance by almost four times. The same increased risk was observed for the other criteria of sepsis like blood urea(odd ratio 2.25, 95% CI0.88-5.71) serum creatinine (odd ratio 5.5 95% CI2.12-13.74) and fasting blood sugar (odd ratio 4.77, 95% CI 0.57-39.82). It is observed that the same said variables did not show the positive odds ratio for Homa β cell function, representing the rather inverse relationship.

Table 2: Odds ratio analysis of IR and Homa β cell on different parameters studied among study cases (n=50) and controls (n=50)

Parameters	**Day 1**		**Day 3**		**Day 7**	
	IR	**Homa β cell function**	**IR**	**Homa β cell function**	**IR**	**Homa β cell function**
	OR (95%CI)	**OR (95%CI)**	**OR (95%CI)**	**OR (95%CI)**	**OR (95%CI)**	**OR (95%CI)**
Glasgow Coma Scale	0.19 (0.04-0.80)	1.21 (1.10-1.33)	1.64 (1.39-1.93)	1.07 (1.01-1.12)	0.62 (0.08-4.64)	0.62 (0.08-4.64)
Temperature	0.59 (0.25-1.35)	1.81 (0.58-5.68)	0.76 (0.33-1.74)	1.75 (0.30-10.06)	0.21 (0.08-0.15)	1.39 (0.59-3.27)
TLC	6.50 (2.58-16.36)	0.70 (0.59-0.83)	4.38 (1.77-10.83)	0.54 (0.09-3.11)	4.44 (1.90-10.38)	0.18 (0.07-0.46)
Blood Urea	2.25 (0.88-5.71)	0.07 (0.02-0.29)	1.84 (0.75-4.50)	1.09 (1.01-1.17)	4.62 (1.44-14.86)	0.44 (0.17-1.13)
Serum Creatinine	5.4 (2.12-3.74)	0.66 (0.54-0.81)	3.78 (1.58-9.05)	0.17 (0.02-1.56)	2.47 (1.09-5.58)	0.22 (0.09-0.55)
Serum pH	0.71 (0.31-1.63)	4.54 (1.20-17.12)	0.38 (0.16-0.88)	0.56 (0.09-3.25)	1.01 (0.40-2.58)	2.06 (0.73-5.79)
Serum HCO_3	0.72 (0.28-1.81)	5.33 (1.72-16.50)	0.78 (0.34-1.81)	3.52 (0.61-20.28)	1.62 (0.71-3.70)	1.15 (0.50-2.65)
Fasting Blood Sugar	4.77 (0.57-3.98)	0.33 (0.07-1.50)	2.88 (2.19-3.78)	1.06 (1.01-1.12)	2.83 (1.07-7.50)	0.30 (0.12-0.76)

The association of mortality with both the prognostic markers was evaluated (Table 3). It is observed that the mortality among study cases, i.e. 6, was high with increased mean value of Homa IR (6.55±1.44) in comparison to the control group (2.77±0.31) ($p<0.01$). On the contrary the mortality, i.e. 2, was low with high values of Homa β cell among control cases (152.37±5.06) in comparison to study controls.(37.17±25.59, $p<0.001$). The observed relationship is that Homa IR values are directly and Homa β cell values are inversely related to mortality.

Table 3: Association of mortality among study participants

Variables	**Study cases**		**Control cases**		**T**	**p**
Mortality	**6**		**2**			
	Mean	**SD**	**Mean**	**SD**		
HOMA IR	6.55	1.44	2.77	0.31	3.49	0.01
Homa β cell	37.17	25.59	152.37	5.06	6.01	0.001

Discussion

Sepsis causes significant mortality and in turn creates financial burden on resources of health services. Very limited studies have evaluated the state of the β cells in non-diabetic critically ill patients who either survived or died during this acute illness. Therefore, we decided to evaluate β cell function and insulin resistance by applying the homeostasis model of assessment HOMA-β cell function and HOMA-IR in these non-diabetic subjects during critical illness.

According to present study, insulin resistance increased in critically ill sepsis patients compared to control participants. Insulin resistance (IR) increased from day of hospitalization to 3rd day then decreased at 7th day, which is in accordance to the study of Das et al[9]in 2009. He enrolled 80 consecutive patients, 60 were followed up to 7th day, 16 patients died and 4 did not agree to follow up. The mean value of insulin resistance IR in all the 80 patients studied on the day of hospitalization was 6.67±10.65. The initial high values of serum insulin and insulin resistance (IR) were significantly reduced ($p<0.05$) as these patients recovered from their critical illness.

The present study observed that there was continuously decreased β cell function on day 1,3 and day 7in study group as compared to control group. These findings showed that β-cell function was continuously decreasing in critically ill multiple organ dysfunction syndrome (MODS) patients. This depicts β-cell over exhaustion and finally β-cell failure in study group.

Critically ill multiple organ dysfunction syndrome (MODS) patients are relative insulin deficient because of β cell failure, thus insulin supplementation in these patients reduce the risk for sepsis by decreasing insulin resistance (IR) and improving β cell function. Fasting blood sugar was 13.66±1.60, 15.77±1.37 and 15.98±2.30 mmol/l on day 1,3, and 7 respectively in sepsis patients. These finding suggest that there was continuous β-cell dysfunction during stress which leads to continuous stress hyperglycemia.

The overall high mortality among sepsis patients in comparison to control patients was observed in this study. In sepsis patients mortality was higher in those patients who had more insulin resistance (IR) and less β-cell dysfunction compared to those who had less insulin resistance and more β-cell dysfunction. This is in accordance to Das et al[9] and Ausk et al.[11] In present study other contributing factor for severity of sepsis were leukocytosis, increased blood urea and serum creatinine, increased fasting blood sugar, metabolic acidosis, increased temperature and low Glasgow Coma scale. By initial analysis of insulin resistance (IR) and β-cell function we can assess the severity and can guide about the prognosis, hence IR and β-cell functions are important indicator of severity of sepsis.

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