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Sepsis Outcome in Patients with Metabolic Syndrome and its Correlation to Procalcitonin and C-Reactive Protein

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Abstract

Background: Metabolic syndrome (MetS) is the emerging subject where people are more prone to illness due to varied causes. Sepsis is the most common cause of death in a hospitalised individual – more than myocardial infarction. In this study we will elicit the correlation of metabolic syndrome and its outcome in sepsis patients with reference to markers like C-Reactive Protein (CRP) and Procalcitonin (PCT). We aimed to assess outcome of patients in accordance with severity of sepsis in MetS and study its relationship with serum PCT and CRP levels.

Methods: This was a comparative, case-control study carried out between November 2014 and 2016. 140 subjects with definable sepsis were studied; 70 each with or without MetS. All of them were worked-up for MetS and also for sepsis markers like PCT and CRP.

Results: 50.7% patients belonged to the age group 51 - 70 years with male preponderance in the case group. 84.5% patients who had sepsis and MetS succumbed to their illness compared to the control group (15.9%). Higher the value of PCT in cases, higher was the mortality (88.2% vs 19.6%). The rate of organ dysfunction and SOFA scores was also higher (97.2%, 90.1% vs 52.2%, 46.4%) and (15.1 vs 10.3) respectively among the cases when compared to that of control group.

Conclusion: Patients with sepsis and MetS had higher mortality rates than individuals without MetS. Also the SOFA score among the cases was higher with increased PCT values and decreased duration of stay in hospital due to mortality.

Key words: Metabolic syndrome, Sepsis, Procalcitonin, CRP.

Introduction

Metabolic Syndrome (MetS) is emerging as a global epidemic; more than one quarter of the world's adult population is affected by it and with a steadily increasing presence in many countries. MetS is an inflammatory entity which combines obesity, dyslipidaemia, insulin resistance, and hypertension, albeit with incompletely understood mechanisms. Worldwide prevalence of MetS ranges from <10% to as much as 84%[1,2]. MetS is a state of chronic low grade inflammation as a consequence of complex interplay between genetic and environmental factors[3,4]. Sepsis is the most common cause of death in a hospitalised individual than myocardial infarction. It is defined and diagnosed by nonspecific alterations in physiology that would be amenable to specific interventions. The morbidity and mortality of patients in sepsis with MetS is higher. Sepsis and MetS are inter-related and are inflammation-related diseases where MetS can increase the risk of complications in sepsis[5]. CRP and PCT are a few of the many markers used in the diagnosis of sepsis and its severity.

CRP is designated as an acute phase reactant which is released in inflammatory states like rheumatoid arthritis and infection[6]. The CRP response is very non-specific and can never be used as a single diagnostic tool; however, it is very helpful in several disease states. Besides its use in the diagnosis and severity of sepsis, CRP has also been evaluated as a prognostic marker.

PCT is produced in response to pro-inflammatory stimuli, in particular by bacterial products[7], hence it is a perfect tool to differentiate between viral and bacterial infections, (e.g., Gendrel *et al* 1999)[8]. Patients with bacteraemia usually have significantly high PCT levels[9] and persistent increase or failure to decline in the PCT levels has been related to higher mortality rates in various studies[10].

In this study, we studied the correlation of MetS and its outcome in patients of sepsis with reference to the above mentioned markers. There have been some studies on MetS and its correlation to diabetes, hypertension, and other non-infectious diseases like COPD. However, there are not many studies that have looked at the intraction of infection and MetS. In this study we tried to assess the outcome of patients in accordance with severity of sepsis in MetS and to find its relationship with serum PCT and CRP levels.

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Material and Methods

This was a comparative, case-control study carried out over a period of two years between November 2014 and August 2016. Subjects with sepsis with MetS who were diagnosed as per the WHO criteria and were being treated for the same were enrolled. Controls included patients with sepsis without MetS. The proposed study sample size was 70 subjects and 70 controls. The sampling was done by simple random method. The detailed patient data was obtained and documented in a proforma which included detailed history, clinical examination. All individuals underwent biochemical tests like fasting venous blood sugar, fasting lipid profile, total leukocyte count, renal function and liver function tests, serum CRP, and serum PCT. Patients were included in the study if they gave informed consent, were greater than 18 years and met the criteria of sepsis and were included in the cases group of the study it they met criteria for MetS. Pregnant women, trauma cases, surgical cases, patients with cardiac shock and those who refused to give an informed consent were excluded from the study.

Statistical methods used in the study were chi square test. Mann-Whitney test was used as an alternative test to the independent sample t-test. Independent-samples T-test was used compare to means for two groups of cases. Kruskal-Wallis test was used. All the statistical calculations were done using SPSS for windows (Version 16.0).

Methods of collection of data: Individuals admitted to JSS Hospital's intensive care unit with sepsis with/without MetS were screened as per inclusion and exclusion criteria after obtaining their consent. All study subjects were subjected to a detailed clinical examination to see whether the individuals met the criteria of sepsis and assessed for vital parameters and SOFA score (Appendix 1). Examination for metabolic syndrome: Central obesity: waist girth ≥90 cm, dyslipidaemia: TG ≥1.7 mmol/L (150 mg/dL), HDL-C <40 mg/dL (male), <50 mg/dL (female), Blood pressure ≥140/90 mmHg (or treated for hypertension), fasting plasma glucose ≥6.1 mmol/L (110 mg/dL) was also done.

PCT was measured in Roche e411 Electrochemiluminescence (ECLIA) automated analyser using PCT kit from BRAHMS Diagnostica, Berlin, Germany. A value of PCT >0.5 ng/mL was taken as pathological, 0.5 to 2 ng/mL indicated that systemic infection could not be ruled-out, 2 to 10 ng/mL indicated greater chances of sepsis, and a value of PCT above 10 ng/mL indicated severe bacterial sepsis.

CRP was performed using immunoturbidimetric (Tina-quant CRP detection method; Roche Diagnostics Indianapolis) performed on a Hitachi 717 automated analyser.

Appendix 1

Sepsis criteria:

1. Fever (oral temperature >38° C [>100.4° F]) or hypotharmia (<36° C [<96.8° F]).
2. Tachypnoea (>24 breaths/min).
3. Tachycardia (heart rate >90 beats/min).
4. Leukocytosis (>12,000/μL), leukopenia (<4,000/μL), or >10% bands.
5. Cardiovascular: Arterial systolic blood pressure ≥90 mmHg or mean arterial pressure ≥70 mmHg that responds to administration of IV fluids.
6. Renal: Urine output <0.5 mL/kg per hour for 1 h despite adequate fluid resuscitation.
7. Respiratory: PaO_2/FIO_2 ≥250 or, if the lung is the only dysfunctional organ, ≥200.
8. Haematologic: Platelet count <80,000/μL or 50% decrease in platelet count from highest value recorded over previous 3 days.

Results

140 patients who participated in this study were between the age group 30 to 80 years with highest percentage of individuals of MetS being in the age group of 51 - 70 years (50.7%). Among 140 patients, 61 were females and 79 were males. When correlated to MetS, there was male preponderance (54.9% vs 45.1%).

Of total 140 cases, most patients were diagnosed to have bronchopneumonia with sepsis, followed by urinary tract infection and acute febrile illnesses (22.8%,22.1% and 20% respectively). The mean leukocyte count among individuals with MetS was 17,446 cells/cumm with a standard deviation of 8,182 which was higher when compared to the mean of individuals without MetS ($p < 0.001$). The mean SOFA Score among individuals with MetS was higher when compared to individuals without MetS (15.1 vs 10.3, $p < 0.001$) Table I. We noted that patients with MetS had a higher percentage of renal and hepatic derangement (97.2%,90.1% vs 52.2%, 46.4%), which was statistically significant.

In the present study, the mean and median PCT among individuals with MetS was much higher than individuals without MetS (68.13 ng/mL and 72.00 ng/mL, *versus* 24.11 and 20.00 respectively). When C-reactive protein was compared in individuals between the two groups, the mean values were found to be 79.99 mg/L and 80.24 mg/L respectively which was statistically significant ($p = 0.015$).

When duration of hospital stay was taken into consideration, the mean value of individuals without MetS was 9.51 days with a standard deviation of 4.66 days, and was higher than in the patients with MetS (4.55 days, SD 4.00 days, p <0.001) as there were more deaths among this group (Table II).

With respect to outcome, the percentage of patients without MetS who improved was higher (84.1% vs 11.3%) and mortality was higher (84.5 vs 15.9% p <0.0001) in the MetS group (Table III).

Table I: Total leukocyte count and SOFA score in correlation to metabolic syndrome.

	Without Metabolic Syndrome	With Metabolic Syndrome
Mean	**Mean (SD)**	**Mean (SD)**
Total Leukocyte Count/mm^3	12652 (5847)	17446 (8182)
SOFA Score	10.3 (2.5)	15.1 (3.6)

Table II: Correlation of procalcitonin, C-reactive protein, duration of hospital stay.

	Without Metabolic Syndrome			With Metabolic Syndrome			P value
	Mean	**SD**	**Median**	**Mean**	**SD**	**Median**	
PCT (ng/mL)	24.11	18.67	20.00	68.13	36.92	72.00	**<0.001**
CRP (mg/L)	79.99	38.37	75.00	80.24	61.43	54.00	**0.015**
Duration of stay in hospital (days)	9.51	4.66	10.00	4.78	4.55	4.00	**<0.001**

Table III: Correlation of outcome in the study.

		Without Metabolic Syndrome		With Metabolic Syndrome	
		Number of patients	**Percentage of patients**	**Number of patients**	**Percentage of patients**
Outcome	Improved	58	84.1%	8	11.3%
	DAMA*	0	.0%	3	4.2%
	Death	12	15.9%	59	84.5%

*P <0.0001, *Discharge Against Medical Advice.*

High CRP values, among people who died, were observed in 49 individuals with MetS (84.5%) and 53 patients with high CRP values (84.1%) improved (non-significant p value). But PCT values in individuals with MetS who succumbed were higher compared to those who improved with high PCT levels in the control group with percentage of 88.2% and 80.4% respectively (p <0.0001) (Table IV). The median SOFA score among individuals with MetS was higher (16) compared to those individuals without MetS (12.0) Table V.

Table IV: Correlation of outcome in CRP and PCT with metabolic syndrome.

			Without Metabolic Syndrome			With Metabolic Syndrome		
			Improved	**DAMA**	**Death**	**Improved**	**DAMA**	**Death**
CRP	Normal	No. of patients	5	0	1	1	1	11
		%	83.3	0	16.7	7.7	7.7	84.6
	High	No. of patients	53	0	10	7	2	49
		%	84.1	0	15.9	12.1	3.4	84.5
	p value			0.9			0.7	
PCT	Normal	No. of patients	17	0	1	3	0	0
		%	94.4	0	5.6	100	0	0
	High	No. of patients	41	0	10	5	3	60
		%	80.4	0	19.6	7.4	4.4	88.2
	p value			0.2			**<0.0001**	

Table V: Correlation of SOFA score with metabolic syndrome in relation to outcome.

		SOFA Score	
			Median
Without Metabolic Syndrome	Outcome	Improved	10.0
		DAMA	.
		Death	12.0
With Metabolic Syndrome	Outcome	Improved	11.5
		DAMA	16.0
		Death	16.0

When the diagnosis of sepsis and outcome of the patients were correlated with MetS, we found that mortality was significantly elevated in patients with MetS and the number of patients improved was higher in the control group.

Discussion

MetS and Sepsis represent an inter-related escalating disease burden for modern healthcare systems. The

association between them is related to their inflammatory link. Sepsis is an acute inflammatory reaction which recruits several systems, whereas in MetS, inflammation is chronic and subclinical, without the classic clinical inflammatory manifestation. There are no studies correlating sepsis in MetS; most of the studies are done on outcome of patients with obesity in critical illness.

This study attempts to relate the severity of sepsis to increased morbidity and mortality in patients with MetS, apart from other known risk factors. The subjects in the study with sepsis and MetS were comparatively older than those in the control group (sepsis without MetS).

Similar to our study, Shastri *et al*[11], showed that TLC was higher in patients with MetS with statistically significant difference ($p < 0.0001$). Thus, TLC in obese patients of MetS can be used as a predictor for future complications.

Procalcitonin (PCT) has the highest diagnostic accuracy. It is also useful for monitoring the course and severity of the systemic inflammation. Meisner *et al*[12] found that higher SOFA score levels were associated with significantly higher PCT plasma concentrations whereas CRP was elevated irrespective of the scores observed which was in contrary to the present study. In a study by Castelli[13], PCT and CRP concentrations were higher in patients in whom infection was diagnosed at comparable levels of organ dysfunction although correlation with the SOFA score was weak.

The PCT was elevated in about 119 individuals with a maximum percentage of individuals among cases, of sepsis with MetS resulting to 88.2% among individuals who died and this was backed by a study done by Balci *et al*[14].

In this study we found that patients with MetS admitted with sepsis had higher mortality (84.5%) compared to those without MetS ($p < 0.0001$). A study done by Olivgeris *et al*[15] also showed increased mortality among obese ICU patients (76.3% versus 43.7%; $P = 0.001$).

Sepsis is the leading cause of death in hospitals despite the structured approaches. Additionally, MetS increases the risk for complications of sepsis, likely relating in part to the maladaptive cardiometabolic alterations. Of a total of 140 cases, most of the patients were diagnosed to have bronchopneumonia with sepsis, followed by urinary tract infection and acute febrile illnesses, occupying a percentage of 22.8%, 22.1% and 20% respectively. Among them, patients with urinary tract infection and bronchopneumonia with MetS had higher mortality compared to the control group, reason for which is beyond the scope of this article.

Our results indicate that PCT concentrations are associated with the severity of MODS as assessed by the SOFA score. These results are in general agreement with studies in which PCT levels were compared with the severity of sepsis by sepsis-related score systems. PCT has several advantages in severely ill patients compared with CRP. The most striking one demonstrated in this study, is the enormous range of PCT reactivity resulting in a marked increase in PCT plasma levels, especially during severe stages of sepsis and systemic inflammation. In contrast, CRP levels are often found to be already increased to maximal concentrations in patients with low SOFA scores. Thus, CRP cannot provide information as to further increases in organ dysfunction and the inflammatory progress respectively. Further advantages of PCT are its more rapid kinetics; PCT reacts faster than CRP both during an increase or decrease of inflammation. Novel scientific tools are being sought for insights into underlying biological mechanisms, with impressive attempts at new therapies. Increasing understanding of the inflammatory cascade has given new insights and provided several markers that, in conjunction with other manifestations of sepsis, can be useful indicators of infection.

To conclude, the mortality and morbidity along with multiorgan dysfunction is higher among individuals with sepsis and MetS than in individuals without MetS. PCT is a better marker of sepsis than CRP in predicting outcome of sepsis.

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