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Original Research Article

# An Observational Comparative Study of the Effect of Sepsis on Serum C-Peptide and Insulin Levels in Patients with Type 2 Diabetes Mellitus

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**Abstract**

**Introduction:** Type 2 diabetes mellitus (T2DM) is a chronic metabolic disorder characterized by insulin resistance and a relative deficiency in insulin secretion. Patients with T2DM are more susceptible to infections and sepsis due to the immunocompromised state associated with chronic hyperglycemia. The interplay between C-peptide, insulin, and HbA1c levels during sepsis requires careful monitoring and management to optimize glycaemic control and improve patient outcomes. Understanding these dynamics is crucial for effectively managing T2DM patient.

**Aim:** To assess serum c-peptide and insulin levels in type 2 diabetes with or without sepsis.

**Material and Methods:** This observational comparative study, conducted at SMS Medical College, Jaipur, included 180 participants divided into three groups: diabetic patients with sepsis (Group A), diabetic patients without sepsis (Group B), and non-diabetic patients with sepsis (Group C). Each group underwent clinical evaluation and laboratory investigations, including C-peptide, insulin levels, CBC, and SOFA score, with sepsis diagnosed using Sepsis-3 criteria. Data were analyzed to compare organ dysfunction and inflammatory responses across groups.

**Results:** Our study shows that sepsis elevates both C-peptide and insulin levels, with a more pronounced increase in C-peptide, particularly in diabetic patients, reflecting its immune-modulating role. Additionally, sepsis significantly impacts platelet counts, GCS scores, SOFA scores, albumin levels, and TLC, emphasizing its systemic effects.

**Conclusion:** Our findings demonstrate that sepsis enhances pancreatic activity, as shown by increased C peptide and insulin levels, but this response is influenced by the presence of diabetes. Thus, C peptide serves as a valuable marker for assessing pancreatic function in the context of sepsis, highlighting the complex interplay between diabetes and sepsis on pancreatic and insulin dynamics.

**Keywords**: Type 2 Diabetes Mellitus, sepsis, C-peptide, insulin.



## Introduction

Type 2 diabetes mellitus (T2DM) is a chronic metabolic disorder characterized by insulin resistance and a relative deficiency in insulin secretion. It is one of the most common noncommunicable diseases globally, with significant health, economic, and social implications [1]. Patients with T2DM are more susceptible to infections and sepsis due to the immunocompromised state associated with chronic hyperglycemia. The bidirectional relationship between sepsis and T2DM complicates the management of both conditions. Sepsis can exacerbate hyperglycemia and insulin resistance, leading to a vicious cycle of worsening metabolic and inflammatory status. This interaction necessitates careful monitoring and management of blood glucose levels in septic patients with T2DM to improve outcomes [2]. C-peptide, a byproduct of insulin synthesis, is released in equimolar amounts with insulin from pancreatic beta cells. It is cleaved from proinsulin to form insulin and C-peptide, which then enter the bloodstream. Unlike insulin, C-peptide is not extracted by the liver, giving it a longer half-life in the circulation. Measuring serum C-peptide levels provides an indirect assessment of endogenous insulin production and pancreatic beta cell function. This is particularly useful in differentiating between type 1 and type 2 diabetes, assessing beta cell function in various clinical settings, and guiding therapeutic decisions [2].

Typically, normal fasting C-peptide levels range from 0.5 to 2.0ng/mL (0.17 to 0.67 nmol/L). Elevated C-peptide levels above 2.0 ng/mL may be indicative of insulin resistance and compensatory hyperinsulinemia, common in early T2DM. Conversely, levels below 0.5 ng/mL may be seen in individuals with severe beta-cell dysfunction, where insulin production is insufficient to maintain normal glucose levels [3]. During sepsis, HbA1c levels provide insight into long-term glucose control but may not reflect acute fluctuations in glucose levels due to the stress response whereas C-peptide levels can become unpredictable. Elevated insulin resistance may not always correlate with proportional increases in C-peptide levels due to concurrent stress or damage to pancreatic beta cells [3]. Overall, the interplay between C-peptide, insulin, and HbA1c levels during sepsis requires careful monitoring and management to optimize glycaemic control and improve patient outcomes. Understanding these dynamics is crucial for effectively managing T2DM patients [4]. This research aims to enhance patient care by deepening our understanding of the interplay between sepsis, insulin, and C-peptide levels. By evaluating serum C-peptide and insulin levels in patients with type 2 diabetes mellitus, both with and without sepsis, the study seeks to identify the impact of sepsis on these biomarkers. The primary objective is to determine how sepsis affects serum C-peptide and insulin levels in both diabetic and non-diabetic patients, and to assess whether serum C-peptide can serve as a marker of pancreatic response to sepsis. Additionally, the study will investigate the effect of exogenous insulin on the C-peptide to insulin ratio in these patient groups. The anticipated outcomes will inform more effective management strategies, aiming to reduce the morbidity and mortality associated with sepsis, and optimize resource utilization in critical care settings. Insights from this study will help shape future clinical protocols and guidelines, ensuring more personalized and effective treatment approaches for patients.

## Aim

To assess serum c-peptide and insulin levels in type 2 diabetes with or without sepsis.

## Materials and Methods

This hospital-based observational comparative study was conducted in the Department of Medicine, SMS Medical College and Attached Group of Hospitals, Jaipur from February 2023 onwards, for one year or until the sample size was achieved, with an additional two months for data compilation and analysis. The study included 180 cases with and without T2DM, based on a previous study that reported a prevalence of sepsis of 80% (conducted by Laurent Bitker et al.), with a 7% absolute error fulfilling the inclusion and exclusion criteria and providing informed consent.

Patients who were willing to participate in the study after giving informed consent, age above 18 years and all patients with T2DM diagnosed by clinical and biochemical methods were included in the study. Study participants with history of diabetic ketoacidosis or hyperglycemic hyperosmolar syndrome, chronic renal disease was excluded.

The study subjects were evaluated through history, clinical examination, vital parameters (BP, HR, RR, PR), and blood parameters, including serum C-peptide, insulin levels, CBC, HbA1c, RBS, fasting blood sugar, postprandial blood sugar, RFT, LFT, lipid profile, lactate, bicarbonate, and pH. Sepsis was diagnosed according to Sepsis-3 criteria. Sepsis-associated organ dysfunction was assessed using the Sequential Organ Failure Assessment (SOFA) score, and the inflammatory response was evaluated with the white cell count. Subjects were divided into three groups: 60 consecutive diabetic patients were included in Group A diagnosed with sepsis, Group B comprised of 60 consecutive patients with T2DM but without sepsis, and Group C consisted of 60 consecutive non-diabetic patients diagnosed with sepsis. These parameters were analysed and compared between the three groups. The study was approved by institutional ethical committee

## Statistical Analysis

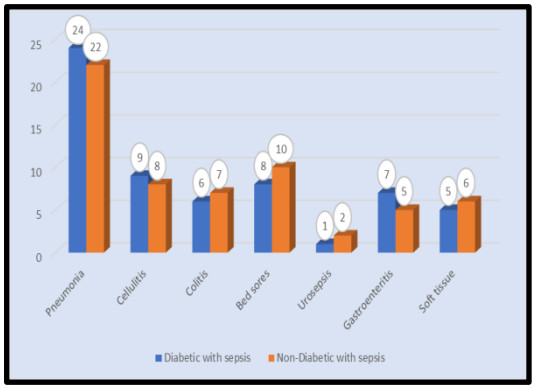
Data were analyzed using SPSS software, Version 22, with a p-value of less than 0.05 considered statistically significant. Continuous variables were presented as mean ± standard deviation (SD), while categorical variables were expressed as counts and percentages. Baseline variable comparisons across the three study groups were conducted using the Kruskal-Wallis test for continuous variables, followed by post-hoc analysis between groups using the Tukey method.

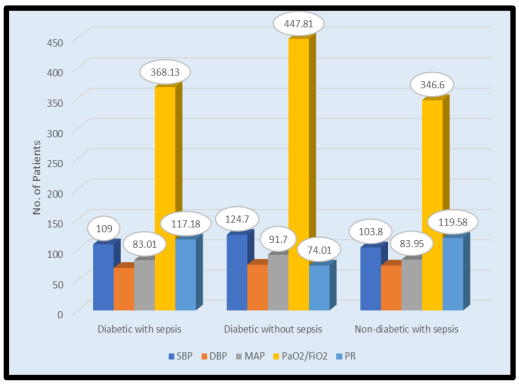
## Result

**Table 1: Age wise distribution of study subjects**

| Groups | Age group (years) Mean ± SD | P value |
|---|---|---|
| Diabetic with sepsis(n=60) Group A | 62.41 ± 7.7 | 0.98 |
| Diabetic without sepsis(n=60) Group B | 62.20 ± 7.6 | |
| Non-diabetic with sepsis(n=60) Group C | 62.54 ± 7.9 | |

The age distribution among the groups was comparable, with no statistically significant differences (p = 0.98), minimizing age as a confounding factor in the analysis.




Pneumonia was the most common infection in both diabetic and non-diabetic sepsis groups, with variations in other infections like bed sores and cellulitis. Vital signs analysis revealed significantly worse cardiovascular stability in diabetic patients with sepsis compared to those without sepsis, with similar hemodynamic profiles observed between diabetic and non-diabetic sepsis groups.

**Table 2: Platelet counts and GCS score among study subjects**

| Groups | Platelets($10^{x3}$) (Mean ± SD) | P-value | GCS Score (Mean ± SD) | Group comparison |
|---|---|---|---|---|
| **Diabetic with Sepsis (Group A)** | 106.96 ± 19.17 | No significant difference (A vs C) | 10.83 ± 1.4 | Significant difference <0.05 (A vs C) |
| **Diabetic without Sepsis (Group B)** | 227.66 ± 19.50 | Significant difference **<0.05** (A vs B) | 15.00 | Significant difference **<0.05** (A vs B) |
| **Non-Diabetic with Sepsis (Group C)** | 101.93 ± 19.20 | Significant difference **<0.05** (B vs C) | 12.23 ± 1.19 | Significant difference **<0.05** (B vs C) |

Sepsis significantly reduced platelet counts and GCS scores, with diabetic patients experiencing the most pronounced effects. Diabetic patients with sepsis showed lower platelet counts and GCS scores compared to diabetic patients without sepsis and non-diabetic patients with sepsis, highlighting greater sepsis-associated impairment in this group.

**Table 3: SOFA score and Creatinine levels among study subjects**

| Groups | SOFA Score (Mean ± SD) | Group comparison | Creatinine (mg/dl) (Mean ± SD) | Group comparison |
|---|---|---|---|---|
| **Diabetic with Sepsis (Group A)** | 7.4 ± 1.60 | Significant difference **<0.05** (A vs C) | 1.6 ± 0.41 | Non -Significant difference >**0.05** (A vs C) |
| **Diabetic without Sepsis (Group B)** | Not applicable | Not applicable (A vs B) | 0.65 ± 0.21 | Significant difference <0.05 (A vs B) |
| **Non-Diabetic with Sepsis (Group C)** | 6.3 ± 1.42 | Not applicable (B vs C) | 1.41 ± 0.52 | Significant difference <0.05 (B vs C) |

Diabetic patients with sepsis had significantly higher SOFA scores and creatinine levels compared to diabetic patients without sepsis, indicating a greater impact of sepsis on organ dysfunction and renal function. Non-diabetic patients with sepsis also showed elevated creatinine levels, though not significantly different from diabetic patients with sepsis.

**Table 4: Total Leucocyte Counts and Glycated Hb (HbA1C) among study subjects**

| Groups | HbA1c (%) (Mean ± SD) | Group comparison | TLC (109/L) (Mean ± SD) | Group comparison |
|---|---|---|---|---|
| **Diabetic with Sepsis (Group A)** | 7.01 ± 0.59 | A vs C Significant difference **<0.05** | 12.7 ± 3.05 | A vs C No significant difference |
| **Diabetic without Sepsis (Group B)** | 7.30 ± 0.59 | A vs BNo Significant difference >**0.05** | 6.27 ± 1.50 | A vs B Significant difference **<0.05** |
| **Non-Diabetic with Sepsis (Group C)** | 4.87 ± 0.46 | B vs C Significant difference **<0.05** | 13.5 ± 2.41 | B vs C Significant difference **<0.05** |

The study highlighted significant differences in HbA1c and total leukocyte count (TLC) across groups based on diabetes and sepsis. While HbA1c levels were significantly lower in non-diabetic patients with sepsis compared to diabetic groups, TLC was highest in non-diabetic patients with sepsis, with both parameters showing notable variations influenced by diabetes and sepsis status.

**Table 5: C peptide and Insulin levels among study subjects**

| Groups | C-Peptide(ng/mL) (Mean ± SD) | P-value | Insulin(µU/mL) (Mean ± SD) | Group comparison |
|---|---|---|---|---|
| **Diabetic with Sepsis (Group A)** | 12.02 ± 4.46 | A vs C no significant differences | 12.69 ± 4.80 | < 0.05 (A vs C) |
| **Diabetic without Sepsis (Group B)** | 2.11 ± 0.61 | **<0.05** (A vs B) | 4.10 ± 0.99 | <0.05 (A vs B) |
| **Non-Diabetic with Sepsis (Group C)** | 13.35 ± 3.97 | <0.05 (B vs C) | 17.06 ± 5.58 | <0.05 (B vs C) |

The study revealed significant differences in C peptide and insulin levels across groups based on diabetes and sepsis. Diabetic patients with sepsis had higher levels than those without, while non-diabetic patients with sepsis showed the highest levels, highlighting a comparatively poor insulin response in diabetics with sepsis.

**Discussion**

Sepsis triggers stress-induced hyperglycemia, which serves as a marker of illness severity and may affect survival by altering the immune response. While hyperglycemia can negatively impact the immune system, C-peptide, released alongside insulin by pancreatic β-cells, plays a beneficial role by modulating inflammation. It reduces leukocyte adhesion, pro-inflammatory cytokine secretion, and reactive oxygen species production.

In our study, the mean ages were 62.41 years in Group A, 62.20 years in Group B, and

62.54 years in Group C, with no statistically significant differences between the groups. This suggests that age is unlikely to influence comparisons between diabetic and nondiabetic patients with sepsis. Similarly, a study by Crysman et al. [5] (2017) reported that the mean age of sepsis patients was 69 years, whereas patients without sepsis had a mean age of 60 years.

All patients with sepsis in Group A and C were evaluated for source of infection and etiology. In the diabetic group (Group A), pneumonia was the most common infection with 24 patients, followed by bed sores (8 patients), gastroenteritis (7 patients), cellulitis

(9 patients), colitis (6 patients), soft tissue infections (5 patients), and urosepsis (1 patient). In the non-diabetic group (Group C), pneumonia was also the most common infection with 22 patients, followed by bed sores (10 patients), cellulitis (8 patients), colitis (7 patients), soft tissue infections (6 patients), gastroenteritis (5 patients), and urosepsis (2 patients). The findings from our study are consistent with those of Chávez-Reyes J et al. [6] 2021 who reported that pneumonia is the most prevalent infection in both diabetic and nondiabetic patients. Their research highlighted that skin infections, including cellulitis and bed sores, were also common across both groups. Gastrointestinal infections such as gastroenteritis and colitis, along with soft tissue infections, were frequently observed in both diabetic and non-diabetic individuals. Urosepsis was less common but still present in both groups. This pattern underscores that pneumonia is a predominant infection type, with similar infection-related complications observed across diabetic and non-diabetic patients.

In our study, platelet counts were significantly lower in sepsis patients compared to those without sepsis. This finding is consistent with other studies, such as a study by Cheng J et al. [7] (2023), which demonstrated that thrombocytopenia is common in sepsis

due to increased platelet consumption and destruction during systemic inflammation.

We observed that sepsis is linked to lower GCS scores, especially in diabetic patients compared to those without diabetes. Our findings align with the study conducted by Singer et al. [8] (2016), which examined the Sepsis-3 criteria. This study emphasized that altered mental status, reflected by decreased GCS scores, is a prevalent issue among septic patients. Furthermore, it noted that individuals with pre-existing conditions like diabetes may experience more significant cognitive impairment during episodes of sepsis.

The SOFA score was also higher in patients with both sepsis and diabetes compared to those who only had sepsis. This finding aligns with the results of Karakike et al. [9] (2019), which indicated that the SOFA score is a valuable early prognostic marker of 28day mortality, suggesting its potential as an endpoint in future sepsis trials alongside mortality outcomes.

In our study, we found that sepsis, particularly in diabetic patients, is associated with lower albumin levels; as highlighted by Gupta L et al. [10] 2012 hypoalbuminemia is frequently observed in dcritically ill patients and is directly linked to patient prognosis, with this association being more pronounced in cases of severe sepsis and septic shock compared to sepsis alone, leading us to conclude that monitoring serum albumin levels is of significant clinical importance for evaluating the prognosis of patients with severe sepsis and septic shock.

In our study, sepsis significantly impacts total leucocyte counts (TLC) in diabetic patients, reflecting a general increase in TLC associated with sepsis, regardless of diabetic status. This finding aligns with Li Q et al. [11] (2021) reported that leukocytosis, indicated by increased TLC, is a characteristic feature of sepsis and correlates with poor outcomes, particularly in individuals with underlying conditions such as diabetes.

In our study, diabetic patients with sepsis had an average C-peptide level of 12.02 ± 4.46 ng/mL, which was significantly higher than observed in diabetic patients without sepsis (2.11 ± 0.61 ng/ mL). In non-diabetic patients with sepsis, the average C-peptide level was 13.35 ± 3.97 ng/mL. These differences were statistically significant, with a p-value of less than 0.05 when comparing diabetic patients with and without sepsis. However, no significant difference was observed between diabetic patients with sepsis and nondiabetic patients with sepsis ($p > 0.05$). These findings suggest that C-peptide levels are increased in both the group of patients with sepsis.

In patients with diabetes and sepsis, the mean insulin level was 12.69 ± 4.8 μU/mL, significantly higher compared to diabetic patients without sepsis, who had a mean insulin level of 4.1 ± 0.99 μU/mL. Non-diabetic patients with sepsis exhibited the highest mean insulin level at 17.06 ± 5.58 μU/mL. The differences between these groups were statistically significant, with a p-value of less than 0.05 for the comparison between diabetic patients with and without sepsis. These findings suggest that insulin levels are affected by both diabetes and sepsis, with the highest levels observed in non-diabetic patients with sepsis and the lowest levels in diabetic patients without sepsis. Studies by van den Berghe et al. [12] (2001) indicates that sepsis causes significant metabolic disturbances, including both insulin resistance and elevated insulin levels. Studies have demonstrated that critically ill patients, such as those with sepsis, often have increased insulin levels as a result of heightened insulin resistance. This observation is consistent with the elevated insulin levels found in non-diabetic patients with sepsis in the data (mean 17.06 ± 5.58 μU/mL).

Our findings show that sepsis increases C-peptide levels, and that this increase is greater than the increase in insulin levels. In line with the immune-modulating effects of C Peptide.

## Conclusion

The study concluded that sepsis significantly affects serum C peptide and insulin levels, with distinct variations observed between diabetic and non-diabetic patients. Non-diabetic patients with sepsis had the highest serum C peptide levels, indicating a strong pancreatic response to sepsis. Diabetic patients with sepsis also showed elevated C peptide levels, but these were lower than those in non-diabetic patients with sepsis. This suggests that while sepsis stimulates C peptide production, diabetes may moderate this response. Insulin levels mirrored this pattern, being highest in non-diabetic patients with sepsis, which reflects the considerable impact of sepsis on insulin secretion. Conversely, diabetic patients had lower insulin levels, implying that diabetes might reduce the insulin response to sepsis. Overall, these results demonstrate that sepsis enhances pancreatic activity, as shown by increased C peptide and insulin levels, but this response is influenced by the presence of diabetes. Thus, C peptide serves as a valuable marker for assessing pancreatic function in the context of sepsis, highlighting the complex interplay between diabetes and sepsis on pancreatic and insulin dynamics.

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