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Review Article

Management of critically ill septic patients with diabetes

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ABSTRACT

Diabetes and sepsis are major contributors of morbidity and mortality around the world, with diabetic patients accounting for the majority of post-sepsis comorbidities and escalating mortality rates. Diabetes is undoubtedly a key comorbid syndrome due to its high frequency and propensity to affect critical parts of sepsis pathogenesis; however, the precise impact of diabetes on infection and sepsis progression is elusive. In diabetic individuals with sepsis, dysfunctional immunological pathways, which are frequent in both sepsis and diabetes, promotes worsening of the host response. The effect of diabetes on sepsis mortality is still debatable. While poor glycemic management is linked to the incidence of a large proportion of severe infections, treatment with insulin or commercially available oral antidiabetic drugs are linked to lower sepsis incidence and even death. Optimal glycemic control has been reported to improve immunological adaptability, resulting in a lower mortality rate in diabetes patients with sepsis. The present review is an attempt to gather literature pertinent to glycemic control and risk of sepsis. An additional body of reports are also included on the effect of insulin and other anti-diabetic medications on the incidence and mortality for sepsis along with the strategies employed for the management of the said illness.

Keywords: Type 2 diabetes mellitus, Sepsis, Randomized trial, Insulin, Metanalysis, Hyper-glycemia

INTRODUCTION

A dysfunctional host response to an infection causes sepsis. Despite significant breakthroughs in immunological pathology, the incidence of sepsis has not improved significantly.[1] Sepsis is still the primary cause of death in intensive care units.[2] Given the continually growing senior population with significant comorbidities, physiological impairment, and immunological senescence, sepsis mortality is expected to climb at an alarming rate within next few decades.[3] The rising expenditures connected with treating septic patients are equally worrisome. While over handful of clinical trials have been executed in sepsis, no FDA-approved therapeutics to increase sepsis survival are currently available.[4] Advances in clinical treatment regimens, on the other hand, have contributed to higher in-hospital survival rates from life-threatening sepsis and organ failure.

T2DM is a complicated clinical disease characterized by recurrent hyperglycemia in the context of impaired insulin secretion and sensitivity, resulting in a slew of abnormal metabolic alterations.[4] T2DM affects the outcome of pathogenic infections, including mortality risk from infections and sepsis in T2DM individuals, according to published clinical data.[5,6] Sepsis has a broad consequence on the immune system because it affects the lifetime, generation, and functionality of innate and adaptive immune cells, causing immune cell homeostasis to be disrupted.[7]

This balance may be disrupted in T2DM patients due to overnutrition and elevated adiposity. The increasing prevalence, intensity, and persistence of infections are definitely due to metabolic-induced immunological disturbances.[8]

The question of whether inflammatory/anti-inflammatory mechanisms or innate/adaptive immune dysfunction are more damaging to lifespan in sepsis is still debated.[9] Studies have discovered that an inflammatory and anti-inflammatory state that is sustained and propelled by a malfunctioning innate immune system and repressed adaptive immunity. These factors combine to cause chronic organ impairment, inflammation, and patient mortality.[10,11] Patients with T2DM have a faulty immune system from the outset. T2DM patients remains to have high morbidity and death in about months to a year following the primary acute septic event. Long-term morbidity and death, may be caused by lasting dysregulation in the cellular activities of the innate and adaptive immune systems.

The predominance of T2DM is predicted to exceed 700 million globally in the coming years, attaining alarming proportions as a result of the soaring endurance to Western diet and lifestyle.[12] T2DM and its associated complications are also a prominent trigger of hospitalization, impairment, and fatality.[13] T2DM will emerge a more prominent comorbidity observed in the healthcare setting as the sluggish, calorie-rich western lifestyle expands to penetrate the worldwide panorama.[14] Patients with T2D are more likely to contract infections and incur sepsis. T2D significantly impairs infection expectancy, with sepsis-related morbidity and mortality being higher in T2D patients.[15] Because of the rising incidence, prevalence, and mortality rates of people with T2D, as well as the growing risk of infections, a quickly expanding patient population is utilizing more medical expenses. Multiple reports have demonstrated that diabetic patients have a compromised immune system leading to incidences of infection and a heightened risk of sepsis as compared to non-diabetic individuals with a higher sepsis-related morbidity and mortality.[16-18] Diabetic patients are also more prone than non-diabetics to be colonized by resistant microorganisms, such as methicillin-resistant Staphylococcus aureus.[19] These factors reinforce the notion that diabetes is becoming a more prevalent comorbidity among septic patients. [20]

Despite recent advances in detection and treatment choices, diabetes and sepsis continue to be frequent, expensive, and devastating worldwide.[21] Hence the present review is an attempt to gather literatures pertinent to glycemic control and risk of sepsis. An additional body of reports are also included on the effect of insulin and other anti-diabetic medications on the incidence and mortality for sepsis along with the strategies employed for the management of the said illness.

RELATIONSHIP BETWEEN GLYCEMIC CONTROL AND RISK OF SEPSIS

Glycated hemoglobin (HbA1c) seems to be the extensively recognized marker of long-term gluco-regulation and a potential sign for the emergence of diabetic sequelae.[22] It enables to differentiate non-diabetic individuals perceiving stress hyperglycemia from individuals with originally undiagnosed diabetes in hyperglycemic sepsis and to recognize stress-induced glycemic decline in patients with an initial medical diabetes diagnosis by correlating actual blood glucose attributes with HbA1c-estimated average values during preadmission.[23]

A group of 191 patients treated with intense glucose control (primary objective of 80-140 mg/dL) was studied to see if there was a link between glycemic control and the degree of sepsis. Hypoglycemia and hyperglycemia were shown to be more common in individuals with severe sepsis or septic shock, according to the reported study.[24] In the efficacy of volume substitution and insulin therapy in severe sepsis (VISEP study), standard therapy was matched to intensive insulin therapy, and resuscitation of fluids i.e., 10% pentastarch vs modified Ringer's lactate were also studied.[25] It was noted that strict glucose control had no effect in patients with severe sepsis, and the study was terminated early for safety concerns owing to the increase rate of hypoglycemic incidences. A sample study of the NICE-SUGAR trial found no benefit in mortality in septic patients.[26] According to the surviving sepsis campaign guidelines, insulin therapy should be started after two successive blood glucose readings with noted range above 180 mg/dL and an optimum goal level of 180 mg/dL.[27]

Another large retrospective cohort study was reported which included more than 150,000 patients, out of which about 85,000 were T2DM patients.[28] The study was designed to establish an associated link between poor glycemic control and increased risks of serious infections. It is a known fact that diabetic patients, irrespective of glycemic control, have higher infection-related hospitalization risks than non-diabetic ones. Impaired metabolic control was linked to a threefold increase in the probability of hospitalization in diabetes individuals. Altogether, HbA1c values of less than 6-7% corresponding to 42-53 mmol/mol have been linked to 6.7 % of infection-related deaths, 16.5% of infection-related hospitalizations, 6.8% of infections needing a prescription, and incidences of approximately 20% of sepsis occurrences. The incidence rate ratio for sepsis varied from 1.2 to 3.64. Surprisingly, even strict metabolic management was linked to an increased probability of infections in the elderly, who were shown to have a larger infectious risk and poor prognosis. Hence it was inferred in the study that a less severe glycemic control would be more advantageous, but a stricter control would be correlated with greater hazards.

A retrospective large national database review reported by Van Vught et al reported that in diabetic patients, serious hypoglycemia in the lack of hyperglycemia was noted to be associated with increased 90-day mortality while multiple combinations of abnormal glucose levels were correlated with greater 90-day mortality rates as

noted in non-diabetic individuals.[44] In support of the above findings, another report published by Chang and co-workers also reported in a group of 16,497 ICU septic patients that following adjustment for age, gender, comorbidities, and the frequency of acute organ dysfunctions, there was no link between diabetes and 90-day mortality.[45]

EFFECT OF GLUCOSE CONTROL DURING SEPSIS

Hypoglycemia is frequently connected with sepsis and is thought to be an early sign of serious organ dysfunction before death. Even though processes and linkages between hypoglycemia and the extent of the said disease in septic patients are still being disputed, inflammatory cytokines have been suggested as a possible factor.[37]

Patients assigned to surgical ICUs randomly allocated to undergo intensive insulin therapy (blood glucose level of 80-110 mg/dl)/ standard therapy (aim of 180-200 mg/dl).[38] Result of study indicated that intense insulin therapy lowered nosocomial septicaemia occurrences by 46%. Tight glucose control (TGC), corresponding to a blood glucose levels less than 110 mg/dl noted to be linked to 43% lower mortality rate in ICU.

This outcome, though, is based on the advantage observed in the group of patients whose stay was more than 5 days in the ICU. However, the findings of the mentioned study established that TGC minimized morbidity in all the enrolled patients, but only reduced death in those who stayed in the ICU for at least 3 days. Furthermore, there were reservations raised about the higher rates of hypoglycemia episodes in the studied subset of patients. A post-hoc study of pooled data from the two investigations indicated that TGC was associated with a considerably increased incidence of hypoglycemia.[39] The specific numbers referred to 11.3 % of TGC patients experiencing hypoglycemia as compared to 1.8% of those on traditional insulin therapy (p=0.0001). However, if hypoglycemia was not linked to early fatalities or neurological complications, it was linked to an increased risk of death. TGC dramatically lowered morbidity and death in mixed medical/surgical ICUs, according to the pooled data, especially in hospitalized patients with a stay of at least 3 days. TGC has also been shown to improve all patient groupings, including those with sepsis. There was no survival advantage reported for diabetes patients alone. The paucity of TGC effectiveness in diabetic patients has been attributed to quick stabilization of blood glucose concentrations rather than hypoglycemic episodes.

Closed-loop glucose management technologies and immunomodulatory therapeutic alternatives were recommended for diabetic patients with severe sepsis in order to circumvent hypoglycemia following insulin therapy and thereby reduce the surge in systemic cytokine concentration.[40]

IMPACT OF INSULIN AND OTHER ORAL ANTI-DIABETIC DRUGS ON THE INCIDENCE AND MORTALITY FOR SEPSIS

A handful of observational studies have shown that hyperglycemia, specifically sepsis-induced hyperglycemia, is associated with elevated mortality rate as compared to mortality attributable to pre-existing diabetes mellitus.[46] A randomized controlled trial reported in 2001 found that intensive insulin administration (80-110 mg/dL) contributed in decreased hospital mortality in the intensive care unit, which was ascribed to a decline in sepsis-related mortality.[38] Clinicians enthusiastically accepted it as a successful therapy for these patients based on the encouraging findings. Successive randomized controlled trials failed to back up this positive finding. In contrast to the positive finding, the VISEP research, which was the first to look into intensive insulin therapy for septic patients, revealed no evidence of a substantial reduction in mortality rate.[48] Then, in randomized controlled studies, the mortality advantage in septic patients was not replicated.[49,50] Despite the ongoing dispute, the Surviving sepsis campaign includes a blood glucose upper limit of 180 mg/dL in their standards, which were based on systematic assessments of research involving critically ill people.[48] Though sepsis is the leading reason of death in ICUs, it's unclear whether the effects and risks of intensive insulin therapy are identical in septic patients as they are in critically ill patients.

A study was published which included 4,100 individuals who were enrolled in 12 randomized controlled trials, with 2,094 in the intensive insulin group (IIT) and 2,006 in the control group. The results indicated that IIT did not lower overall mortality (risk ratio [RR]=0.98, 95% confidence interval [0.85, 1.15], 28-day and 90-day mortality, ICU mortality, hospital mortality, severity of disease, or duration of ICU admission, according to a meta-analysis. Hypoglycemia, on the other hand, was much more common in the group of subjects treated with intensive insulin group. The report inferred the fact that IIT and cautious glucose management have equivalent efficacy in sepsis patients, although intensive insulin group is linked to a greater rate of hypoglycemia.[35] The correlation between dysglycemia incidence and hospital mortality in a total of 90,644 septic patients (5127 of them having insulin treated diabetes mellitus, ITDM) patients with and without a preadmission diagnosis of ITDM. It was discovered that septic ICU patients with ITDM had reduced hospital mortality rate with higher overall blood glucose levels in the first 24 hours, as compared to non-ITDM patients. In comparison to those without ITDM, septic patients with a pre-existing diagnosis of ITDM have a distinct link between hospital mortality and peak glucose levels and glycemic fluctuation in the first 24 hours. These data reinforce the use of an ITDM-specific paradigm to the dysglycemia therapy.[36]

Table 1: A list of studies.

Name of OADs	Study design	Number of Subjects	Outcome	Inference	Reference
Metformin, sulfonylureas, TZDs, meglitinides and DPP-4 inhibitors	Nested case-control study	43,015 patients who were initially hospitalized for sepsis and 43,015 matched controls	Metformin usage was linked to a lower risk of emerging sepsis, but meglitinide use was affiliated with a higher risk of evolving sepsis. Existing and recent thiazolidinedione users had a decreased chance of developing sepsis. The employment of sulfonylureas and dipeptidyl peptidase-4 inhibitors, however, was not linked to the onset of sepsis.	The findings underscore the importance of considering OADs' possible pleiotropic action against sepsis in combination to blood glucose reduction.	Shih et al,[32] 2015
Metformin	Nationwide sample cohort study	34,041 in the metformin user group and 43,296 in the control group	Both the risk of sepsis and the associated risk of 30-day mortality after diagnosis of sepsis were not significantly linked with metformin usage.	Prior metformin medication was not linked to a higher risk of sepsis or 30-day mortality after a sepsis diagnosis in diabetic patients.	Song et al,[31] 2020
Metformin	Observational cohort studies	1282 patients	Five observational cohort studies including 1282 patients were considered, all of which were assessed to have a low risk of bias. Metformin use was linked to a significantly decreased mortality rate (OR, 0.59; 95% CI, 0.43-0.79, p=0.001) in the meta-analysis report.	Metformin usage prior to admission was linked to decreased mortality in septic adult patients with diabetes mellitus, according to this meta-analysis. This research suggests that future clinical trials should look into the likely implications of metformin.	Liang et al,[33] 2019
DPP-4 inhibitors	Nested case control study	-	Infection incidence was greater in people on DPP-4 inhibitors than in those taking biguanides (ROR 2.3 [95 % CI 1.9-2.7]). The usage of DPP-4 inhibitors was linked to a higher risk of upper respiratory tract infections (ROR 12.3 [95% CI 8.6-17.5]).	Subjects who were administered DPP-4 inhibitors reported more incidences of infections, particularly upper respiratory tract infections, than users of other antidiabetic medicines, according to the present study. However, the limits of sudden reporting systems such as underreporting, the Weber effect, and reporting bias needs to be considered.	

Biguanides (metformin), sulfonylureas, alpha-glucosidase inhibitors, meglitinides, thiazolidinediones (TZDs), dipeptidyl peptidase-4 (DPP-4) inhibitors, and novek sodium-glucose cotransporter 2 (SGLT2) inhibitors are among the commercially available oral anti-diabetic drugs (OADs). OADs have been linked to immunomodulation in numerous preclinical study reports.[29,30] In reality, individuals with T2D are more prone to infection and sepsis, which may have an influence on T2D mortality and health-care expenditures. However, the potential pleiotropic role of OADs on sepsis consequences has not to be thoroughly verified in large-scale clinical research settings.

PROTECTIVE ACTION OF DIABETES DURING INFECTION

According to some findings, diabetes at times may actually protect the individuals in systemic infection. Therapeutic benefits of exogenously delivered insulin, protection of acute lung injury, adaptability to past oxidant stress, and a superior nutritional substrate in obese diabetic patients are some of the hypothesized pathways.[41]

A study reported that included records from both retrospective and prospective ICU patient datasets revealed that diabetes had a defensive impact on critical patient prognosis. Diabetes had a reduced adjusted OR for death in the studied populations. Furthermore, a population-based cohort research in Denmark indicated a tendency toward decreased mortality rates in diabetic participants.[42] Diabetic patients were less prone to build acute respiratory failure and had a significantly lesser mortality rate in a large epidemiological study involving 12,500,000 septic subjects from the United States national hospital discharge survey.[43]

Sampling error, smaller sampling size, inadequate acquisition of data pertaining to type of diabetes, metabolic parameters, supplementary diabetes-related complications are all possible causes of disparities among these different diabetes outcome measures.

CONCLUSION

Sepsis is a leading cause of death around the world, and diabetes is a prevalent and growing comorbidity among septic patients. Diabetic individuals have an increased risk of acquiring infection, according to reported clinical studies. However, it is unclear whether diabetic individuals with infection have an inferior prognosis. Clinical evidence shows both extremities, with some research suggesting a negative link between diabetes and mortality and others demonstrating no link or a protective effect. Furthermore, the role of intensive insulin therapy in extremely unwell septic patients is debatable.

Although diabetic individuals have an elevated risk of infection, the influence of diabetes on sepsis outcomes and the principles underpinning their interconnections are still being explored. The influence of diabetes and sepsis on the immune system, the influence of glycemic control and the prospective beneficial role of anti-diabetic medications on the onset of sepsis and its prognosis are all critical problems that ought to be clarified. To effectively comprehend the dynamic interactions of diabetes and sepsis in individuals, future research endeavors should focus on diabetes as a syndrome, accounting for the crucial confounding factors such as hyperglycemia, obesity, secondary micro- and macrovascular comorbidities, insulin therapy, endothelial disorder, and many others. In addition, novel immunomodulatory strategies targeting the multiple pathways triggered in diabetes and sepsis must be investigated further, as well as the design of larger prospective research and randomized controlled trials could result in greater clinical advantages.

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