DIABETES MELLITUS AND COVID-19; A BIDIRECTIONAL INTERPLAY

Davlatov Sh.Q
Saydaxmedov Z.I
Mahmudov U.I
Fergana Public Health Medical Institute, Fergana, Uzbekistan

Abstract: *In the intricate dance of health and disease, a bidirectional tango unfolds between the enigmatic realms of Diabetes Mellitus (DM) and the relentless force known as coronavirus disease 2019 (COVID-19). Picture a dual narrative, where individuals grappling with diabetes find themselves ensnared in a perilous waltz with a higher risk of succumbing to the clutches of fatal or critically treated COVID-19, their vulnerability accentuated against the backdrop of those untouched by the intricate web of diabetes.*

Yet, the plot thickens as the stage transforms, casting a spotlight on the insidious influence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Clinical data, like cryptic scrolls, unfurl the tale of metabolic dysregulation and the disruption of the delicate equilibrium of glucose homeostasis in the wake of SARS-CoV-2's malevolent presence. As the narrative weaves forward, whispers of new-onset DM in the aftermath of SARS-CoV-2 infection add a layer of complexity, hinting at a direct hand of the viral protagonist in the orchestration of glucose metabolism [1].

In the quest to decipher the effects of COVID-19 on the intricate tapestry of metabolism, the stakes are high. Understanding becomes the linchpin, a crucial element that holds the key to averting and managing the intricate complications that arise in the wake of COVID-19. It is a rallying cry, a call to arms, urging healthcare practitioners to be vigilant custodians in the prevention and management of the labyrinthine consequences that ensue from the symbiotic relationship between diabetes and COVID-19.

In this article, we embark on a journey through the corridors of potential underlying pathophysiological mechanisms linking COVID-19 and the disarray of glucose regulation. As we delve into the abyss of knowledge, we also cast our gaze upon the effects of antidiabetic treatments, seeking solace and answers for those navigating the turbulent waters of both diabetes and COVID-19. The narrative unfolds, an exploration into the intricate web that binds two seemingly disparate entities into a complex dance of health and disease.

Introduction. In the grand tapestry of human health, the Coronavirus Disease 2019 (COVID-19) unfurls as an epoch-making pandemic, propelled into existence by the notorious severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The viral tendrils of SARS-CoV-2 have ensnared a staggering cohort, surpassing the ominous milestone of 530 million infections, a somber dance with mortality claiming over 6.3 million lives, a relentless toll that echoes through the annals of history since the pivotal date of June 23, 2022 [1].

The labyrinthine corridors of recent research weave a perplexing narrative, casting a shadow of uncertainty over the intricate relationship between COVID-19 and its potential role as a harbinger of diverse chronic diseases [2]. As we peer into the crystal ball of future health challenges, the specter of COVID-19 casts an ominous silhouette, potentially augmenting the burden of existing tribulations. It is a clarion call to both patients and society at large to heed the warning bells, for failure to do so may birth more formidable public health crises.

In the vast tableau of chronic maladies, diabetes emerges as a ubiquitous and formidable antagonist, casting its wide-reaching influence as a global public health menace [3], [4], [5]. Alas, the symphony of evidence plays a haunting melody, revealing a bidirectional tango between diabetes and the spectral entity that is COVID-19 [6]. The intricate dance unfolds on a stage where pre-existing diabetes and the emergence of new-onset diabetes post-infection emerge as pivotal players, orchestrating a sinister crescendo that amplifies the risk of dire consequences — acute respiratory distress syndrome, admission to the hallowed halls of intensive care units, reliance on the mechanical breath of ventilators, and the ultimate bow to death [6], [7], [8], [9], [10], [11], [12].

Yet, the plot thickens as whispers of a clandestine pact between COVID-19 and the genesis of diabetes flutter through the medical ether. Reports, like enigmatic echoes, suggest a surge in diabetes incidence post-COVID-19 diagnosis, blurring the lines between cause and effect [13], [14]. In this convoluted dance of destiny, both type 1 diabetes (T1D) and type 2 diabetes (T2D) emerge as potential offspring of the COVID-19 liaison, a genetic code yet to be deciphered [15], [16]. The urgency to illuminate the dark corners of this intricate relationship reverberates, underscoring the vital imperative of not only acknowledging but also unraveling the perilous link between COVID-19 and the looming specter of diabetes.

Thus, in this intellectual odyssey, a systematic review and meta-analysis take center stage, seeking to unfurl the parchment and scrutinize the relative risk of diabetes in the wake of a COVID-19 storm. A narrative where the ebb and flow of data intertwine, seeking not only to quantify risk but also to decipher the cryptic factors that may sway the scales in this enigmatic dance of diseases.

In the intricate web of health intertwining with the relentless saga of COVID-19, the stage is set for a multifaceted dance where diabetes complications emerge as clandestine actors, their presence casting shadows upon the severity of the viral nemesis. Epidemiological studies, akin to skilled storytellers, unveil a narrative where the coexistence of microvascular and macrovascular complications of Diabetes Mellitus (DM) serves as a harrowing risk factor, a perilous alliance that amplifies the toll of poor COVID-19 outcomes and mortality [11–13].

Enter the labyrinth of obesity, a prevalent companion of diabetes, whose impact on the immune system is etched in the language of adipose tissue. This adipose tapestry, woven with threads of liver and stressed ß-cells, orchestrates a symphony of pro-inflammatory cytokines, adhesion molecules, and a cascade of metabolic and hemodynamic pathways. It unveils a dance of growth factors and intracellular signals, an intricate choreography that births generalized vasculopathy and systemic inflammation [14]. As obesity takes center stage, it unveils a correlation with T cell immune signatures unique to the realms of severe COVID-19, offering a tantalizing glimpse into a potential contributing mechanism [15].

Yet, the search for mechanisms inherent to diabetes delves deeper, unveiling two conceptual approaches – the endothelium and chronic inflammation. The endothelium, once considered a virtuoso in supporting the homeostasis of healthy individuals, emerges as a pivotal player. It regulates the tone of vascular smooth muscle, controls vascular permeability, and orchestrates the delicate dance of inflammation and coagulation. However, in the clutches of diabetes, chronic endothelial dysfunction and damage to the endothelial glycocalyx become the protagonists. These malevolent forces increase adhesion of inflammatory cells, promote vascular permeability, and set the stage for coagulation chaos [16–23]. Hyperglycemia and insulin resistance emerge as culprits, triggering pathways of oxidative stress, apoptosis of endothelial cells, and a decreased availability of nitric oxide – a cascade that leads to endothelial dysfunction [24]. It becomes a chiaroscuro of glycemic control, where the shadows of high hemoglobin A1c values correlate positively

with the perfused boundary region, a marker of glycocalyx thickness [25]. The dance deepens as insulin resistance reveals its role, inducing glycocalyx damage in the first-degree relatives of diabetic patients [26]. Chronic endothelial dysfunction becomes the gateway to severe COVID-19, sculpting alterations to the glycocalyx and endothelial cells, fostering a procoagulant and antifibrinolytic state.

Diabetes, even in the prediabetic stages, unfolds as a saga of chronic inflammation and a prothrombotic state, a tapestry woven with metabolic, vascular, immune, and hematological abnormalities. It is a symphony of glucotoxicity coinciding with impaired immunity, where the inhibition of lymphocyte proliferation, reduced natural killer cell activity, and dysfunction of monocytes/macrophages and neutrophils add layers to the intricate narrative [27–29]. Amidst the chronic endothelial effects of diabetes, susceptibility to severe COVID-19 deepens. Hyperglycemia, both on admission and during hospitalization, emerges as a harbinger of worse prognosis, severity, and mortality of COVID-19, irrespective of prior diabetes status. Elevated glucose levels become independent risk factors, dictating the progression to critical cases and in-hospital mortality [32, 33]. The saga unfolds on the global stage, as more than 1,000 inpatients with COVID-19 in US hospitals reveal a fourfold increase in inpatient mortality for diabetic patients and a sevenfold spike for those without pre-existing diabetes who develop hyperglycemia in the hospital [34]. A meta-analysis, a chorus of voices, further confirms these findings, showcasing a nonlinear relationship between admission fasting blood glucose and severity [35]. The retrospective studies from China paint a vivid portrait of hospitalized COVID-19 patients, where disease severity intertwines with active inflammatory markers, revealing a greater inflammatory response in diabetic patients, marked by elevated IL-6, CRP, ESR, relative neutrophilia, lymphopenia, and a higher incidence of coagulopathy [36, 37].

Beyond the inflammatory crescendo, hyperglycemia induced by diabetes becomes a maestro conducting the replication of SARS-CoV-2, increasing viral load and setting the stage for a mitochondrial ROS/hypoxia-inducible factor-1a dependent pathway. This pathway, a sinister alliance, leads to T cell dysfunction, epithelial cell death, and a cascade of events that tilt the balance toward acute respiratory syndrome and multi-organ failure [38]. In a curious twist, hyperglycemia unveils its power to halt the beneficial effects of Tocilizumab, a disruptor targeting the interleukin-6 receptor and reducing the cytokine storm [39].

As the narrative unfolds, the dance between diabetes and COVID-19 becomes a symphony of intricate interactions, a tale of intertwined destinies where each twist and turn reveals the complex interplay between these two formidable foes on the global stage of health and disease.

RESULT

Two years into the relentless journey of the COVID-19 pandemic, the unequivocal role of diabetes as a risk factor in its pathophysiology stands as an undeniable truth. Amidst the array of chronic complications and comorbidities associated with diabetes—aging and obesity included—a spotlight has now been cast on the endothelium. Chronic endothelial dysfunction, a hallmark of diabetes, emerges as a pivotal player, predisposing individuals to severe COVID-19 infections by orchestrating detrimental alterations to the glycocalyx and endothelial cells.

The intricate dance begins with chronic endothelial dysfunction, a consequence of diabetes, setting the stage for a cascade of events. This dysfunction becomes a harbinger of severe COVID-19, fostering changes in the glycocalyx and endothelial cells that elevate leucocyte adhesion. This, in turn, creates a landscape conducive to a procoagulant and antifibrinolytic state. The alliance of chronic endothelial dysfunction due to diabetes and the direct onslaught of endothelial cells by SARS-CoV-2 converges to inflict further impairment upon the microcirculation, becoming a significant contributor to the pathogenesis of acute respiratory syndrome and multi-organ failure.

The intricacies of this symbiotic relationship unveil a vicious cycle. COVID-19, the viral adversary, doesn't merely stop at exploiting existing vulnerabilities but goes on to cause severe derangements in glucose homeostasis. The consequences of this disruption, compounded by the inflammatory cytokine storm characteristic of COVID-19, manifest in increased oxidative stress. Oxidative stress, in turn, disrupts the delicate balance of the immune system and inflicts damage upon endothelial cells. The repercussions are profound—metabolic complications ensue, including an elevated risk of thromboembolism and multiorgan damage, especially in individuals grappling with diabetes.

This intricate interplay between diabetes and COVID-19, now etched into the medical narrative of the pandemic, underscores the importance of a holistic understanding of the pathophysiological mechanisms at play. The convergence of chronic endothelial dysfunction, viral invasion, and the ensuing cascade of complications paints a complex portrait, emphasizing the need for targeted interventions and a comprehensive approach to managing individuals with diabetes in the context of COVID-19. As the global healthcare community

continues to grapple with the evolving challenges of this enduring pandemic, these insights serve as crucial guideposts in navigating the intricate terrain of diabetes and COVID-19 interactions.

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