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Review

The Roles of Glutathione and Oxidative Stress in Diabetes and COVID-19

Evan Los †, George Ford †, Dawn Tuell †, Demetrio Macariola, Jr. † and William Stone *,†

Department of Pediatrics, Quillen College of Medicine, Johnson City, TN 37614, USA; losea1@etsu.edu (E.L.); fordga@etsu.edu (G.F.); tuell@etsu.edu (D.T.); macariol@etsu.edu (D.M.J.)

* Correspondence: stone@etsu.edu

† These authors contributed equally to this work.

Abstract: Evidence suggests that COVID-19 infection increases the risk of type 1 (T1D) and type 2 diabetes (T2D). Diabetes, in turn, increases COVID-19 susceptibility and contributes to increased COVID-19 morbidity and mortality. Oxidative stress has emerged as a common factor driving the pathogenesis of diabetes and COVID-19 caused by the severe acute respiratory syndrome coronavirus. The mechanistic links between oxidative stress, diabetes, and COVID-19 have primarily been studied in adults and will be summarized in this review. However, we suggest that studying these interconnections in children and young adults is critical since early intervention is optimal for improving outcomes. At the height of the pandemic, COVID-19 was a leading cause of death in children and young people, and people in this age group are as susceptible to COVID-19 as adults and the elderly. Glutathione is the primary water-soluble intracellular antioxidant and can be deficient in both diabetes and COVID-19. Glutathione is a tripeptide containing cysteine, glutamic acid, and glycine. Strategies to increase glutathione levels may be beneficial in helping to manage COVID-19-induced diabetes and diabetes-induced COVID-19 risk. Dietary supplementation with glycine plus n-acetyl-l-cysteine may be optimal since it contains two metabolic glutathione precursors.

Keywords: glutathione; oxidative stress; diabetes; COVID-19; reactive oxygen species; N-acetyl-L-cysteine; glycine

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1. Introduction

This narrative review will focus on the bidirectional interplay between coronavirus disease 2019 (COVID-19) and diabetes, emphasizing the synergistic role of oxidative stress (OxS) in promoting disease progression and poor outcomes. OxS is most often viewed as an unfavorable balance between the production of reactive oxygen species (ROS) and/or reactive nitrogen oxide species RNOS) and antioxidant defense mechanisms [1]. In addition to the possibility of direct damage to macromolecules and subcellular organelles, ROS/RNOS can alter signal transduction pathways with negative (or positive) consequences. Particularly relevant to this review is the effect of OxS on mitochondrial functions [2]. Mitochondrial OxS can cause insulin resistance, which, in turn, can result in chronic hyperglycemia [3–5]. COVID-19-induced OxS in mitochondrial dynamics may also promote chronic inflammation [6]. As recently reviewed, hyperglycemia can induce localized and systemic OxS through multiple pathways, such as the formation of advanced glycation end products (AGEs) and activation of the polyol pathway [7]. Central obesity has been linked to the development of insulin resistance and, therefore, is a relevant physiological factor contributing to OxS [5,8].

Glutathione (GSH) is the primary water-soluble intracellular antioxidant and can be deficient in both diabetes [9–13] and COVID-19 [14–16]. As shown in Figure 1, GSH is a tripeptide containing cysteine (CYS), glutamic acid (GLU), and glycine (GLY) and is unique due to its high intracellular concentration [17]. A significant function of GSH

(gamma-GLU-CYS-GLY) lies in its essential role in the glutathione peroxidase (GPX) antioxidant system (see Figure 1), which reduces hydrogen peroxide (or lipid peroxides) to water (or lipid alcohols) [18,19]. Strategies to increase GSH levels may be beneficial in managing COVID-19-induced diabetes [20] and diabetes-induced COVID-19 risk [21]. In 2020, Silvagno et al. [22] reviewed the data suggesting that GSH could be critical in protecting against the acute inflammatory response and the associated OxS triggered by SARS-CoV2. These authors comprehensively reviewed the potential benefits of dietary supplementation with GSH precursors to restore GSH and tissue concentrations [22].

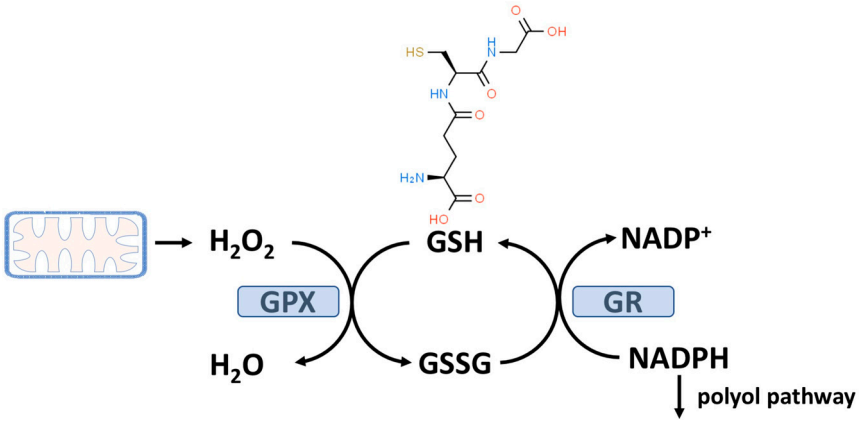

Figure 1. The glutathione peroxidase system and oxidative stress (OxS). Mitochondrial hydrogen peroxide (H_2O_2) emission (upper left) can promote transitory oxidative stress and insulin resistance in skeletal muscle (see Section 2.3 of text). The reduction of H_2O_2 is catalyzed by glutathione peroxidase (GPX) utilizing reduced glutathione (GSH) with the formation of oxidized glutathione (GSSG). GSSG is recycled back to GSH by glutathione reductase with the consumption of NADPH. For cell types primarily relying on insulin-independent GLUT transporters, hyperglycemia can activate the polyol pathway with the concurrent consumption of NADPH (lower right). A decreased level of NADPH can result in a diminished capacity to regenerate GSH from GSSG and a decreased GSH/GSSG ratio indicative of increased OxS.

Dietary supplementation with GlyNAC may be optimal since it contains two metabolic GSH precursors, i.e., n-acetyl-l-cysteine (NAC) and GLY [19]. Moreover, circulating and RBC levels of GLY can be low in T2D patients [10,23,24]. GLY is known to be rate-limiting for GSH synthesis, and McCarty et al. have suggested that dietary GLY supplementation could increase in vivo GSH synthesis [25]. The mechanisms accounting for low serum GLY in T2D are not clear, but this amino acid participates in many metabolic processes in addition to its role as a GSH precursor [24]. Pilot data suggest that GlyNAC might be helpful in the management of both diabetes [26,27] and COVID-19 [14].

The Potential Interconnections between Diabetes and COVID-19

As outlined in Figure 2 (and detailed below), evidence suggests that COVID-19 infection increases the risk of developing both type 1 (T1D) and type 2 diabetes (T2D) [28–33]. Diabetes, in turn, has been found to increase COVID-19 susceptibility and contribute to increased COVID-19 morbidity and mortality [34–36]. COVID-19 infection is caused by the severe acute respiratory syndrome coronavirus (SARS-CoV2), an RNA virus with a frequently changing range of genetic variants [37,38]. We will summarize the key etiological and epidemiological links between OxS, diabetes, and COVID-19. The epidemiological links are particularly problematic since they suggest the probable emergence of a global increase in COVID-19-induced diabetes with its long-term cardiovascular consequences [39–41]. Many of the etiological links support the synergistic COVID-19/diabetes-induced OxS damage, with increased organ damage and morbidity [42].

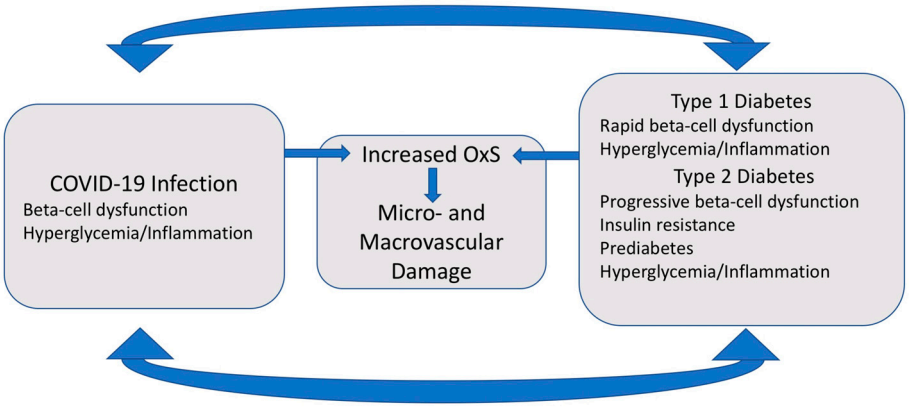

Figure 2. The potential bidirectional links between COVID-19 and diabetes. Both COVID-19 and diabetes mutually contribute (blue arrows) to local and systemic oxidative stress (OxS), resulting in micro- and macrovascular damage. Hyperglycemia induced by either diabetes or COVID-19 is a crucial mechanism driving OxS (see text).

2. The Epidemiology and Etiology of COVID-19 and Diabetes

The overall demographics of COVID-19 and diabetes have been recently reviewed [43,44]. In 2020, the World Health Organization (WHO) declared COVID-19 a pandemic; from 2020 to 2021, there was an estimated excess mortality burden of 14.9 million people [45]. COVID-19 cases reached 687 million worldwide as of 2023, with about 104 million cases in the USA [46]. The emphasis was placed on older people in the pandemic's initial stages since this population showed a very high mortality rate. It is now well recognized that many individuals are either asymptomatic or present with only mild symptoms/signs [47]. A 2021 global meta-analysis found that 40% of the study population with confirmed COVID-19 were asymptomatic [47].

A "confirmed" COVID-19 diagnosis is a positive result using the real-time reverse transcription polymerase chain reaction assay (rtRT-PCR). The rtRT-PCR measures the active presence of the SARS-CoV-2 virus. To determine if an individual was previously infected by SARS-CoV-2, a serologic test is utilized to detect the presence of an antibody against the SARS-CoV-2 virus in the serum. The true prevalence of SARS-CoV-2 infection is best measured by seroprevalence, i.e., the proportion of the study population with a positive test for serum antibodies [48].

2.1. Children and Young Adults Are as Susceptible to COVID-19 as Adults and the Elderly

It is now clear from seroprevalence data that children contract COVID-19 as readily as adults or older people but generally develop milder cases [49,50]. Nevertheless, during the delta and omicron waves, COVID-19 was a leading cause of death in children and young people (aged 0 to 19 years) [51]. It has been estimated that about 6 million children could be living with "long COVID", in which symptoms continue/emerge after the initial SARS-CoV2 infection [52]. While increasing evidence suggests that COVID-19 can be diabetogenic in some adults, this critical link has not been extensively studied in children who have had an asymptomatic SARS-CoV2 infection [39].

2.2. The Worldwide Burden of Diabetes Is Rapidly Increasing along with the Threat of More Severe COVID-19 Outcomes

Early observations suggested that individuals with diabetes before a COVID-19 infection have more severe outcomes [53]. A comprehensive meta-analysis recently confirmed that the global prevalence of diabetes (T1D plus T2D) is associated with COVID-19 severity and that diabetes accounts for 9.5% of severe COVID-19 cases and 16.8% of COVID-19 deaths [54]. In a cohort study, Atwah et al. found that adult patients with diabetes had an increased risk of developing more severe COVID-19 and suggested future increases in intensive care unit admissions and mortality [55].

Global data from the 2021 IDF Diabetes Atlas reveal an ever-increasing concern: about 10% of the world's population is living with diabetes, with a healthcare expenditure of USD 966 billion, i.e., a 316% increase over the last 15 years [56]. As indicated in Figure 2, both COVID-19 and diabetes adversely affect the vasculature's endothelial cells; in both cases, OxS is considered a critical etiological mechanism [6,57].

Diabetes is traditionally designated as either type 1 (T1D) or type 2 (T2D), with T1D being an autoimmune disease and T2D being primarily a metabolic disease. Moreover, T1D was initially viewed as having a childhood or young adult onset, and T2D as having an adult onset. These traditional age distinctions have since proven problematic since there is an increasing incidence of pediatric T2D and a substantial number of T1D cases occurring during adulthood [58–60]. Although not a mainstream viewpoint, Brooks-Worrell and Palmer have argued that diabetes be considered a continuous spectrum with immune system involvement [58].

2.3. Oxidative Stress Is Increased in Both T1D and T2D

In T1D, the critical outcome (see Figure 2) of this autoimmune disease is the rapid and predominantly irreversible destruction of pancreatic beta cells, which produce the insulin required by cellular insulin-responsive glucose transporters (e.g., GLUT4) for glucose uptake; the absence of insulin in T1D results in chronic hyperglycemia (and OxS) [7,61]. Plasma markers of OxS are markedly increased in early childhood-onset T1D and further increased by early adulthood [9].

T2D (90% of all diabetes cases) starts with insulin resistance and progresses to prediabetes, T2D with fasting hyperglycemia, and T2D with marked micro- and macrovascular damage (see Figure 2). Considerable evidence supports the role of OxS in both the initiation and progression of T2D [62,63]. Insulin resistance primarily results from impaired insulin-stimulated GLUT4 translocation to the cell surface of skeletal muscle and adipose tissue [64]. As previously reviewed, insulin resistance in skeletal muscle is considered the initiating defect, eventually resulting in T2D [19]. Anderson et al. [3] have demonstrated that excess dietary calories can promote skeletal muscle mitochondrial hydrogen peroxide emission in both human and animal models, resulting in transient insulin resistance. Mitochondrial hydrogen peroxide emission also results in OxS, as measured by a reduction in the GSH/GSSG ratio. Long COVID (3 to 4 months post-acute infection) in adults (mean of 28 years) has been associated with new-onset insulin resistance [65]. As indicated in Figure 1, the GPX system is a key mechanism for reducing hydrogen peroxide via GSH.

2.4. Skeletal Muscle Insulin Resistance Contributes to Postprandial Glycemia (PPG), Chronic OxS, and T2D Progression

In susceptible individuals, it is plausible that skeletal muscle insulin resistance can contribute to increased postprandial glycemia (PPG) and eventually to postprandial hyperglycemia, chronic OxS, and T2D disease progression [7,66]. In cells relying on insulin-independent glucose transporters, such as GLUT1, intracellular glucose levels will equilibrate with plasma glucose concentration and, if sufficiently high, can activate the polyol pathway with the conversion of excess glucose to fructose and the consumption of intracellular NADPH (see Figure 1). Decreased NADPH levels can result in a diminished capacity of the GPX system to reduce GSSG to GSH, causing an increased level of OxS. Vascular endothelial cells rely on GLUT1 and are a target for COVID-19 and diabetes, with OxS as a key pathology driver [67,68].

2.5. COVID-19 Increases the Risk of Developing T2D in Patients with Prediabetes

In prediabetes, plasma glucose levels are elevated above normal but have not yet reached the threshold defining clinical diabetes. In a retrospective cohort study, Xu et al. [69] found that patients (average age of 57 years) with prediabetes had an increased risk of developing persistent diabetes five months after COVID-19 compared to COVID-19-negative patients with prediabetes. The prevalence of prediabetes in the pediatric population has

increased at an alarming rate in parallel with the global increase in childhood obesity [70]. Increasing evidence supports the etiological role of OxS in both insulin resistance [71] and prediabetes [66,72].

2.6. Beta-Cell Dysfunction Is a Component of T2D and COVID-19

In addition to its role in T1D, beta-cell dysfunction (see Figure 3) is also a component of T2D but is gradual and thought to be primarily a result of insulin resistance, inflammation, and OxS [73,74]. Beta-cell dysfunction in T2D was once regarded as progressive and irreversible, but clinical trial evidence (in adults) has shown that weight loss can restore insulin secretion in early-onset T2D [75,76]. However, the reversibility of beta-cell function is limited to T2D with a duration of less than ten years [75]. Determining if weight loss in children and young adults would effectively reverse beta-cell dysfunction would be an essential future goal. A recent review of beta-cell dysfunction in T2D has concluded that "a better understanding of molecular mechanisms underlying pancreatic beta-cell loss will provide an opportunity to identify novel targets for T2D" [77]. Leenders et al. [78] have suggested that OxS is a mechanism leading to impaired pancreatic beta-cell function due to a loss of beta-cell identity. The low antioxidant capacity and the high ROS/RNOS production rate in beta cells have been cited as key factors leading to OxS-driven beta-cell failure [79,80].

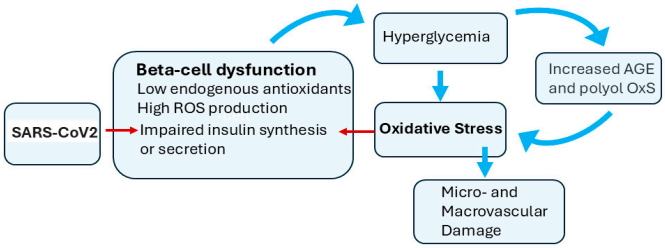

Figure 3. Beta-cell dysfunction can be induced by SARS-CoV2 infection and hyperglycemia-induced oxidative stress. Impaired beta-cell synthesis or secretion can result from SARS-CoV2 infection and oxidative stress resulting from hyperglycemia (red arrows). Progressive beta-cell dysfunction, in turn, can drive increased hyperglycemia with increased AGE formation and polyol-induced oxidative stress, which will further increase beta-cell dysfunction. As shown by the blue arrows, these series of events can result in a positive feedback loop if not slowed or stopped by antioxidant interventions (see Sections 2.6 and 3 for references).

As outlined in Figure 3, extensive in vitro and ex vivo work by Wu et al. [81] has demonstrated that SARS-CoV-2 infects and kills human beta cells, decreasing insulin levels. A prospective clinical study found that adult (59 years old) patients with severe COVID-19 developed hyperglycemia with beta-cell dysfunction as the underlying cause [82]. Hyperglycemia resulting from decreased insulin secretion is a central pathophysiological mechanism that drives oxidative stress [83]. Oxidative stress, in turn, is a driving factor for beta-cell dysfunction [83].

3. COVID-19 Increases the Risk of Diabetes and Diabetes Increases COVID-19 Susceptibility

Increasing evidence suggests that COVID-19 infection increases the risk of T1D and T2D diabetes [28,30–32,84,85]. A large-scale association study by Qeadan et al. found that contracting COVID-19 increases the risk of developing T1D compared to those not contracting COVID-19 [28]. The increased T1D risk was highest in pediatric patients under one year of age and among the elderly. As an association study, their research was not able to establish causality. T1D and T2D are complex polygenetic diseases with risk contributions from hundreds of genetic variants [86,87]. In young children with a high genetic risk of T1D, COVID-19 has been reported to double the risk of early T1D [85].

Wang et al. [88] have suggested several mechanisms whereby COVID-19 could potentially trigger beta-cell damage, resulting in T1D. These include direct COVID-19-induced beta-cell death, autoimmune-mediated beta-cell death, and an indirect loss of beta cells due to COVID-19 infection of essential surrounding cells. The potential synergy between COVID-19 infections and T1D risk in young children and the elderly is a high-priority area for future research.

In a large adult cohort study, Kwan et al. showed that T2D risk increased after COVID-19, suggesting that this infection could accelerate T2D progression [32]. Moreover, this increased T2D risk endured throughout the dominance of the omicron variant of SARS-CoV-2 [32]. A large-scale study has found that individuals with long-term COVID-19 have a 40% higher risk of new-onset diabetes (T1D or T2D) compared to controls [29]. Collectively, these data are troubling since health experts posit that many/most people worldwide will eventually develop a COVID-19 infection.

Recent research supports the view that people with either T1D or T2D are more susceptible to COVID-19 infection, with OxS being a potential contributing factor [34,89]. The overlap between diabetes and the COVID-19 pandemics significantly contributes to the global disease burden and requires a robust multi-factorial health policy response [40,54]. OxS due to GSH deficiency has emerged as a common factor driving the pathogenesis of diabetes and COVID-19 [16,19]. Polonikov, in 2020, postulated that GSH deficiency was "the most likely cause of serious manifestations and death in COVID-19 patients" [90].

4. Glutathione Deficiency in Diabetes and COVID-19

In both T1D and T2D with poor glycemic control, there is a decreased level of red blood cell (RBC) GSH compared to control subjects [9,12,13]. RBC GLY levels were also found to be lower ($p < 0.01$) in T2D patients compared to controls [10]. Human peripheral blood mononuclear cells (PBMCs) from T2D patients with poor glycemic control also show a GSH deficiency [91]. Kalamkar et al. conducted a long-term (6-month) randomized clinical trial in which 125 elderly T2D patients were given 500 mg of oral GSH daily [92]. Compared to controls ($n = 125$), the GSH supplementation was found to increase RBC GSH content, increase fasting insulin, and improve glycemic control (as measured by HbA1c) [92].

Kumar et al. [14] have reported that adult patients ($n = 60$) hospitalized with COVID-19 have increased plasma biomarkers for OxS and markedly reduced RBC levels of GSH compared to uninfected controls ($n = 24$). OxS in the COVID-19 patients increased with age but was also present in the younger age groups. An in-hospital cohort study with adults found that serum GSH levels were significantly lower in COVID-19 non-survivors than survivors [93]. These investigators suggest that GlyNAC could be particularly effective in restoring COVID-19-induced GSH deficiency since it has already been shown to be "highly effective" in diverse populations, including diabetic patients [94].

Encouragingly, critically ill adult patients with COVID-19 ($n = 70$) treated with a continuous infusion of NAC showed improved clinical outcomes and lower inflammatory biomarkers compared to critically ill adult patients ($n = 70$) with COVID-19 not treated with NAC [95]. GSH deficiency in COVID-19 is strongly linked to increased SARS-CoV-2 replication, pro-inflammatory cytokine release, and thrombosis [15].

5. Lifestyle Factors in COVID-19 and Diabetes

The relationship between lifestyle factors and diabetes is well established. Effective lifestyle interventions are also critical in the prevention of COVID-19 and have become "a pressing need" [96,97]. Overweight and obesity are major risk factors for T2D [98] and poor COVID-19 outcomes [99]. Moreover, both moderate and severe obesity are associated with an increased risk of developing long COVID [100]. The global scale of overweight and obesity is of ever-growing concern. A recent study reported that more than one billion people worldwide are living with obesity, which is more than quadruple the number in 1990 [101]. In 2022, the WHO reported that 43% of adults (worldwide) aged 18 and over were overweight, and 16% were living with obesity [102]. Moreover, adult obesity has

more than doubled since 1990, and adolescent obesity has quadrupled. For children (under the age of five) and young adults (between 5 and 19 years), the picture (in 2022) is equally dismal: over 390 million were overweight, including 160 million living with obesity [102]. Severe obesity in children aged 2 to 4 years in the USA is also on the increase [103]. A meta-analysis of children and adolescents with COVID-19 found that obesity markedly increased the risk of hospitalization compared to the normal-weight population [104]. As reviewed by Savini et al., obesity has long been associated with chronic OxS and "may be the mechanistic link between obesity and related complications" [105]. The potential of reducing OxS in T2D by lifestyle modifications looks very promising, as recently reviewed [62,83].

6. Future Research Directions

We previously asserted that a systems medicine approach emphasizing redoxomics would be optimal in designing healthcare strategies for children with T2D [62]. Systems medicine utilizes an integrative approach leveraging conventional clinical information (e.g., assays for glycemic control and inflammation) with data from "omics" techniques such as genomics, proteomics, and metabolomics. Redoxomics is a branch of systems medicine emphasizing redox status [106]. A redoxomics approach would also be ideal for studying the relationships between OxS, COVID-19, T2D, lifestyle factors, and dietary intervention with GSH precursors.

While a wide range of natural antioxidants have the potential for lowering either COVID-19-induced or diabetes-induced OxS, dietary GSH precursors have an excellent safety record for long-term use. Moreover, GSH is the most abundant water-soluble antioxidant, and its role in protecting against diabetes-induced oxidative stress is supported by clinical studies and has a firm biochemical foundation.

A critical first goal would be a long-term (e.g., six months), small-scale, double-blind, placebo-controlled clinical trial with GlyNAC (and placebo) in children and young adults seropositive for SARS-CoV2 and with T2D. A matched population not seropositive for SARS-CoV2 and without T2D would serve as the control. A power analysis could then be performed to design a large multi-site study including GLY alone, NAC alone, and GlyNAC and placebo intervention groups. Utilizing a dietary nutritionist to provide lifestyle modification advice to all research subjects would also be essential.

7. Conclusions

The bidirectional etiological links between diabetes and COVID-19 have been strengthened over the last few years. Similarly, oxidative stress has emerged as a critical factor driving disease progression for both COVID-19 and diabetes. The current and projected epidemiological trends are particularly worrisome. The consumption of excess high-calorie ultra-processed food and a lack of physical activity are driving a worldwide increase in obesity and diabetes. Evidence suggests that COVID-19 accelerates diabetes disease progression and that diabetes promotes COVID-19 severity. In addition to high-priority lifestyle changes, dietary supplementation with glutathione precursors may prove to be a practical approach for helping to manage the mutual oxidative stress problems arising from diabetes and COVID-19. Large-scale clinical trials that include children and young people should be a high priority since early intervention is critical.

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