COVID-19–Induced New-Onset Diabetes: Trends and Technologies

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The coronavirus disease 2019 (COVID-19) global pandemic continues to spread worldwide with approximately 216 million confirmed cases and 4.49 million deaths to date. Intensive efforts are ongoing to combat this disease by suppressing viral transmission, understanding its pathogenesis, developing vaccination strategies, and identifying effective therapeutic targets. Individuals with preexisting diabetes also show higher incidence of COVID-19 illness and poorer prognosis upon infection. Likewise, an increased frequency of diabetes onset and diabetes complications has been reported in patients following COVID-19 diagnosis. COVID-19 may elevate the risk of hyperglycemia and other complications in patients with and without prior diabetes history. It is unclear whether the virus induces type 1 or type 2 diabetes or instead causes a novel atypical form of diabetes. Moreover, it remains unknown if recovering COVID-19 patients exhibit a higher risk of developing new-onset diabetes or its complications going forward. The aim of this review is to summarize what is currently known about the epidemiology and mechanisms of this bidirectional relationship between COVID-19 and diabetes. We highlight major challenges that hinder the study of COVID-19–induced new-onset of diabetes and propose a potential framework for overcoming these obstacles. We also review state-of-the-art wearables and microsampling technologies that can further study diabetes management and progression in new-onset diabetes cases. We conclude by outlining current research initiatives investigating the bidirectional relationship between COVID-19 and diabetes, some with emphasis on wearable technology.

Coronavirus disease 2019 (COVID-19) is a global pandemic responsible for approximately 216 million confirmed cases and 4.49 million deaths that continues to spread rapidly (1). The virus responsible for COVID-19, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was first identified in Wuhan, China, in 2019 and spreads via droplet transmissions, leading to variable symptoms that can range from asymptomatic or mild respiratory illness to severe multiorgan failure and death in infected individuals. Individuals with type 1 diabetes (T1D) or type 2 diabetes (T2D) often have comorbidities such as hypertension, obesity, and cardiovascular disease (2), all of which have also been implicated in increased susceptibility to and mortality from COVID-19 infection (3). Similar to the SARS-CoV-1 outbreak in 2003 (4) and respiratory syncytial virus infection (5), there is an increase in hyperglycemic conditions and complications in COVID-19 patients both with and without diabetes. Specifically, new-onset diabetes has been observed following COVID-19 infection (6), including acute hyperglycemia in COVID-19 patients without diabetes, diabetic ketoacidosis in COVID-19 patients with preexisting diabetes, and new-onset diabetes in COVID-19 patients (7,8).

Given the evolving nature of the COVID-19 pandemic, it is not yet known whether new-onset SARS-CoV-2–induced diabetes occurs via established mechanisms in T1D or T2D or instead represents an atypical form of diabetes. Moreover, it remains unclear whether COVID-19 patients remain at higher risk for developing new-onset diabetes or related complications following viral clearance and recovery.

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Despite intensive global vaccination efforts to combat the COVID-19 pandemic, circulating SARS-CoV-2 genetic variants and sustained case and transmission rates underline the need for increased attention to diabetes and diabetes complications after COVID-19 diagnosis and recovery. Several studies have reported wearable technologies as one potential tool for the early detection of COVID-19 (9). This review article covers the current state of new-onset diabetes following COVID-19 and new technologies to address this topic.

Epidemiology

Patients With Diabetes Are Largely at Risk for Severe COVID-19 Complications and Mortality

Many COVID-19 patients that experience severe morbidity and mortality also have underlying preexisting conditions such as hypertension (43.1%), diabetes (33.2%), and/or coronary heart disease (26.0%) (10). COVID-19 patients with comorbid diabetes commonly experience diabetic kidney disease, ischemic heart disease, and pneumonia, which can lead to kidney or heart failure (11). Likewise, COVID-19 patients with diabetes are also at increased risk for intensive care unit (ICU) admission (17.6% vs. 7.8) and mortality (20.3% vs. 10.5) (12) compared with COVID-19 patients without diabetes. Hospitalized COVID-19 patients with diabetes have a higher likelihood of developing acute respiratory distress syndrome (ARDS), a condition specific to severe COVID-19 cases that can lead to respiratory failure and death and requires mechanical ventilation for treatment (13). Several studies reported that mortality is higher in subjects with diabetes with COVID-19, varying from 22% to 31% of all COVID-19 patients (14). A U.K. study examined the death of 23,804 hospitalized COVID-19 patients and found that 32% had T2D and 1.5% had T1D (15).

Interestingly, obesity, which is a T2D risk factor, is significantly associated with COVID-19 severity; one cohort study of 2,741 hospitalized patients found that obesity was one of the factors most strongly associated with COVID-19 hospitalization and critical illness (16). Another retrospective study of 1,158 hospitalized COVID-19 patients in Kuwait found that subjects with morbid obesity were more likely to experience ICU admissions (odds ratio [OR] 5.18) (17). According to one study with 383 hospitalized COVID-19 patients, obese patients were more likely to experience severe forms of COVID-19 compared with those with normal BMI; overweight subjects had increased odds of developing severe COVID-19 (OR 1.84; $P = 0.05$), while obese subjects had increased odds of developing severe disease (OR 3.40; $P = 0.007$) (18). From an English population-based cohort study of over 3 million diabetes patients, high BMI, has been associated with COVID-19 mortality (19). When compared with a BMI of 25–29.9 kg/m^2 in T1D patients, overweight T1D patients with a BMI of ≥40.0 kg/m^2 had a hazard ratio [HR] of 2.33 ($P < 0.0001$) (19). Surprisingly, underweight T1D patients with a BMI <20.0 kg/m^2 also reported an HR of 2.45 ($P < 0.0001$). The corresponding HRs for T2D were 2.33 ($P < 0.0001$) and 1.60 ($P < 0.0001$) (19).

Current Research Suggests That COVID-19 Patients With Diabetes Experience Worsening Complications and High Mortality Rates

Clinical reports of hospitalized patients with viral infections such as human herpes virus 8 and SARS show that acute hyperglycemia and insulin resistance are known sequelae during infection periods that may reflect normal antiviral responses (20). However, these conditions also represent disruptions of glucose homeostasis that may increase the risk of developing T1D or T2D (4,20). During the SARS-CoV-1 outbreak in 2003, one study examined 39 SARS-CoV-1 patients without diabetes history and reported that 20 patients became diabetic during hospitalization, with two of those patients remaining diabetic despite glycemic management over 3 years of follow-up (4). The relationship between new-onset diabetes and COVID-19 can be summarized as shown in Fig. 1 and Table 1.

SARS-CoV-2 can impair insulin secretion, leading to the development of new-onset diabetes (2), which is also an independent predictor of COVID-19 mortality (HR 3.75) (38). A study of 453 COVID-19 patients reported 94 patients with new-onset diabetes (FPG ≥7 mmol/L and HbA_{1c} ≥6.5% [48 mmol/mol] at hospital admission) (39). In the same study, COVID-19 patients with new-onset diabetes reported higher risk of all-cause mortality (HR 9.42), ICU admissions (11.7%), and intermittent mandatory ventilation assistance (11.7%) than COVID-19 patients with normal glucose (HR 1; 1.5% and 2.3%, respectively), hyperglycemia (HR 3.29; 6.2% and 4.7%, respectively), and existing diabetes (HR 4.63; 4.1% and 9.2%%, respectively) (39). Furthermore, the COVID-19 patients with preexisting diabetes and new-onset diabetes reported more severe complications including ARDS (3.1–10.5% vs. 0.8–3.1%), acute kidney injury (15.3–17.0% vs. 1.5–3.1%), shock (11.2–23.4% vs. 2.3–4.7%), hypoalbuminemia (36.7–39.4% vs. 10.8–19.4%), and severe COVID-19 complications (82.7–89.4% vs. 61.4–72.1%) compared with COVID-19 patients with normoglycemia or hyperglycemia (39). Similarly, one study of 605 COVID-19 patients found that 29% of patients with new-onset diabetes experienced a greater rate of in-hospital complications (OR 3.99) and all-cause death (HR 2.30; $P = 0.002$) compared with normoglycemic COVID-19 patients over a 28-day period (40). Finally, another study of 413 subjects found a significant increase in ICU admission and death in new-onset COVID-19–related diabetes patients compared with COVID-19 patients with preexisting diabetes (relative risk 3.06 vs. 1.55) or normoglycemia (8), while another study did not find a significant increase (OR 2.61; $P = 0.09$) (22). Even though studies have indicated a correlation between new-onset diabetes and COVID-19, several studies (36,37) have also reported an inconclusive relationship between the increase in T1D cases during the COVID-19 pandemic, due

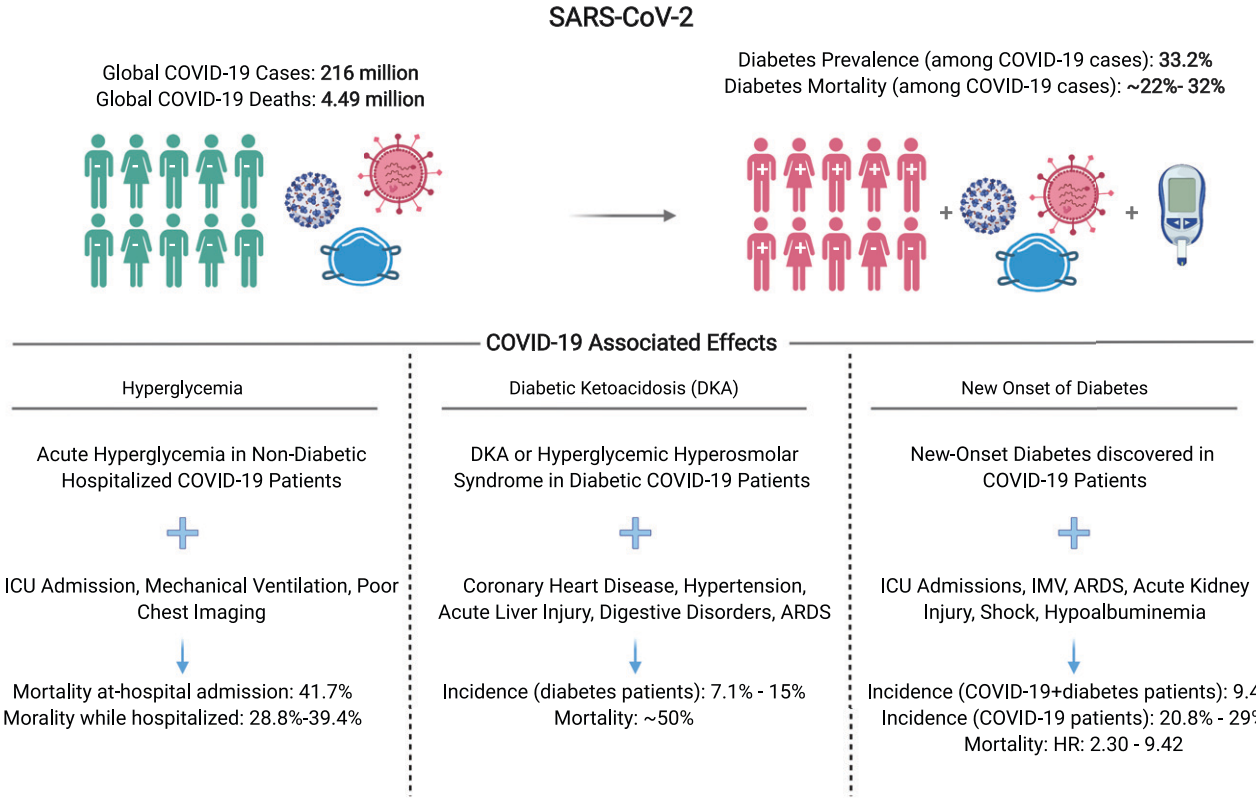

Figure 1—Epidemiological breakdown of COVID-19 and new-onset diabetes. This figure provides epidemiological data for COVID-19 cases and deaths, prevalence, and mortality of diabetes in COVID-19, and new-onset diabetes post–COVID-19 diagnosis (incidence, complications, and mortality). IMV, intermittent mandatory ventilation.

to a lack of supporting evidence. Therefore, the consensus maintains that additional research must be conducted to decipher the interconnected relationship between COVID-19–induced diabetes and complications thereof.

Potential Mechanisms

SARS-CoV-2 Canonical Entry

SARS-CoV-2 is a positive-sense single-stranded RNA coronavirus comprising four major protein components: membrane (M), envelope (E), nucleocapsid (N), and spike (S) proteins. S proteins facilitate viral entry into the host cell by interacting with angiotensin-converting enzyme 2 (*ACE2*), a membrane-bound receptor expressed across cells of the respiratory system. Bound S proteins are cleaved by membrane-bound serine protease TMPRSS2, activating endocytic machinery to permit viral entry into the cell for downstream replication (see Fig. 2).

SARS-CoV-2 Can Lead to Severe COVID-19 Complications in Patients With Diabetes or Trigger New-Onset Diabetes

ACE2 expression is detected across multiple tissues throughout the body (41), but pancreatic *ACE2* expression is of clinical interest due to initial reports that detailed an increase in new-onset hyperglycemia and ketoacidosis cases, raising concerns that COVID-19 induced acute T1D through β-cell failure (BCF) (6–8). Several research groups have examined nondiabetic, diabetic, and COVID-19 pancreatic tissues for the expression of canonical (*ACE2* and *TMPRSS2*) and noncanonical SARS-CoV-2 entry factors to assess its diabetogenic potential, which has already been extensively reviewed elsewhere (36,37). Most studies agree that ACE2 and TMPRSS2 protein are found in pancreatic ducts and endothelial cells of the microvasculature that could support indirect impairments of pancreatic islet function in COVID-19. But data regarding *ACE2* and *TMPRSS2* expression in exocrine β-cell remain inconsistent as studies that find entry factors excluded from the β-cell do not detect SARS-CoV-2 nucleocapsid protein in COVID-19 pancreas tissues (36,37). In contrast, studies identifying higher levels of entry factors in β-cells not only detect SARS-CoV-2 nucleocapsid protein in COVID-19 pancreatic tissues but can infect human islets with SARS-CoV-2 ex vivo to directly disrupt insulin homeostasis and induce β-cell apoptosis, resulting in extensive pathology that could drive T1D-associated hyperglycemia (36,37). While the data remain inconclusive and await further study to resolve, the extensive β-cell destruction observed by direct infection of SARS-CoV-2 is not consistent with many autopsy reports that typically observe normal morphologies in postmortem

Table 1—Summary of studies that have investigated the bidirectional relationship between COVID-19 and new-onset diabetes

Study	Support	Sample size	Associated effect	Conclusion
Iacobellis et al. 2020 (21)	+	85 COVID-19 patients (27 with diabetes)	Hyperglycemia	Acute hyperglycemia is the best predictor of high "ground glass" opacities in SARS-CoV-2 radiographic imaging results, regardless of diabetes status
Zhang et al. 2020 (22)	+	166 COVID-19 patients (mixed diabetes and no diabetes)	Hyperglycemia	In COVID-19 patients, those with new-onset hyperglycemia have higher rates of ICU admission, mechanical ventilation, and mortality than those with normoglycemia
Muller et al. 2021 (23)	+	ACE2 pancreatic islet cells	New-onset diabetes	SARS-CoV-2 infection can disrupt hormone positivity through cytokine and/or ER stress, followed by β-cell degranulation and dedifferentiation
Coppelli et al. 2020 (24)	+	271 hospitalized COVID-19 patients (mixed diabetes and no diabetes)	Hyperglycemia	COVID-19 patients with new-onset hyperglycemia (without preexisting diabetes) experience higher mortality rate compared with those with normoglycemia
Reiterer et al. 2021 (25)	+	4,102 COVID-19 patients (with and without ARDS)	Hyperglycemia	Insulin resistance is the prevalent cause of hyperglycemia in COVID-19 ARDS patients
Li et al. 2020 (26)	+	42 COVID-19 patients with ketosis	Diabetic ketoacidosis	Ketosis increases coronary heart disease, hypertension, and mean hospital stay in COVID-19 patients with diabetes
Chee et al. 2020 (7)	+	1 COVID-19 patient with diabetic ketoacidosis	Diabetic ketoacidosis	A COVID-19 patient with diabetes developed metabolic complications and diabetic ketoacidosis
Ebekozien et al. 2020 (27)	+	33 COVID-19 patients (adults and children) with T1D	Diabetic ketoacidosis	Approximately one-half of confirmed COVID-19 patients with T1D developed diabetic ketoacidosis
Unsworth et al. 2020 (28)	+	30 patietns with new-onset T1D (with and without COVID-19)	New-onset diabetes	First report to describe an apparent increase in new-onset T1D in children during the COVID-19 pandemic, with evidence of SARS-CoV-2 infection or exposure in a proportion of those tested
Fadini et al. 2020 (8)	+	21 COVID-19 patients with new-onset diabetes	New-onset diabetes	In COVID-19 patients, those with new-onset diabetes reported more ICU admission and mortality compared with those with preexisting diabetes or normoglycemia
Armeni et al. 2020 (29)	−	35 COVID-19 patients with diabetes	Diabetic ketoacidosis	COVID-19 patients with diabetes can experience hyperglycemic emergencies leading to DKA and ketosis; however, more research is needed
Lawrence et al. 2021 (30)	−	4,200–7,200 childredn with T1D (aged <18 years) without COVID-19	Diabetic ketoacidosis	Higher frequency of DKA diagnosis during the pandemic; however, no causal relationship with COVID-19 diagnosis
Tittel et al. 2020 (31)	−	Registry of 216 German pediatric diabetes centers	New-onset diabetes	T1D incidence per 100,000 patients increased from 2011 to 2019–2020 (COVID-19 lockdown period); however, there is no causal relationship with COVID-19 diagnosis
Marchand et al. 2020 (32)	−	29-year-old woman with COVID-19 and gastric bypass	New-onset diabetes	COVID-19 patients without diabetes were diagnosed with diabetes after 1.5 months; however, causal relationship cannot be confirmed

Continued on p. 2737

Table 1—Continued

Study	Support	Sample size	Associated effect	Conclusion
Bode et al. 2020 (33)	−	1,122 COVID-19 patients (451 with diabetes or without diabetes and hyperglycemia)	Hyperglycemia	COVID-19 patients with diabetes or without diabetes and uncontrolled hyperglycemia experience higher in-hospital mortality compared with those without preexisting diabetes or uncontrolled hyperglycemia
Hippich et al. 2020 (34)	−	15,771 children, without COVID-19, under T1D screening program	New-onset diabetes	Children with SARS-CoV-2 antibodies did not develop T1D
Zubkiewicz-Kucharska et al. 2021 (35)	−	Lower Silesia T1D pediatric registry (2000–2020)	New-onset diabetes	T1D incidence per 100,000 increased from 2000 to 2019 (COVID-19 lockdown period). DKA incidence increased from 2000–2019 (31.75%) vs. first 4 months of 2020 (36.67%); however, there is no causal relationship with COVID-19 diagnosis
Ibrahim et al. 2021 (36)	−	Mass literature review	New-onset diabetes	COVID-19 β-cell injury lacks evidence of acutely leading to diabetes
Drucker et al. 2021 (37)	−	Mass literature review	New-onset diabetes	Concerns about SARS-CoV-2 triggering T1D; however, no supporting evidence of an increase in T1D incidence associated with COVID-19

Studies have either a positive/supported (+) or a negative/unsupported (−) conclusion. Several studies suggest the association between COVID-19 and acute hyperglycemia, diabetic ketoacidosis, and new-onset diabetes in patients with and without diabetes; however, more research still needs to be conducted to solidify the relationship. DKA, diabetic ketoacidosis; ER, endoplasmic reticulum.

pancreas samples, even among donors with T1D or T2D, except in rare cases. Relatedly, several epidemiological studies do not support large increases in T1D incidence rates between 2020 and prior years (31,36,37). Taken altogether, the infection and destruction of exocrine β-cells by SARS-CoV-2 may occur in rare instances but seems unlikely to underlie current rates of new-onset hyperglycemia or diabetes, although this could change in time given the slower onset of autoimmune T1D and requires continued monitoring.

Adipose tissue (AT) is another metabolic organ with high ACE2 levels that could exhibit SARS-CoV-2 tropism. Obesity and aging are comorbid with T2D and insulin resistance (IR) and are implicated in severe COVID-19. Obesity and aging also increase visceral and abdominal fat mass, resulting in adipocyte hypertrophy that induces low-level inflammation and IR (42). AT is a source of inflammatory adipokines and cytokines that modulate glycemia and IR; inflammatory T2D agents, including TNF-α, IL-6, MCP-1, and angiotensin, are elevated in critically ill COVID-19 patients (42,43). SARS-CoV-2 infections may stress adipocytes and enhance chronic inflammation that worsens IR, hyperglycemia, and COVID-19 outcomes in people with diabetes. COVID-19 patients with uncontrolled glycemia exhibit higher concentrations of inflammatory biomarkers than patients without diabetes, including C-reactive protein (CRP), ferritin, and IL-6 (3). IL-6, a prognostic marker for COVID-19 severity (44), promotes neutrophil production and peripheral trafficking, hyperactivates proinflammatory $CD4^+$ Th1 cells, and represses the differentiation of immunosuppressive Tregs associated with cytokine storms (43). Chronic IL-6 exposure also triggers hepatic insulin resistance, compromising insulin sensitivity in COVID-19 patients with diabetes that can lead to hyperglycemia and ketosis. While few studies have examined COVID-19 postmortem or biopsied ATs to confirm viral tropism, one report detected SARS-CoV-2 by IHC in 10 of 16 postmortem ATs (62.5% SARS-CoV-2^+) and described nucleocapsid protein surrounding the cytoplasm of lipid droplets, although this was not quantified (45).

SARS-CoV-2 Infection and Insulin Resistance

Standard clinical care rarely assesses IR, obscuring its impact on COVID-19 outcomes. Studies are now assessing IR metrics that may highlight AT dysfunction in COVID-19. Reiterer et al. (25) found that among 4,102 U.S. hospitalized COVID-19 patients, those with ARDS had a higher prevalence of hyperglycemia with poor outcomes (85%) than those without ARDS (37%) . They screened plasma samples for hormones that regulate glucose homeostasis and could distinguish between hyperglycemia-associated IR or β-cell failure. Serum C-peptide and amylin were elevated in COVID-19 patients with ARDS, suggestive of hypersecretory β-cell phenotypes that are incongruent with hypotheses of widespread β-cell failure in COVID-19. COVID-19 patients with ARDS also had high C-peptide–to–glucose ratios, supporting rates of IR

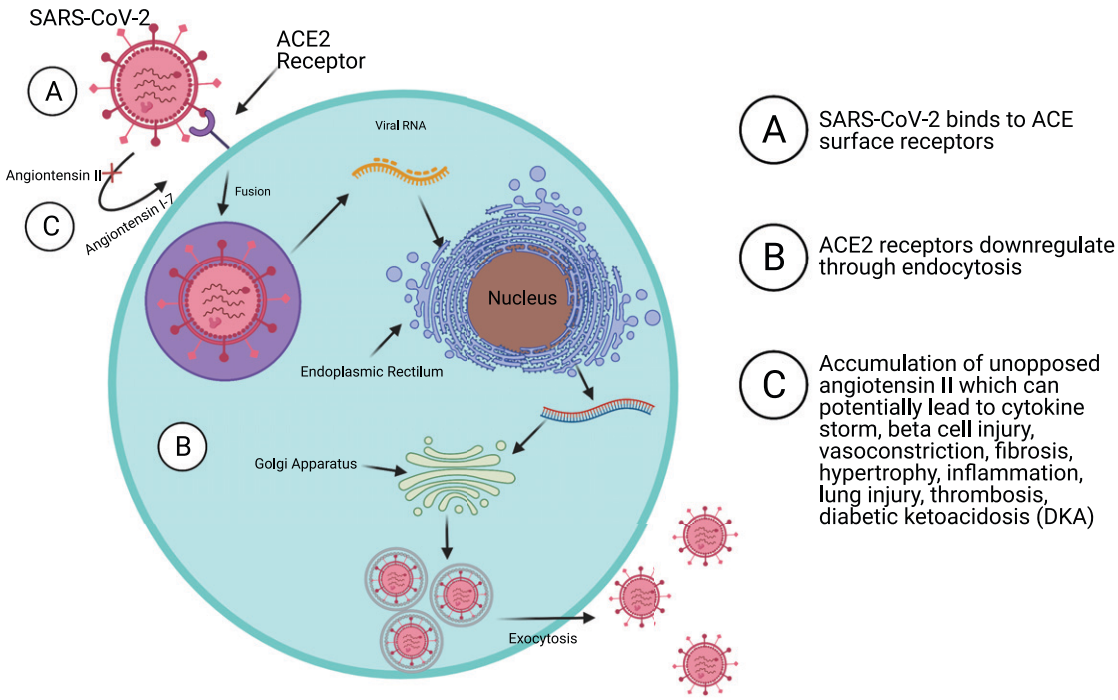

Figure 2—Mechanism of SARS-CoV-2 entry to the cell through ACE2 receptors and interaction with the renin-angiotensin-aldosterone system (RAAS). SARS-CoV-2 binds to ACE2 receptors commonly found on the surface of organs and tissue cells. Through endocytosis, the virus fuses through the host cell membrane. Then the nucleocapsid uncoats and viral RNA interacts with ribosomes near the nucleus to undergo replication and translation, hence producing viral proteins and RNA. Afterward, viral proteins and RNA pass are modified, assembled, and packaged through the Golgi–endoplasmic reticulum complex. Through exocytosis, the virus can exit the host cell and further infection. In the process, ACE2 can downregulate and inhibit the conversion of angiotensin II to angiotensin (1–7), a hormone that opposes the harmful molecular and cellular effects of angiotensin II. The overaccumulation of angiotensin II can lead to several complications in patients including cytokine storms, β-cell dysfunctioning, vasoconstriction, fibrosis, hypertrophy, inflammation, lung injury, thrombosis, and diabetic ketoacidosis (DKA). This mechanism is suggested to be involved with the development of new-onset diabetes in COVID-19 patients.

that were three- to-sixfold higher than among control subjects, and 62% of which had no prior diabetes history. Serum adiponectin was reduced by 50–60%, whereas leptin was elevated in COVID-19 patients with ARDS, resulting in adiponectin-to-leptin ratios that would support AT dysfunction in IR. SARS-CoV-2-infected Syrian hamsters experimentally confirmed reduced adiponectin levels in serum, subcutaneous, and visceral ATs as a consequence of infection. While SARS-CoV-2 nucleocapsid IHC was not performed to confirm viral replication among AT cell types, nucleocapsid transcripts were detected in ATs, supporting that SARS-CoV-2 may infect ATs in vivo.

Montefusco et al. (46) shared similar insights into COVID-19 and IR but also tested long-term impairments in glucose homeostasis following acute COVID-19. Among 551 hospitalized Italian patients, 253 patients (46%) with no prior diabetes history exhibited new-onset hyperglycemia during acute COVID-19. Among this subset, 35% remained hyperglycemic 6 months after COVID-19 recovery while an additional 2% were diagnosed with T2D, indicating that new-onset hyperglycemia can predispose individuals to long-term glycemic abnormalities. Continuous glucose monitoring (CGM) revealed that glycemic profiles, including time blood glucose spent >140 mg · dL^{-1} and postprandial glycemia, were impaired during acute COVID-19 and persisted for 2 months following recovery. Similar to Reiterer et al. (25), T2D patients, patients with acute COVID-19, or patients recovered from COVID-19 all displayed higher levels of insulin and C-peptide secretion in response to arginine stimulation, consistent with acute and long-term β-cell hypersecretion and IR following COVID-19. Larger studies are thus warranted to confirm if these long-term dynamics sufficiently alter new-onset diabetes incidence rates.

Studies using metabolomic approaches to identify lipid biomarkers in critically ill COVID-19 patients also provide evidence supporting IR in COVID-19 (47). Higher plasma levels of free fatty acids (FFAs) or triglycerides (TGs) occur in moderate-to-severe COVID-19 cases that suggest disruptions in lipid and energy metabolism. Insulin and adiponectin inhibit the release of adipocyte-stored fatty acids into circulation and FFA uptake from circulation by the liver, which is required for hepatic TG synthesis to fuel gluconeogenesis. Increased IR and reduced adiponectin as demonstrated by Reiterer et al. (25) may enhance AT lipolysis to elevate plasma FFAs and TGs among

COVID-19 patients, exacerbating hyperglycemia and IR. Because plasma samples were taken within 24–48 h of hospital admission, elevated FFA and TG levels could reflect stress-associated hyperglycemia and transitory IR that commonly occur during critical illness. But the long-term persistence of hyperglycemic and IR phenotypes that may predispose individuals toward new-onset diabetes after COVID-19 resolution (46) advocate for the longitudinal study of lipid and metabolome dynamics to better understand how COVID-19 influences long-term glycometabolic phenotypes and transformations.

Challenges Associated With Studying New-Onset of Diabetes and a Proposed Design for an Optimal Study to Discover and Monitor New-Onset of Diabetes

Since COVID-19 symptoms usually develop 7–14 days post-infection, a major challenge in studying new-onset diabetes is identifying and recruiting participants with early SARS-CoV-2 infections. We recently developed an algorithmic framework to detect physiological signs of SARS-CoV-2 up to 4–9 days before overt symptoms appear using resting heart rate from Fitbit smart watches (9). Once participants are recruited, biological samples can be collected and glucose levels measured as an early baseline for these study participants.

Another challenge is dissecting the mechanism of new onset of diabetes. While COVID-19 patients with new-onset diabetes display similar physiological responses and clinical diagnoses, each individual engages different molecular pathways prior to or during SARS-CoV-2 infection that dictate whether new-onset diabetes symptoms and complications are transient or persist long-term following viral clearance. Underlying processes cannot be fully captured by any single clinical or molecular assay alone, and experimental studies need to approach this complexity with comprehensive systems biology strategies that help discover mechanisms involved in new-onset diabetes. Longitudinal deep profiling of multiple omics host data sets, including the genome, epigenome, transcriptome, proteome, metabolome, lipidome, and microbiome, can improve the biological understanding of diabetes development and progression with high resolution and accessibility. When combined with clinical tests, longitudinal multiomic profiles establish healthy baseline variations for clinical and molecular measurements that are highly distinct between individuals (48). Clinical outlier analyses using multiomic data sets can detect individual patient outliers relative to healthy populations, highlighting longitudinal trajectories and underlying health conditions that contribute to new-onset diabetes.

Experimental studies can integrate longitudinal multiomic profiling with continuous physiological monitoring using CGM and wearable technologies for quantifying lifestyle (diet, physical activity, sleep, and stress), establishing physiological and molecular taxonomies for COVID-19 that improve risk prediction, early detection, and diagnostic monitoring of new-onset diabetes, its outcomes, prognosis, and other post–COVID-19 pathologies. Such parameters can easily be collected with peripheral blood, stool, and urine samples during COVID-19 in-hospital stays. To measure these physiological parameters of diabetes post–COVID-19, large cohorts of COVID-19 participants will need to regularly self-report demographic, health history, and lifestyle information through microsampling devices, wearables, and online surveys that summarize symptoms, diet and nutrition, and physical activity (48). Once normalized, self-reported metrics can be readily integrated with multiomic profiles and analyzed with the same statistical techniques, providing environmental and physiological context to molecules and pathways that associate with new-onset diabetes.

Another challenge for studying new-onset diabetes is determining whether large cohorts of research participants without reported diabetes history are insulin-resistant or have prediabetes before study recruitment and COVID-19 diagnosis. Prediabetes occurs in insulin-resistant individuals with elevated blood glucose levels that are above normal glycemic ranges but are subclinical to T1D or T2D diagnoses. Most individuals with prediabetes in the U.S. remain unaware of their status and, as a result, have elevated risk for developing T2D. To elucidate molecular mechanisms governing new-onset of diabetes by COVID-19, studies must recruit individuals with normoglycemia. This is a challenging task because most individuals do not have regular assessments for IR, and many routine tests for IR are too expensive, labor intensive, or impractical to apply to large research cohorts. The homeostasis model assessment of insulin resistance (HOMA-IR) is a key index that utilizes clinical fasting plasma glucose and insulin measurements to quantify insulin resistance and β-cell function and is commonly used to screen high-risk groups for primary prevention of diabetes (49).

Figure 3 summarizes our proposed framework for studying COVID-19–induced new-onset of diabetes. Participants are recruited once they contact SARS-CoV-2 and monitored longitudinally for at least 6 months. The framework has four pillars of data collection: omics assays, remote health monitoring devices, gold standard physiological tests, medical records. Omics assays will be used to dissect the mechanism of the new-onset of diabetes and whether it is related to COVID-19 or not. Continuous remote health monitoring can be achieved via the use of wearables and microsampling devices. Physiological tests will be used to have a gold standard measure on organ functions, and medical records would be integrated in the analysis to account for patient history.

Technologies to Monitor Glucose Levels and Lifestyle

This section highlights a few wearable technologies that can monitor hyperglycemia and lifestyle pre/post–COVID-19 diagnosis, ultimately with potential to help the scientific community further dissect the mechanism behind COVID-19 new-onset diabetes (Fig. 4).

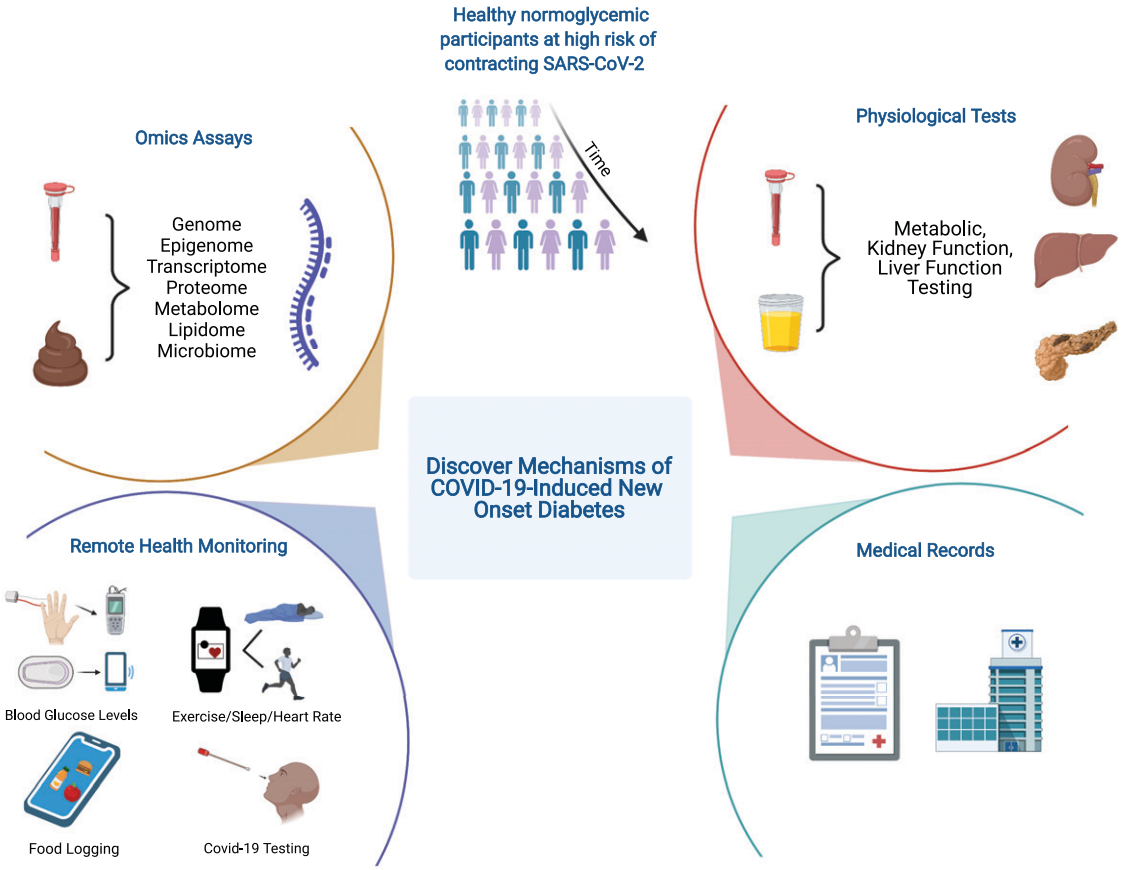

Figure 3—Our proposed framework for studying COVID-19–induced new-onset of diabetes. Participants are recruited once they contact SARS-CoV-2 and monitored longitudinally for at least 6 months. The framework has four pillars of data collection: omics assays, remote health monitoring devices, gold standard physiological tests, medical records. Omics assays will be used to dissect the mechanism of the new-onset of diabetes and whether it is related to COVID-19 or not. Continuous remote health monitoring can be achieved via the use of wearables, and microsampling devices. Physiological tests will be used to have a gold standard measure on organ functions, and medical records would be integrated in the analysis to account for patient's history.

Microsampling Devices

Microsampling devices capture and analyze a limited number of metabolites from small samples of biofluids. The most popular microsampling device is the glucometer, which allows users to collect small samples of blood from mechanical pricks, usually to the finger, via a disposable testing. Glucometer models contain many different components and advanced features that cater to the needs of users. Despite their benefits, the lack of real-time monitoring may require users to perform multiple tests per day to understand glucose trends over time.

The second most popular microsampling devices are HbA_{1c} at-home testing kits, which allow patients to regulate glucose levels and understand the potential risks of diabetes. Multiple kits require small amounts of blood (0.5–4 μL). Some can be synchronized with electric devices and applications. Given the correlation between HbA_{1c} and regulated health outcomes, adequately developed HbA_{1c} at-home testing kits can be an effective method of monitoring new-onset diabetes complications in COVID-19 patients, following lifestyle changes or appropriate medication can be administered to prevent severity. Additionally, given that HbA_{1c} assays measure results from the previous 3 months, patients may have difficulty precisely determining when glucose levels may have changed (50).

Continuous Glucose Monitoring for Managing Diabetes

One of the most common wearable technologies for diabetes management is the continuous glucose monitoring (CGM) device. CGMs are medical devices that detect trends to help patients maintain a healthy glycemic range by taking and analyzing blood glucose measurements in real-time. CGMs typically comprise a small sensor that is placed under the user's skin to measure interstitial glucose every few minutes and a transmitter that manually scans or wirelessly transfers the readings to a nearby receiver or smartphone device for display (51). CGM devices are broadly accessible to multiple patient groups, with some models that have been tested in individuals as young as 2 years of age. Advanced CGM device models can further integrate with insulin pumps to provide the user with automatic insulin adjustments based on CGM

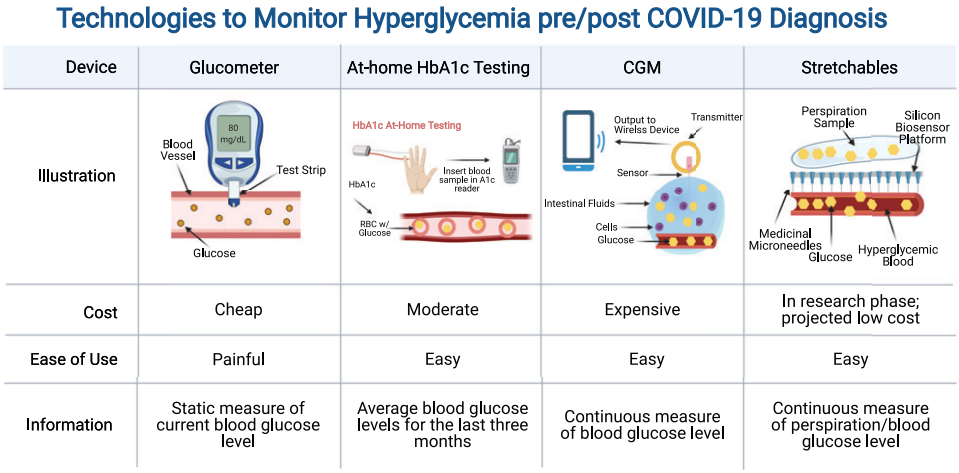

Figure 4—Technologies that assist with diabetes monitoring and management. Several technologies are available for the management of diabetes conditions and related complications such as continuous glucose monitoring (CGM), glucometers, HbA_{1c} at-home testing, smartphone applications for food, fitness, and sleep, and stretchable electronics. Stretchable glucose monitoring can monitor glucose levels through perspiration samples. Microneedles can either use perspiration samples or track blood glucose and inject medications such as insulin and metformin in patients with diabetes. RBC, red blood cell.

recordings (52). One of the disadvantages of using CGM devices is the sensors' short lifetime, which, depending on the model, averages 7–14 days. However, the Senseonics Eversense CGM device is one model that is surgically implanted under the skin with a sensor life span of 90 days (53), making it ideal for in-hospital or long-term glycemic management.

Stretchables Electronics to Monitor, Regulate, and Manage Diabetes

Stretchable electronics, also known as soft electronics or stretchables, are a relatively new class of wearable devices that are easily concealable due to their small form factor, adhesiveness, and conformability to movement (54). Stretchables are characterized by electrical circuits embedded in a pliable silicon- or polymer-based material that allows for measurements to be taken with built-in biosensors. These biosensors, which mainly comprise a bioreactor system, a signal transducer, and an output system, can track features of interest in easily accessible bodily fluids like sweat, saliva, or even tears. Biosensors are vital to diabetes management, as they can closely track many different parameters in perspiration and blood, including glucose levels, that are associated with diabetes onset and progression (55,56). Similar to some CGM devices, some stretchable devices go beyond glucose monitoring and facilitate diabetes treatment through automated infusions of insulin or metformin upon detection of hyperglycemia (57,58). A potential challenge in the clinical implementation of most stretchable devices is their reliance on using perspiration to detect and manage glucose levels. Because perspiration is a variable occurrence, these stretchable devices are currently not well-suited for the continuous, real-time monitoring of glucose levels that is critically important for effective diabetes management and treatment. As innovation continues to improve the biocompatibility of stretchable devices for therapeutic and diagnostic purposes, they have the potential to be an effective method for new-onset diabetes management post–COVID-19 diagnosis.

Mobile Applications Can Track Dietary Lifestyles With Corresponding Glucose Levels in Patients With Diabetes

Given the outsized importance that dietary lifestyle has on diabetes onset and progression, several mobile applications have been developed to monitor and regulate the nutrition of at-risk individuals. Specifically, algorithms have been developed to help users understand how variables such as food, carbohydrate levels, insulin doses, HbA_{1c}, glycemic index, blood pressure, and weight interact with the user's health. Several applications can provide newly diagnosed diabetes patients with healthy eating and drinking plans as well as tips for managing their conditions with the benefit of synchronizing with their glucometers for real-time measurements. Daily nutrition can be regulated through manual logging, electronic barcode scanning, and photo-generated data. Using artificial intelligence–driven and deep learning algorithms, smart camera applications can estimate serving size and create a detailed nutritional report and estimate in a few seconds. From the wide variety of dietary tracking applications available for diabetes patients, researchers can tailor them to best assist diabetes management following COVID-19 diagnosis.

Wearable Technology for Early Detection and Management of COVID-19

Wearable technologies can provide a potential alternative to PCR testing because of their capacity to monitor

several physiological health parameters in real time that are affected during COVID-19 infection. Recently, we have developed algorithms and framework to detect physiological signs of the SARS-CoV-2 virus as early as 4–9 days before symptoms first appeared using resting heart rate from Fitbit smart watches (9). However, various wearable devices to detect COVID-19 and manage diabetes need to be integrated to be able to early identify new-onset of diabetes. Nonetheless, algorithms and machine learning models need to be developed and tested to fuse all these multimodal data.

Current Initiatives to Explore the Bidirectional Relationship Between COVID-19 and New-Onset Diabetes

As COVID-19 cases increase and vaccination protocols start being implemented globally, uncertainty remains regarding the effective management of new-onset diabetes in patients that become infected with the virus. Therefore, several clinical trials are being conducted to study the relationship between COVID-19, diabetes, and wearable technology.

The COVID-19 and T1D Multicenter Study, sponsored by the Hospital of South West Jutland, measures the impact of COVID-19 on the incidence and phenotype of adults with newly diagnosed T1D patients in Denmark and Portugal. Participants include T1D patients with and without SARS-CoV-2 who are aged 18 years and older and already attend hospital units in Denmark or Portugal due to T1D. Through clinical study and epidemiological follow-ups every year for 2 years, participants will be tested and compared with each other for β-cell functioning. From this data, the study will also be able to estimate the number of newly diagnosed T1D patients with COVID-19 over previous years (59).

The CoviDIAB project at King's College London and Monash University is a global registry that seeks to characterize the phenotype of new-onset diabetes in COVID-19 patients with a negative history of diabetes or hyperglycemia and normal HbA_{1c} levels. To evaluate pathogenesis, epidemiology, management, and outcomes data, the registry will also study COVID-19 patients with preexisting diabetes—diabetic ketoacidosis, hyperosmolarity, severe insulin resistance—and severe metabolic disturbances. Through global collaboration with various medical networks, the registry may uncover the epidemiology of this new onset of diabetes. However, it may still be difficult to dissect the mechanism of the new onset of diabetes (60).

The COVID-19, wearables, and diabetes initiative at Stanford University is an example of a comprehensive design to detect COVID-19 and study its long-term effect (61). The goal of this study is to evaluate the use of algorithms for predicting the early detection of COVID-19 and the identification of new-onset diabetes. The research team recently completed the first step of their study and found that wearables can detect COVID-19 illness approximately 4–9 days before symptoms appear (21). Participants are expected to self-report symptoms and activities when the algorithm detects significant changes in wearable health data. Additionally, participants will longitudinally measure their HbA_{1c} via microsampling devices to identify cases with new onset of diabetes following COVID-19. Regular blood samples will be collected for omics analysis (methylation sequencing and single-cell RNAseq) to identify the molecular changes in those who developed new-onset diabetes.

Discussion

The COVID-19 pandemic has placed diabetes populations at increased risk for infection, severe complications (kidney disease, ischemic heart disease), and mortality. Recently, COVID-19 has been found to produce new-onset diabetes in some patients manifesting as acute hyperglycemia in COVID-19 patients without diabetes history, diabetic ketoacidosis in COVID-19 patients with existing diabetes, and new-onset diabetes in COVID-19 patients, either during the course of disease or after convalescence. From current research, these risks can also lead to more severe complications such as ketosis, ARDS, maladaptive immune response, and higher mortality rates.

SARS-CoV-2 spike proteins can interact with the RAS hormonal system and enter the host cell by binding to ACE2 receptors found on the surface of several organs and tissues, specifically pancreatic β-cells. Upon entrance, increased viral load, immune dysregulation, alveolar and endothelial dysfunction, and increased systemic coagulation may place diabetes patients at risk for severe COVID-19 complications. Additionally, from limited research, both the viral entrance of SARS-CoV-2 and resulting upregulation of angiotensin II can lead to new-onset diabetes. As broader research efforts are being made to understand the complications of new-onset diabetes post–COVID-19 diagnosis, effective management of both conditions is very important.

Wearable technology can assist in the early detection and maintenance of COVID-19 as well as the management of diabetes. Specifically, wearables can detect real-time physiological changes (respiration rate, body temperature, sleep, percent saturation of oxygen in the blood ($Sp0_2$), heart rate, heart rate variability, resting heart rate, stress, recovery, and activity) in healthy conditions or in relation to COVID-19. Complementarily, several wearables devices, microsampling devices, and mobile applications can assist in the metabolic management of diabetes, such as CGMs, glucometers, HbA_{1c} at-home kits, and mobile applications for fitness, exercise, and sleep which influence diabetes health. However, there is a lack of intervention that emphasizes new-onset diabetes, specifically after COVID-19.

Therefore, current methods of diabetes and COVID-19 management should be evaluated when determining the

best method for continuous health monitoring. Specifically, benefits and limitations should be considered. Stretchables provide user portability and flexibility; however, concerns toward range of stretchability, adhesion, and biocompatibility still require modifications. CGMs are effective at helping maintain glycemic control within appropriate ranges; however, improvements are needed in sensitivity recognition and time delay between measurements. Glucometers are accurate but inconvenient and require multiple tests to determine glucose trends while disposable strips are restricted to specific glucometer models. Regarding HbA_{1c}, studies have shown the value of at-home HbA_{1c} testing kits in the management of diabetes. However, improvements should be made given that patients may experience time delays since HbA_{1c} increase is usually recorded after glucose dysregulation happens by a few weeks. Additionally, mobile applications for dietary lifestyle, physical exercise, and sleep have been developed but pose different challenges. Despite offering personalization and convenience, many are entirely user-dependent and incompatible with wearable devices that can measure real-time data. Therefore, users are required to manually record glucose information in smartphone applications and there may be higher chances of self-reported bias, which may hinder health management in susceptible populations.

The most effective way of combating the detection of new-onset diabetes post–COVID-19 diagnosis is through wearable technology, which can measure many of the physiological and metabolic parameters in the body in real time. Currently, several clinical trials are being conducted to study the relationship between COVID-19, wearables, and new-onset diabetes and have the potential to provide promising results in the near future.

In summary, new-onset diabetes following COVID-19 is a new public health concern of mounting importance as the pandemic continues. With limited but promising evidence suggesting worsening complications in patients with comorbid diabetes, interventions should be made to prevent and manage this comorbidity. This review article explores the mechanisms, epidemiology, and technologies for new-onset diabetes and COVID-19 and suggests that high priority should be placed on studying both the metabolic and physiological parameters of both conditions using wearable technology for effective management.

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