Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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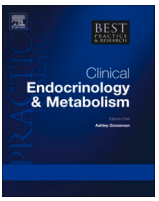

COVID-19 and metabolic syndrome

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Convergence of the two pandemics: metabolic syndrome and COVID-19 over last two years has posed unprecedented challenges to individuals as well as healthcare systems. Epidemiological data suggest a close association between metabolic syndrome and COVID-19 while variety of possible pathogenic connections have been proposed while some have been proven. Despite the evidence of high risk for adverse COVID-19 outcomes in people with metabolic syndrome, little is known about the differences in efficacy and safety among people with metabolic syndrome and without. It is important to recognize that among people with metabolic syndrome This review summarizes the current knowledge and epidemiological evidence on the association between metabolic syndrome and adverse COVID-19 outcomes, pathogenic interrelationships, management considerations for acute COVID-19 and post-COVID sequalae and sustaining care of people living with metabolic syndrome with appraisal of evidence and gaps in knowledge.

Abbreviations: ACE2, angiotensin converting enzyme-2; ARDS, acute respiratory distress syndrome; AST, aspartate transaminase; BMI, body mass index; HDL, high density lipoprotein; ICU, intensive care unit; IGF-1, insulin-like growth factor-1; LDL, low-density lipoprotein; MAFLD, metabolic dysfunction associated fatty liver disease; PCOS, polycystic ovary syndrome; RAAS, renin-angiotensin-aldosterone system; RCT, randomized clinical trial

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Introduction

Metabolic syndrome is a constellation of risk factors for atherosclerosis and cardiovascular disease driven by adiposity, insulin resistance, vascular endothelial dysfunction and inflammatory state. Obesity, dysglycaemia, hypertension and dyslipidaemia are its core elements while polycystic ovary syndrome in women and fatty liver are strongly related. Prevalence of metabolic syndrome is on the rise globally [1]. The evolution of COVID-19 into a pandemic over last three years has led to an era when two global pandemics merged posing unprecedented challenge to health of individuals and sustention of healthcare services.

Metabolic syndrome as a risk factor for adverse COVID-19 outcomes

Epidemiological evidence

Metabolic syndrome is associated with 2.3-fold increased risk of short-term mortality from COVID-19 [2]. An observational study showed that obesity, diabetes and previous stroke confer a higher risk of death from COVID-19 compared to people who die of non-COVID-19 causes [3].

Obesity increases the risk of developing COVID-19, progressing to severe disease, needing hospitalization, intensive care unit (ICU) admission and death [4] (Table 1). Body mass index (BMI) has a J-shaped relationship with risk of COVID-19 severity and death with a nadir at BMI 22 – 24 kg/m^2 [5]. Increased visceral adiposity, but not subcutaneous adiposity predicts severe COVID-19 [6]. Although some studies reported an increased risk of thrombosis among people with obesity, several others found no association between obesity and arterial [7] or venous thromboembolism [8] during COVID-19, after adjusting for covariates. Instead, the risk was directly related to the severity of illness. It is noteworthy that most of these data are from retrospective observational studies and therefore has low certainty of evidence due to high risk of bias [9].

Diabetes increases the risk of developing severe COVID-19, need for ICU care and death [10]. The risk of mortality is higher with type 2 diabetes compared to type 1, after adjusting for age and other co-morbidities [11]. Presence of macrovascular or microvascular complications independently increase the risk of death by 53% and 50% respectively [12,13]. Among people with diabetes, worse control prior to the infection predicts higher mortality from COVID-19 [14].

Among other co-morbidities of obesity, obstructive sleep apnoea is an independent predictor of severe COVID-19 [15]. Similarly dyslipidaemia [16] and hypertension [17] predict severe COVID-19 and mortality. The impact of hypertension appears to be more profound in the extremes of age [18].

Meta-analysis of observational studies suggests that metabolic dysfunction associated fatty liver disease (MAFLD) is an independent risk factor for developing severe COVID-19, requiring hospitalization and ICU admission, but not for mortality [19]. Among obese adults, those with MALFD were 6 times more likely to develop severe COVID-19 compared to those without MAFLD [20]. The degree of liver fibrosis

Table 1
Risk of adverse COVID-19 outcomes in people with metabolic syndrome and its components[a].

Condition	Risk				Reference
	Infection	Severe disease	ICU admission	Death	
Obesity	2.42 (1.58–3.70)	1.62 (1.48–1.76)	1.75 (1.38–2.22)	1.23 (1.06–1.41)	Raeisi 2022 [4]
Type 2 diabetes	-	2.88 (2.29–3.63)	1.59 (1.15–2.18)	1.87 (1.61–2.17)	Kastora 2022 [10]
Hypertension	-	1.74 (1.66–1.83)	1.91 (1.48–2.34)	1.79 (1.68–1.89)	Khairy 2022 [17]
Dyslipidaemia	-	1.27 (1.11–1.44)		2.13 (1.84–2.47)	Liu 2022 [16]
MAFLD	-	3.07 (2.30–4.09)	1.46 (1.12–1.91)	1.45 (0.74–2.84)	Hayat 2022 [19]
Metabolic syndrome	-	3.21 (2.88–3.58)		2.32 (1.16–4.63)	Rico-Martin 2022 [2]

ICU: intensive care unit; MAFLD: Metabolic dysfunction associated fatty liver disease

[a] Risks are presented as odds ratios and 95% confidence interval except for hypertension where relative risk and 95% confidence interval are presented. Data are derived from the most recent and / or largest meta-analysis reporting outcomes. Almost all studies were observational, and majority were retrospective. Majority of included studies reported effect estimates after adjusting for covariates including age, sex and co-morbidities, although the included co-morbidities were widely heterogeneous.

independently predicted adverse outcomes [21]. However, use of FIB-4 score (which uses liver enzymes and platelet levels, which are deranged during acute illness) to predict extent of fibrosis is a limitation. Nevertheless, a meta-analysis of autopsy studies reported that the key histological findings of liver were steatosis (in 55.1%), hepatic vascular thrombosis (in 29.4%) and liver fibrosis (in 20.5%) [22].

Men experience worse outcomes of COVID-19 compared to women [23]. This led to the hypothesis that higher androgen levels and/or increased androgen sensitivity may play a role in worsening disease outcomes. However, anti-androgen therapy among patients with prostate cancer did not increase the risk of developing COVID-19, its complications or mortality in observational studies [24]. No increase in incidence of virologically confirmed COVID-19 were observed between women with and without polycystic ovary syndrome (PCOS) after adjusting for age and other co-morbidities [25].

People who had undergone bariatric surgery in the past had lower risk of severe disease, ICU admission and mortality compared to obese adults who had not [26]. In fact, they had lower BMI and lower prevalence of diabetes. People with lower glycated haemoglobin (HbA1c) on admission had lower risk of severe disease and mortality [14]. These data suggest that achieving weight reduction and improving glycaemia can decrease the risk of adverse outcomes of COVID-19.

Pathogenic mechanisms

Pathophysiological mechanisms driving the adverse COVID-19 outcomes in people with metabolic syndrome are reviewed elsewhere [27–29] and in-depth discussion is beyond the scope of this review.

In brief, metabolic syndrome is characterized by adiposity, insulin resistance, meta-inflammation, endothelial dysfunction, prothrombotic state, atherosclerosis, and impaired host defence. These factors parallel and facilitate the pathogenic mechanisms of COVID-19 and its complications (Fig. 1).

Adipose tissues express ACE-2 (thus acting as a site for viral entry), releases pro-inflammatory cytokines and activates macrophages (and therefore contribute to cytokine storm that drives systemic inflammatory response syndrome, acute respiratory distress syndrome (ARDS) and multi-organ dysfunction). Chemokines from macrophages fuel the endothelial dysfunction and prothrombotic state and formation of reactive oxygen species that induce organ dysfunction. Hyperglycaemia adds to endothelial dysfunction, generation of reactive oxygen species and pro-thrombotic state [28]. Microthrombosis causes tissue hypoperfusion. The prothrombotic state predisposes to venous thromboembolism. Similarly, MAFLD is associated with higher circulatory IL-6 levels, which is a key driver of systemic inflammatory response in COVID-19 [30]. Androgens may increase the expression of ACE2 in heart and kidney and induce changes in the immune system [31] predisposing to COVID-19 and its complications. Women with PCOS show increased renin-angiotensin-aldosterone system (RAAS) activity, decreased plasma ACE2 levels (resulting in loss of lung protection and decreased production of anti-inflammatory angiotensin 1–7), greater basal macrophage activation and lower vitamin D levels which may drive severe COVID-19 [32].

Metabolic consequences of COVID-19

Acute infection

SARS-CoV-2 infection leads to new onset hyperglycaemia or worsening of glucose control in people with pre-existing diabetes. Worsening insulin resistance is the predominant mechanism [33]. The degree of insulin resistance is greater in patients with ARDS due to COVID-19 compared to ARDS due to other causes. In fact, SARS-CoV-2 infection in adipose tissue alters its adipokine expression [33] and upregulates *IRF-1* gene which in turn downregulates several genes relevant for sub-cellular insulin/IGF-1 signalling pathways [34].

People with MAFLD are at increased risk of developing raised liver enzymes [35]. Raised aspartate transaminase (AST) levels predicted mortality [36]. Several mechanisms of liver injury in COVID-19 have been hypothesized including direct viral injury, hypoxia-ischaemia injury, immune mediated cytokine storm and thrombotic state, mitochondrial dysfunction and gut dysbiosis [29]. However, the expression of viral entry proteins in liver cells were not different between people with MAFLD and those without [37].

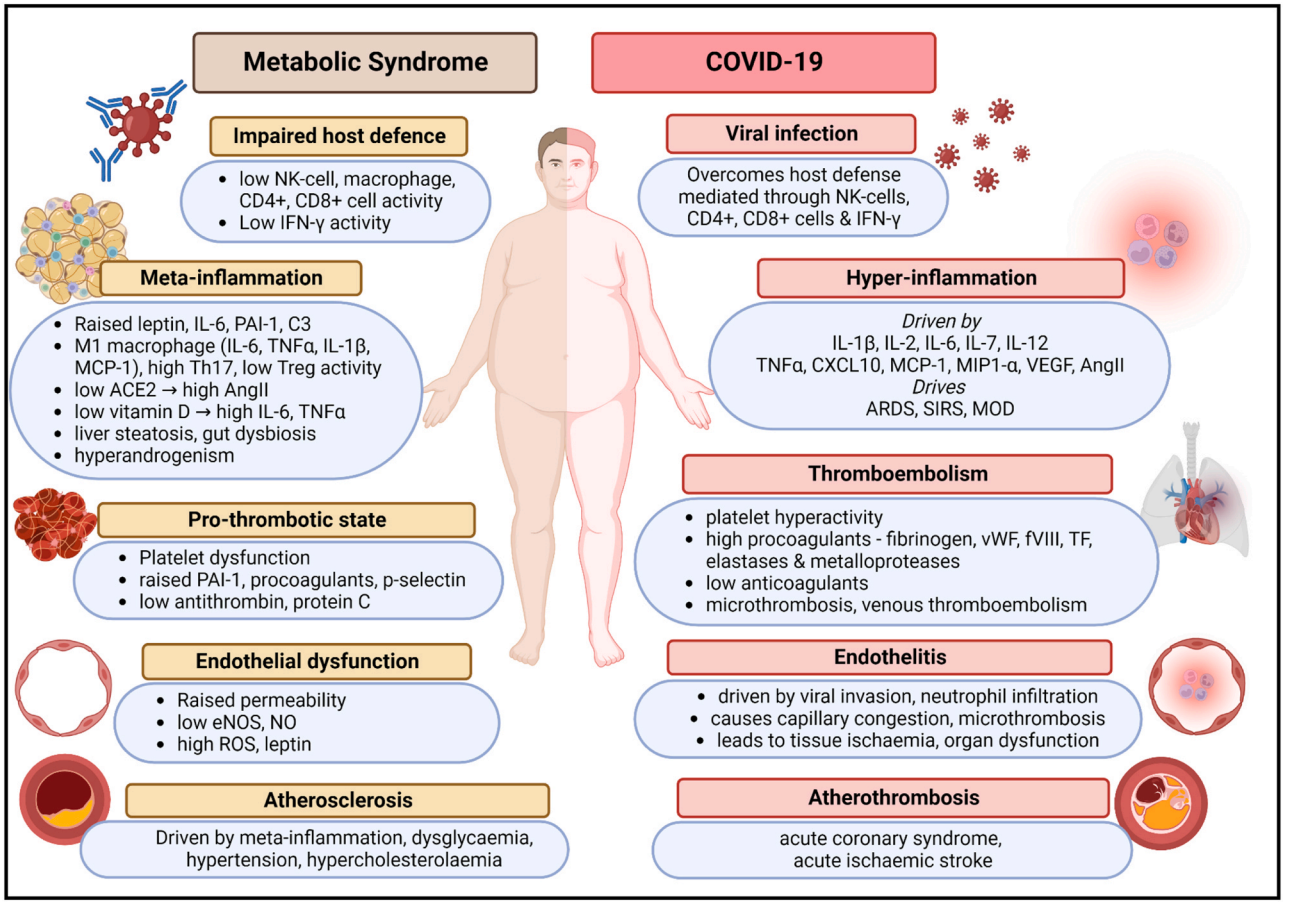

Fig. 1. The overlapping pathogenic mechanisms of metabolic syndrome and COVID-19 (Images Created with BioRender.com). Pathogenic pathways and processes in people with metabolic syndrome are comparable to pathogenesis of COVID-19 and its complications and this may explain the association between metabolic syndrome and adverse COVID-19 outcomes. ACE: angiotensin converting enzyme; AngII: angiotensin-II; ARDS: acute respiratory distress syndrome; CXCL: C-X-C motif chemokine ligand; eNOS: epithelial nitric oxide synthase; fVIII: factor VIII; IFNɣ: interferon-ɣ; IL: interleukin; MCP: monocyte chemoattractant protein; MIP: macrophage inflammatory protein; MOD: multi-organ dysfunction; NK-cell: natural killer cells, NO: nitric oxide; PAI: platelet activator inhibitor; ROS: reactive oxygen species; SIRS: systemic inflammatory response syndrome; TF: issue factor; TNFα: tumor necrosis factor-α; Treg: T regulatory cells; VEGF: vascular endothelial growth factor; vWF: von Willibrand factor.

Variety of pathogenic mechanisms by which COVID-19 could accelerate atherosclerosis has been proposed [38]. Endothelial dysfunction and atherosclerotic plaque instability can lead to plaque rupture and atherothrombosis [27].

During acute COVID-19 illness total testosterone decreases in men and oestradiol increases in women. In both men and women, luteinizing hormone (LH) increases while sex hormone binding globulin (SHBG) decreases [39]. These changes reverse after recovery [40]. Similar changes are known to occur with any critical illness [41]. Changes in androgen levels during the illness and short and long-term health consequences of COVID-19 on women with PCOS are unknown.

Low total, LDL and HDL cholesterol levels during COVID-19 predict severe disease and mortality [42]. Lowering of cholesterol is a known response to sepsis or critical illness [43].

Changes in blood glucose, liver enzymes, sex hormones and lipids are likely to reflect the inflammatory response and similar changes have been observed with other acute or critical illnesses. It is unclear if COVID-19 has a greater impact than other infections. Extent of derangement appear to parallel the severity of illness, and these are probably surrogate markers rather than mediators of severe disease.

Post infection sequalae

Several studies reported increased incidence of diabetes among individuals after developing COVID-19 [44]. However, a more recent study showed that the incidence of new onset diabetes after COVID-19 is not significantly greater than its incidence after any other type of pneumonia [45]. Authors postulate that new onset diabetes after COVID-19 is possibly a response to inflammatory insult of the infection rather than a specific effect of SARS-CoV-2.

A large retrospective analysis demonstrated that the risk of incident cardiovascular events in the first year after COVID-19 is significantly increased compared to contemporary and historic control cohorts [46]. Interestingly, subgroup analysis in this study did not find a significant difference between people with and without obesity, hypertension, diabetes and dyslipidaemia. However, it is unknown whether presence of metabolic syndrome increases the risk of developing cardiovascular events following the resolution of COVID-19.

Preventing and managing COVID-19 in people with metabolic syndrome

Prevention

Vaccination remains the mainstay in preventing COVID-19. Proportion of individuals producing neutralizing humoral immunity after vaccination was lower among people with obesity compared to those without [47]. A meta-analysis of observational studies reported that presence of one or more comorbidities (including obesity, diabetes, hypertension) was associated with lower protection against COVID-19 and severe COVID-19 [48]. Immunogenicity of vaccines appear to be lower in people with diabetes irrespective of the type of vaccine and weaker with higher BMI and worse glucose control [49]. People with diabetes have relatively less protection against infection, hospitalization, severe disease and death [50]. However, these data are derived from observational studies with high risk of bias. Immunogenicity of an inactivated COVID-19 vaccine among patients with MAFLD was 95.5% [51], with acceptable safety profile, comparable to general population. However, higher liver fibrosis score (FIB-4) was associated with lower IgG titres at 7 days after vaccination against COVID-19 [52]. Clinical outcomes, cell mediated immune response and response to different types of vaccines are not known. In general population, vaccination had no impact on fertility [53]. It is unknown if women with metabolic syndrome or PCOS fare differently.

In summary, people with metabolic syndrome may mount a weaker immune response to COVID-19 vaccines and people with diabetes may derive relatively less protection against clinically relevant outcomes. No serious safety concerns for people with metabolic syndrome have been recognized. Considering the increased risk of severe COVID-19 associated with metabolic syndrome and its associated co-morbidities, these individuals should be prioritized for vaccination against COVID-19.

Acute Management of COVID-19

Monitoring and identifying the patient at risk of adverse outcomes

People with no or minimal symptoms with COVID-19 can be managed at home. Diabetes, obesity and hypertension are independent risk factors for developing severe COVID-19 and therefore individuals with these co-morbidities should be monitored closely for disease progression [54]. Remote monitoring of COVID-19 is effective and useful in early identification of patients needing hospitalization while avoiding unnecessary hospital admissions [55]. Using a pulse oximeter at home is recommended for early recognition of deterioration in people with these co-morbidities [54]. Regular monitoring of blood glucose and adapting sick day rules are critical for people with diabetes. Involvement of usual diabetes care provider in the management is advised [54]. Monitoring of blood glucose at least once a day should be considered in people with metabolic syndrome without previously diagnosed diabetes.

Among hospitalized patients, hyperglycaemia on admission predicts severe disease and mortality, irrespective of their diabetes status [56]. Other prognostic markers include biochemical mediators or markers of inflammation (CRP, procalcitonin, ferritin), thrombosis (D-dimer), haematological responses to inflammation (lymphopaenia, leukopaenia) and organ / tissue injury (troponin, lactate dehydrogenase, creatine kinase, AST, creatinine) [57]. Patients with MAFLD developing COVID-19 should be closely monitored for derangements in glucose metabolism and liver injury. Certain COVID-19 therapies may cause hepatocellular injury. Although prognostic markers unique to metabolic syndrome have not been defined, these individuals are likely to have higher perturbations of the above markers. Several prognostic calculators incorporating the clinical, radiological, haematological and biochemical factors have been designed and their use can facilitate triaging the at-risk patients for escalation of care [58].

Pharmacological management of COVID-19

Pharmacological management of COVID-19 in people with metabolic syndrome follows the standard guidelines for general population. Although people with obesity may demonstrate altered pharmacokinetics, standard fixed doses appear to achieve similar blood levels of most medication used in the treatment of COVID-19 and fixed doses are likely to be effective even among people with obesity [59]. The exception is tocilizumab where weight-based dose is recommended. However, these recommendations are based on pharmacokinetic rather than clinical outcome-oriented studies.

Antivirals. Nirmatrelvir/ritonavir, molnupiravir and remdesivir are the antivirals recommended in the treatment of COVID-19. In a randomized clinical trial (RCT) investigating remdesivir, efficacy outcomes in people with diabetes and/or obesity were comparable to the overall trial population [60]. Out-patient molnupiravir therapy among unvaccinated adults developing COVID-19 reduced hospitalizations and deaths in another RCT. Effectiveness was less in participants who had diabetes, but small size of this subgroup precludes making definitive conclusions [61]. In a meta-analysis of clinical outcomes of antiviral therapy, benefits of remdesivir, nirmatrelvir/ritonavir or molnupiravir did not differ with age, sex or severity of COVID-19 [62].

Immunomodulators. Dexamethasone improves outcomes in COVID-19 [63]. However, it raises blood glucose by increasing insulin resistance. New onset hyperglycaemia may occur, particularly among people with metabolic syndrome. People with pre-existing diabetes may experience deterioration of control. Clinical trials on dexamethasone for COVID-19 included patients with diabetes and/or obesity, but any differences in outcomes in these subgroups have not been reported.

IL-6 inhibitors (tocilizumab, sarilumab) give a modest improvement in mortality and other clinical outcomes in COVID-19 [64]. Several observational studies have reported lack of efficacy of tocilizumab among people with diabetes or with in-hospital hyperglycaemia (irrespective of diabetes status) compared to those without diabetes or having lower in-hospital glucose levels [65]. However, this has not been specifically addressed in randomized controlled trials.

Janus kinase inhibitors (eg: baricitinib) improve mortality among patients with severe COVID-19 [66]. It is contraindicated in advanced renal impairment (eGFR < 15 mL/min) and in hepatic impairment. Monitoring of liver enzymes is recommended. An open label RCT is investigating its role in COVID-19 among people with diabetes compared to dexamethasone [NCT04970719]. Given its neutral effect on

blood glucose, if proven non-inferior (or superior) it will be an attractive option for people with diabetes, at least when glucose control is sub-optimal.

On-going management of metabolic syndrome

In-hospital hyper- and hypoglycaemia are associated with higher risk of severe disease and mortality among patients with COVID-19, irrespective of the pre-morbid diabetes status [67]. However, these data are derived from retrospective observational studies and therefore causality is unclear. Furthermore, the impact of confounding by glucocorticoid treatment may be significant. Most studies defined in-hospital hyperglycaemia as greater than 10 mmol/L (180 mg/dL), but no clinical trials have explored the optimal glucose goal for people with COVID-19. Expert consensus is to aim for less than 10 mmol/L while avoiding hypoglycaemia, like in any other acute illness.

Benefits and risks of common medications used in metabolic syndrome management in the setting of COVID-19 are an area of intense research and discussion and have been reviewed in detail elsewhere [68–73]. Data from meta-analyses [74–83], observational studies [25] and randomized controlled trials [84–89] have emerged while several studies are on-going. These are summarized in Table 2.

In essence, the long-term use of these agents was not associated with any adverse COVID-19 outcome, except for insulin. This is likely reflecting the advanced state of diabetes and co-morbidities of people on insulin. Given the possible theoretical mechanisms of harm, further studies are needed on its role during acute illness. Although some agents were associated with better COVID-19 outcomes, quality of evidence is weak due to high risk of bias as almost all studies were retrospective observational in nature.

Data on the use of these medication during acute illness is much limited. Several randomized trials failed to demonstrate any benefit of some agents (dapagliflozin, ACEI, aspirin – see Table 1), and there were no new safety concerns beyond their known adverse effects. These data suggest that most routine medications of people with metabolic syndrome could be continued during COVID-19 while practicing precautions recommended for their use in any acute / critical illness. Interactions with COVID-19 pharmacotherapies should be given due consideration [90].

Follow-up

Persistent physical and psychological symptoms after recovery from COVID-19 have been reported. While there is lack of consensus on defining the long-COVID syndrome, it is estimated to affect 6.2–43% of people surviving COVID-19 [91]. The risk of developing long COVID appears to be related to severity of the acute illness and is possibly increased with obesity [92] and diabetes [93] but the evidence is weak.

Obesity, diabetes and hypertension are among the common co-morbidities of people who develop reinfections, recurrence of COVID-19 and require readmission [94]. However, it is not known whether the risks of these outcomes are greater among people with metabolic syndrome.

Incorporation of telemedicine in the routine post-discharge care has been recommended [54] and is particularly useful among people with metabolic syndrome where metabolic perturbations and adjustment of medications would need regular review in the aftermath of COVID-19. Restoration of metabolic health and discussions on possible increased risk of new onset cardiometabolic diseases at least within the first year following recovering from COVID-19 should be the focus of transition from in-hospital care to routine follow up. Fig. 2 summarizes COVID-19 peventive and management considerations among people with metabolic syndrome.

Managing metabolic syndrome: challenges and innovations in the era of COVID-19

COVID-19 pandemic posed unprecedented challenges to health care systems. People with metabolic syndrome experienced weight gain [95], variable effects on glucose control [96], deteriorating blood pressure control [97], anxiety, uncertainty, isolation and other mental health issues [98].

Limitations on direct contact between healthcare providers and individuals with metabolic syndrome and related comorbidities, diversion of human and infrastructural resources, finances as well as research towards COVID-19 meant that the healthcare services were pressed to adopt remote health delivery mechanisms while individuals were needed to embrace an era of self-management of chronic diseases.

Table 2
Common pharmacotherapies used in the treatment of metabolic syndrome and considerations for their use during COVID-19.

Medication / class	Mechanisms[a]	Clinical evidence			Implications for practice
		Impact of long term use on COVID-19 outcomes	Impact of use during COVID-19 infection	On-going trials	
Metformin	Possible benefit through favourable immunomodulation, inactivation of ACE2 and insulin sensitization [74]	↓ mortality (MOB)[b][74] ↑ lactic acidosis	↔ outcomes (RCT)[84]	metformin [NCT04625985, NCT04510194]	Continue during pandemic / acute infection – guided by standard cautions / contraindications Consider risks of - AKI, DKA with SGLT2 inhibitors - Lactic acidosis with metformin
SGLT2 inhibitors	Possible benefit through favourable immunomodulation, decrease RAS activity and vascular oxidative stress[68]	↓ mortality (MOB)[b][75]	↔ outcomes No safety concerns (RCT)[c] [85]	empagliflozin [NCT04381936], dapagliflozin [NCT04393246]	
GLP1 receptor agonists	Possible benefit through favourable immunomodulation. Enhancing ACE2 expression – increases risk of viral entry, but decreases in inflammatory response[68]	↓mortality (MOB)[b][76]	-	semaglutide [NCT04615871]	
DPP4 inhibitors	Possible benefit through favourable immunomodulatory and anti-fibrotic effects[68]	↓ or ↔ mortality (MOB)[b][78]	↓ mortality (MOB)[b][78]	linagliptin [NCT04542213], sitagliptin [NCT04365517]	
Insulin	Possible harm through proinflammatory response and formation of reactive oxygen species[69]	↑mortality (MOB)[b][77]	-	NCT04542213 (insulin vs linagliptin)	Despite theoretical risks and observational data of harm, insulin remains the best option for glucose control in critically ill
Statins	Possible benefit through anti-inflammatory effects and limiting viral entry in to cells[70]	↓mortality (MOB)[b][79]	↓mortality (MOB)[b][82]	[NCT04486508, NCT04631536., NCT04472611, NCT04904536]	Continue during pandemic / acute infection – guided by standard cautions / contraindications Consider interactions with remdesivir / other antivirals [90]

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Table 2 (*continued*)

Medication / class	Mechanisms[a]	Clinical evidence			Implications for practice
		Impact of long term use on COVID-19 outcomes	Impact of use during COVID-19 infection	On-going trials	
Omega-3 fatty acids	Possible benefit through favourable immunomodulation[70]	-	↓ symptoms and mortality (RCT)[d][86]	NCT04647604	Continue during pandemic / acute infection – guided by standard cautions / contraindications:
ACEI/ARB	Possible benefit through suppression of RAS activation. Increases ACE2 – benefit of anti-inflammatory effects of Ang-II likely to override the risk of facilitation of viral entry in to cells [71]	↓mortality (MOB)[b][80]	↔ mortality & ↑ AKI (MCT)[83,87]	NCT04366050 (ramipril)	Consider risks of: AKI with ACEI Major bleeding with aspirin
Aspirin / antiplatelets	Possible benefit through favourable anti-inflammatory effects Risks of increased bleeding[72]	↓mortality (MOB)[b][81]	↓mortality (MOB)[b][81] ↓thrombosis, ↑ major bleeding ↔ventilation need or mortality (RCT) [99]	Aspirin [NCT04381936, NCT04703608] other antiplatelets [NCT04368377]	
Anti-androgens	Suppression of DHT may decrease endothelial inflammation Spironolactone upregulates ACE2 –facilitate infection, suppress inflammation by increasing AngII[73]	↔ outcomes (OB)[b] [25]	↔ outcomes in men (RCT)[e][89]	NCT04345887, NCT04826822, NCT04345887	

ACE2: angiotensin converting enzyme-2; AKI: acute kidney injury; AngII: angiotensin-II; DHT: dihydrotestosterone; DKA: diabetic ketoacidosis; MCT: meta-analysis of clinical trials, MOB: meta-analysis of observational studies, OB: observational studies, RAS: renin angiotensin aldosterone system, RCT: clinical trials

[a] Key mechanisms by which the medications may affect COVID-19 outcomes, beyond their primary effects on glucose / weight / lipids / blood pressure / clotting. Detailed reviews are referenced.

[b] low certainty of evidence and high risk of bias due to retrospective observational nature of all studies

[c] AKIs may have been under-recognized in the RCT (dapagliflozin)

[d] RCTs limited by small sample size

[e] RCT investigated degarelix with standard care vs standard care on COVID-19 outcomes

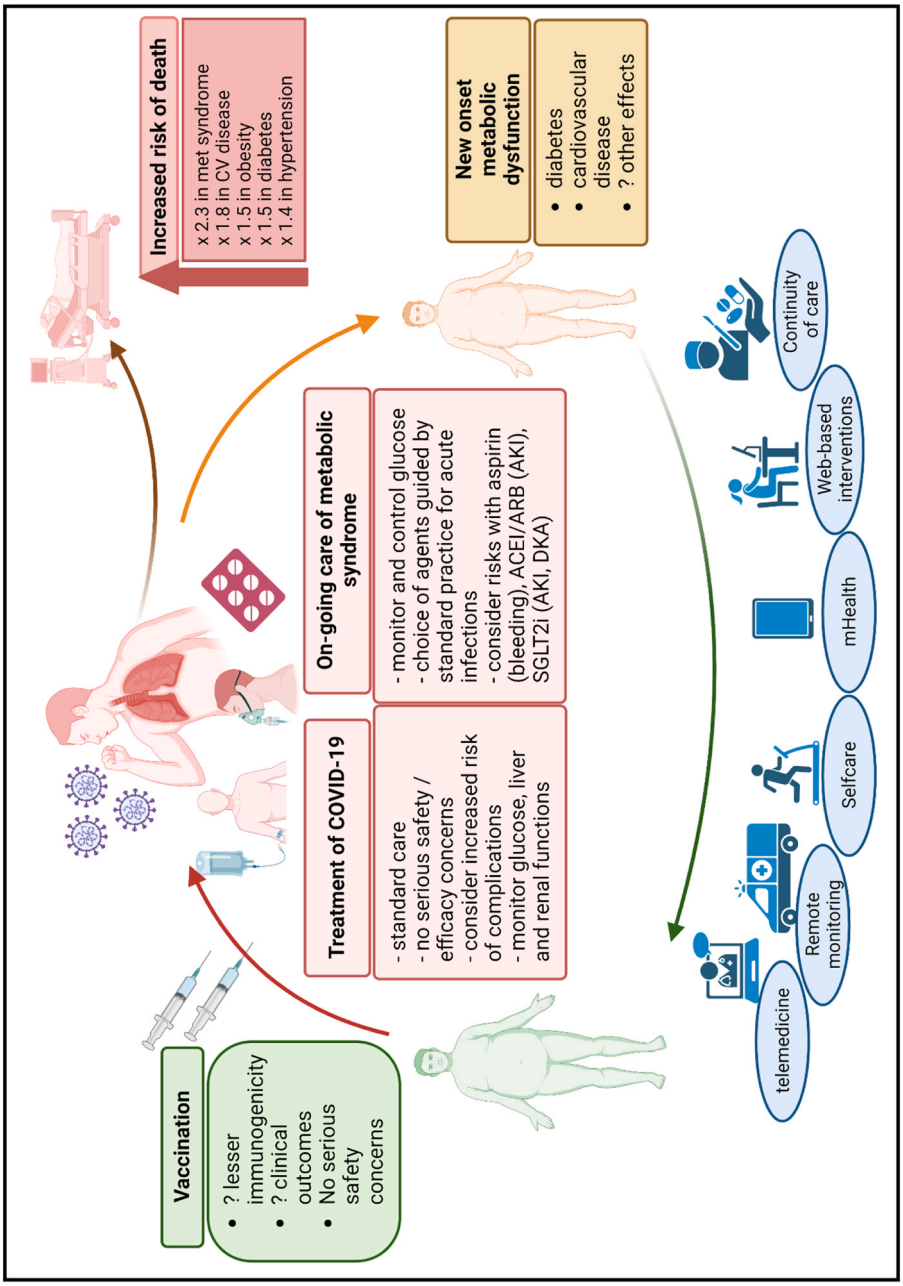

Fig. 2. Prevention and management of COVID-19 and continuing care for people with metabolic syndrome (Images Created with BioRender.com). ACEI: angiotensin converting enzyme inhibitors; AKI: acute kidney injury; ARB: angiotensin receptor blockers; DKA: diabetic ketoacidosis; SGLT2i: sodium-glucose co-transporter-2 inhibitors.

Web based interventions and utilization of artificial intelligence to deliver personalized care have been used effectively in weight loss programmes [99]. Provision of personalized care plans and involvement of expert advice were key contributors towards success. Social support, self-monitoring and goal-setting were characteristics of successful programmes. Home based exercise training and live supervised tele-exercise classes with nutritional and behavioural tele-counselling have shown to be acceptable and possibly effective in maintaining weight loss [100].

Use of mHealth-based intervention, tele-coaching with nurse-led telephone conversations and mobile apps were effective in improving glucose, weight and systolic blood pressure among people with diabetes [101]. Remote monitoring of blood pressure, integrated with telemedicine services has been proven effective in improving blood pressure control among people with hypertension [102]. M-health and telemedicine interventions have been used effectively for weight management and fertility care in women with PCOS [103].

Summary

Among people with metabolic syndrome, the risk of mortality is greater with COVID-19 than with other types of pneumonia. Shared pathogenic mechanisms including meta-inflammation, endothelitis, prothrombotic state and atherosclerosis are likely to explain this association. Despite the epidemiological evidence of increased risk, differences in efficacy and safety outcomes in COVID-19 preventive and therapeutic interventions in this group have not received much attention in many of the trials. Common medications used in the long-term management of metabolic syndrome are safe during the era of COVID-19. Their protective effects against COVID-19 shown in observational studies should be interpreted with caution due to inherent risk of bias in such studies. To date, none of these medications have shown to be protective in the treatment of acute infection, compared to standard care. Safety concerns are limited to the known adverse effects of these agents thus warranting adherence to standard practices in their use in acute illness. Incident cardiovascular events may develop in the aftermath of COVID-19, but it is unclear if people with metabolic syndrome are at increased risk. New onset diabetes is well known to occur, but incidence after COVID-19 in not greater than after any other pneumonia. Ensuring continuity of care on metabolic health can be facilitated by integrating web-based, telehealth, M-health based interventions into the standard care delivery.

Practice points

- People with metabolic syndrome are at risk of developing severe disease and mortality from COVID-19. Therefore, these individuals should be prioritized for vaccination, closely monitored in the event of infection with a low threshold for escalation of care.
- Routine pharmacotherapies of metabolic syndrome should continue with the aim of optimizing metabolic health. These agents are unlikely to adversely affect COVID-19 outcomes.
- During COVID-19 illness, standard COVID-19 treatment approaches should be followed for people with metabolic syndrome.
- Initiation of metabolic syndrome related treatments during the acute illness is not recommended as no acute benefit has been demonstrated. However one's usual treatments should be continued while monitoring for their known complications during acute illness. Consider interactions with COVID-19 therapies.
- People with metabolic syndrome will require support during recovery to ensure restoration of metabolic control and monitoring for new onset cardio-metabolic diseases

Research agenda

- Do people with metabolic syndrome carry a higher risk of developing COVID-19 and its complications than other forms of pneumonia?
- Compared to people without metabolic syndrome, do people with metabolic syndrome derive less protection from vaccination, against COVID-19 infection, complications and death? What is the optimum vaccination strategy for people with metabolic syndrome?
- Are efficacy and safety outcomes of COVID-19 treatments different in people with metabolic syndrome compared to those without?
- Do anti-inflammatory properties of metabolic syndrome medications translate into improvement of clinical outcomes of COVID-19 illness? Do they modulate the risk of long COVID and post-COVID-19 new onset cardiometabolic diseases?

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Conflicts of interest

Nothing to declare.

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Permissions

Not applicable.

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