European Journal of Pharmacology 886 (2020) 173546

Contents lists available at ScienceDirect

European Journal of Pharmacology

journal homepage: www.elsevier.com/locate/ejphar

Full length article

Possibility of magnesium supplementation for supportive treatment in patients with COVID-19

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ARTICLE INFO

Keywords:
Magnesium supplementation
COVID-19
Supportive treatment

ABSTRACT

Magnesium as an enzymatic activator is essential for various physiological functions such as cell cycle, metabolic regulation, muscle contraction, and vasomotor tone. A growing body of evidence supports that magnesium supplementation (mainly magnesium sulfate and magnesium oxide) prevents or treats various types of disorders or diseases related to respiratory system, reproductive system, nervous system, digestive system, and cardiovascular system as well as kidney injury, diabetes and cancer. The ongoing pandemic coronavirus disease 19 (COVID-19) characterized by respiratory tract symptoms with different degrees of important organ and tissue damages has attracted global attention. Particularly, effective drugs are still lacking in the COVID-19 therapy. In this review, we find and summarize the effectiveness of magnesium supplementation on the disorders or diseases, and provide a reference to the possibility of magnesium supplementation for supportive treatment in patients with COVID-19.

Key points.

1. Basic and clinical researches have demonstrated that magnesium sulfate is beneficial for the treatment of lung-related diseases, such as asthma and pneumonia through its anti-inflammation, anti-oxidation, and bronchial smooth muscle relaxation.
2. Magnesium supplementation has been shown to prevent or treat a variety of disorders or diseases related to respiratory system, reproductive system, nervous system, digestive system, and cardiovascular system as well as kidney injury, diabetes and cancer.
3. Serum magnesium level in COVID-19 patients should be monitored.
4. Magnesium supplementation should be given in a timely manner for COVID-19 patients with hypertension, kidney injury, diabetes, or pregnancy complications.

1. Introduction

The coronavirus disease 2019 (COVID-19) caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) creates a global pandemic and affects more than 200 countries/regions. As of July 30, 2020, the cumulative number of confirmed cases of COVID-19 in the world exceeded 16 million (WHO, 2020). SARS-CoV-2-infected patients are more likely to be admitted to the hospital and enter the intensive care unit (Grasselli et al., 2020), with high mortality. The most common symptoms of COVID-19 patients are fever and cough (Escalera-Antezana et al., 2020; Guan et al., 2020). Many patients especially in intensive care unit have organ function damage including acute respiratory distress syndrome (ARDS), cardiac injury, acute kidney injury, and liver dysfunction (Guan et al., 2020; Yang et al., 2020). In spite of that some drugs comprised of broad-spectrum antiviral drugs (Du and Chen, 2020; Elfiky, 2020), anti-malaria drugs (Fantini et al., 2020; Hu et al., 2020) and other miscellaneous systemically acting drugs (Li and De Clercq, 2020), seem to be potentially beneficial to treat COVID-19, there is still a lack of definite clinical evidence, and then the epidemic has not been effectively controlled.

Electrolytes such as *sodium, potassium, calcium, and magnesium* are essential basic elements to maintain cell normal physiological condition function (Hellgren et al., 2006; B. F. Palmer and Clegg, 2016). Magnesium is the main cation in human cells, mainly concentrated in the mitochondria. Its content is the fourth most abundant after sodium, potassium and calcium in human body. Magnesium, an essential substance for basic biochemical reaction, participates in a cluster of normal physiological function and metabolism, such as the transport of potassium ion or calcium ion (Flatman, 1984; Komiya and Runnels, 2015), energy metabolism, protein and nucleic acid synthesis (Ohyama, 2019; Sissi and Palumbo, 2009). Magnesium also has anti-inflammation (Abiri

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https://doi.org/10.1016/j.ejphar.2020.173546
Received 20 May 2020; Received in revised form 30 July 2020; Accepted 8 September 2020
Available online 12 September 2020

and Vafa, 2020; Eshraghi et al., 2015; Han et al., 2018; Kao et al., 2011; Ozen et al., 2020; Rochelson et al., 2007; Turner et al., 2017), anti-oxidation (Güzel et al., 2019; Kao et al., 2011), anti-spasm (Güzel et al., 2019; Yen and Thwaites, 2019), vasodilation (Shimosawa et al., 2004; Wang et al., 2019), and neuroprotection (Bachnas et al., 2019; Jameson and Bernstein, 2019). Therefore, magnesium homeostasis regulates reproductive system, cardiovascular system, digestive system, neurological system and respiratory system, etc, maintaining normal human health.

There are no vaccines or approved drugs available to eradicate the virus for the prevention and treatment of COVID-19 until now. All efforts at drug design and clinical trials of already approved drugs are creditable and worthy. After long-term research, excellent effects of magnesium have been demonstrated in the prevention and treatment of various diseases. In this review, we provide the evidences and novel insights into the role of magnesium supplementation in COVID-19 supportive treatment. We believe that the treatment with magnesium preparation alone or in combination with other drugs is prospective and open the possibility of an effective strategy to fight SARS-Cov-2 infection.

2. Prevention and treatment of magnesium for lung symptoms and diseases

Asthma is a severe respiratory disease characterized by airway inflammation, airway smooth muscle contraction, as well as airway structure change. Exacerbation of asthma may be life-threatening and bring a heavy burden on medical service. More evidences from meta-analyses and comprehensive reviews of randomized clinical trials have demonstrated the beneficial effects of magnesium supplementation on lung diseases, such as asthma and pneumonia (Blitz et al., 2005; Kew et al., 2014; Knightly et al., 2017; Powell et al., 2012; Rowe et al., 2000; Shan et al., 2013; Villeneuve and Zed, 2006).

For the children with acute severe asthma hospitalized in the emergency department, intravenous magnesium sulfate infusion, at a dose of 25 mg/kg (maximum 2 g) with an infusion time of 20 min within the first hour of hospitalization, can significantly reduce the proportion of children requiring mechanical ventilation support (Torres et al., 2012). Intravenous injection and nebulised inhalation of magnesium sulfate show positive clinical effects in children with asthma (Irazuzta and Chiriboga, 2017; Liu et al., 2016; Powell et al., 2013). This injection, a short infusion of 25–75 mg/kg over 20 min (maximum 2–2.5 g/dose) or other optimized dosing regimens, can significantly improve the respiratory function and reduce the hospitalization rate of children with moderate to severe asthma exacerbation (Liu et al., 2016). Timely administration of the appropriate dose (50–75 mg/kg) of intravenous magnesium sulfate prevents hospitalization of patients with acute asthma (Irazuzta and Chiriboga, 2017). One in five children who are treated in the emergency department can avoid being admitted to the hospital. Another method of administration is high-dose continuous magnesium sulfate infusion at a dose of 50 mg/kg/h for 4 h. In non-infectious-mediated asthma, the early use of high-dose continuous magnesium sulfate infusion is better than magnesium sulfate bolus in avoiding admission and expediting pediatric emergency department discharge (Irazuzta and Chiriboga, 2017). Adding magnesium to salbutamol and ipratropium bromide does not cause harm to the human body, and is clinically helpful for some individuals especially in those children with more severe attacks and a shorter duration of exacerbation (Powell et al., 2013). Therefore, aerosolized magnesium has a great clinical effect on worsening symptoms and shorter duration of symptoms in children (Powell et al., 2013). A study in Thailand, children with moderate to severe asthma exacerbation (pediatric respiratory assessment, PRAM score $\geq$ 4) are randomized to receive either three doses of 2.5 ml nebulised magnesium sulfate (6% solution) mixed with neutral salt spray up to 4 ml. Compared with standard therapy of aerosolized ipratropium bromide/fenoterol, there is no statistically significant change and difference in PRAM score assessment without severe side effect (Wongwaree and Daengsuwan, 2019).

For acute asthmatic adults, a single infusion of 1.2 or 2 g of magnesium sulfate intravenously within 15–30 min is reported to reduce the hospitalization rate and improve lung function of the patients who have not responded sufficiently to oxygen, nebulised short-acting β2-agonist and intravenous corticosteroids (Kew et al., 2014). A survey of Turkish doctors' attitudes towards the use of magnesium sulfate to treat exacerbation of acute asthma is also conducted (Baççıoğlu et al., 2016). Oral 340 mg magnesium supplement for 6.5 months improves both objective outcome measures of bronchial response to peak expiratory flow rate and methacholine, and subjective measures of asthma control and quality of life in adults (Kazaks et al., 2010). The two major reasons for using magnesium sulfate are to reduce days of hospital stay (94.7%) and prevent access to the intensive care unit (80.3%). Despite the well-known role of magnesium sulfate in acute severe asthma, of the 456 respondents, only 42.3% dealing with asthma patients have used magnesium sulfate in their practices, and 48.7% agree to include magnesium sulfate in asthma guidelines (Baççıoğlu et al., 2016). Therefore, the education and encouragement for magnesium sulfate use are necessary for the treatment of acute asthma in patients.

Meanwhile, a systematic analysis of adult patients with acute asthma shows that intravenous magnesium sulfate is more effective than placebo in improving lung function in terms of peak expiratory flow and forced expiratory volume in 1 s. Intravenous magnesium sulfate has a modest effect in decreasing hospital admissions in acute asthmatic adults who do not have positive responses to standard therapy (Green, 2016). In adults with community acquired pneumonia, abnormal magnesium levels on admission are associated with the increased 30-day mortality rate, compared with the normal value (Nasser et al., 2018). Magnesium sulfate (a single dose of 1.5 g intravenously within 20 min) enhances the bronchodilation effect of inhaled long-acting β2-agonist in patients with chronic obstructive pulmonary disease (Abreu González et al., 2006). In a clinical trial with a total of 2907 randomized patients, atomized magnesium sulfate, combined with inhaled β2-agonist and ipratropium bromide, have modest additional benefits in terms of pulmonary function and hospitalization (Knightly et al., 2017). Additionally, intraoperative administration of magnesium sulfate (50 mg/kg intravenously for 10 min, followed by continuous infusion of 15 mg/kg/h during the operation) improves lung function in patients receiving video-assisted thoracoscopic surgery, and reduces the doses of rocuronium and postoperative analgesics (Sohn et al., 2017).

Furthermore, magnesium sulfate (100 mg/kg, intravenously) is found to mitigate lung injury score, inflammation response, and oxidative stress induced by bilateral lower limb ischemia-reperfusion in rats (Kao et al., 2011). Magnesium sulfate inhibits inflammatory molecules including chemokine (macrophage inflammatory protein-2), cytokine (Interleukin-6, IL-6), prostaglandin E2, and cyclooxygenase-2 in lung tissue possibly by inhibiting L-type calcium channels (Kao et al., 2011). In a model of acute lung injury, magnesium sulfate (150 mg/kg, intraperitoneally) ameliorates hydrochloric acid-induced lung histopathology including peribronchial inflammatory cell infiltration, alveolar septal infiltration, alveolar edema, and alveolar exudation (Güzel et al., 2019). It also significantly restores oxidative stress and inflammatory response in lipopolysaccharides-induced acute lung injury of mice (Li et al., 2019). These observations demonstrate that magnesium has the antioxidant and anti-inflammatory effects on lung injury. Magnesium sulfate also inhibits airway smooth muscle contraction by blocking the voltage-dependent calcium channels, which is another mechanism of magnesium for the treatment of asthma (Gourgoulianis et al., 2001). However, more detailed molecular mechanisms are still lacking. We summarized representative papers (Table 1) and provided existing possible mechanisms by which magnesium supplementation ameliorates lung symptoms and diseases with anti-inflammation, anti-oxidation and bronchial smooth muscle relaxation (Fig. 1).

Table 1
Magnesium ameliorates lung symptoms and disorders.

Diseases	Study	Country/ Species	Treatment	Dosage	Outcomes/Conclusion
Acute severe asthma in children (age <18 years)	Irazuzta et al. (2017)	-[a] Human	Magnesium sulfate infusion	Intravenous bolus of magnesium sulfate 50–75 mg/kg; or a high-dose continuous magnesium sulfate infusion (HDMI) as 50 mg/kg/h/4 h (200 mg/kg/4 h)	Treatment with intravenous magnesium sulfate reduces the odds of hospital admissions; and emphasizing the role of magnesium sulfate as an adjunctive therapy in acute severe asthma.
	Powell et al. (2016)	UK Human	Nebulised magnesium sulfate	Receive nebulised salbutamol 2.5 mg (ages 2–5 years) or 5 mg (ages ≥ 6 years) and ipratropium bromide 0.25 mg mixed with either 2.5 ml of isotonic magnesium sulfate (250 mM, tonicity 289 mOsm; 151 mg per dose) at approximately 20 min intervals.	Nebulised magnesium has a greater clinical effect in children who have more severe exacerbation with shorter duration of symptoms.
	Wongware and Daengsuwan. (2019)	Thailand Human	Nebulised magnesium sulfate	Three doses of 2.5 ml of isotonic magnesium sulfate nebulizer (6% solution) mixed with neutral salt spray up to 4 ml, 30 min apart	Nebulised magnesium sulfate is non-inferior including clinical benefit and safety compared with nebulised ipratropium bromide/fenoterol among Thai children with acute moderate asthmatic attack.
Asthma in adults (age 18 >years)	Shan et al. (2013)	- Human	Magnesium infusion; nebulised magnesium sulfate	-	Intravenous treatment is associated with a significant effect upon respiratory function in adults; nebulised treatment is associated with significant effect upon respiratory function and hospital admission in adults.
	Kew et al. (2014)	- Human	Magnesium infusion	A single infusion of 1.2 or 2 g intravenous magnesium sulfate over 15–30 min	Intravenous magnesium sulfate reduces hospital admissions and improves lung function in adults with acute asthma who have not responded sufficiently to oxygen, nebulised short-acting beta2-agonists and intravenous corticosteroids.
	Kazaks et al. (2010)	USA Human	Oral magnesium supplementation	340 mg (170 mg twice a day) of magnesium for 6.5 months	Adults orally receiving magnesium supplements show the improvement in objective measures of bronchial reactivity to methacholine and PEFR as well as in subjective measures of asthma control and quality of life.
Others: COPD;	Gonzalez et al. (2006)	Spain Human	Magnesium sulfate infusion	1.5 g of magnesium sulfate in an intravenous solution for 20 min	Intravenous administration of magnesium sulfate enhances the bronchodilating effect of inhaled long-acting beta 2 - agonists.
Lung injury	Kao et al. (2011)	- Sprague-Dawley rats	Magnesium sulfate infusion	Intravenous injection of 10, 50, or 100 mg/kg magnesium sulfate	Magnesium sulfate attenuates oxidative stress, inflammation, and lung injury induced by lower limb ischemia-reperfusion; magnesium sulfate mitigates lung injury induced by bilateral lower limb ischemia-reperfusion in rats, possibly inhibiting L-type calcium channels.
	Güzel et al. (2019)	- Sprague-Dawley rats	Magnesium sulfate infusion	Intraperitoneal injection of magnesium sulfate at 150 mg/kg	Magnesium sulfate and dexmedetomidine ameliorates hydrochloric acid-induced acute lung injury vis anti-oxidation and anti-inflammation; magnesium sulfate shows greater improvement in the pathology of acute lung injury than dexmedetomidine.

Note: [a] No country is mentioned in the paper.

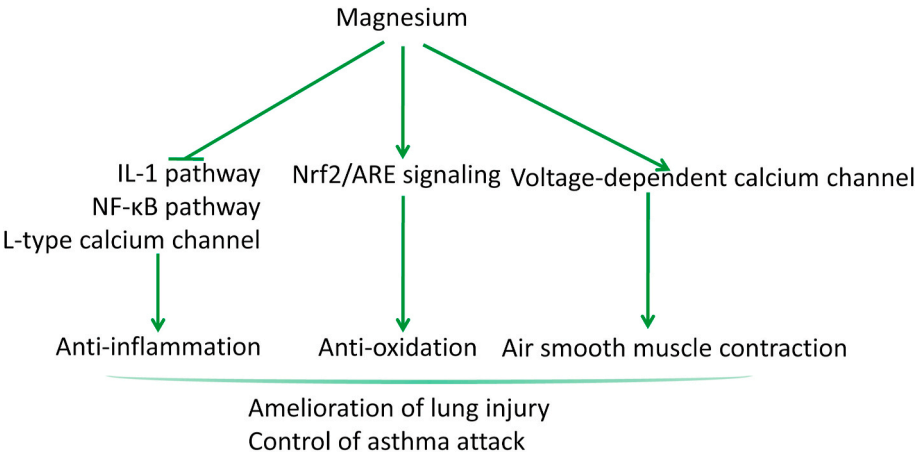

Fig. 1. Summary of possible mechanisms by which magnesium supplementation reduces inflammation, oxidative stress, and bronchial smooth muscle relaxation.

3. Therapeutic application of magnesium in other diseases

3.1. Reproductive system disease

Magnesium sulfate has been widely used in the obstetric environment for several decades (Matsuda et al., 2000; Pritchard, 1955). Magnesium can inhibit the release of acetylcholine from motor nerve endings, block nerve-muscle conduction, and relax skeletal muscle. Therefore, it effectively controls and prevents preterm labor, gestational hypertension, preeclampsia, and eclampsia with few side effects on the fetus (Alexander et al., 2006; Kreepala et al., 2018; Magee and von Dadelszen, 2018). Clinically, magnesium sulfate is utilized for fetal neuroprotection in preterm birth (Bachnas et al., 2019; Rouse et al., 2008). Maternal administration of magnesium sulfate prior to anticipated preterm delivery decreases cerebral palsy in survivors (Rouse et al., 2008). Recent report shows that, in the case of highly "suspicious" preterm births, a single dose injection of 4 μg magnesium sulfate to stimulate the secretion of brain-derived neurotrophic factor effectively protects fetal neurons on the premise of safety (Bachnas et al., 2019). This fetal neuroprotection of magnesium may be involved its anti-inflammatory action.

P2X purinoceptor 7 (P2X7) receptor participates in the regulation of cytokine expression. Magnesium sulfate at 100 mM is observed to significantly decrease mRNA expression of interleukin-1 beta (IL-1β) in human umbilical vein endothelial cells exposed to 100 ng/ml lipopolysaccharide. Furthermore, it down-regulates P2X7 receptor expression to block the initiation and propagation of inflammation in human endothelial vein *in vitro* (Ozen et al., 2020). Magnesium sulfate at doses of 2.5, 5, or 10 mM also resists inflammation by inhibiting nuclear transcription factor-κB (NF-κB) nuclear translocation and alpha inhibitor of NF-κB (IκBα) degradation in human umbilical vein endothelial cells stimulated by 100 ng/ml lipopolysaccharide (Rochelson et al., 2007). In addition, magnesium sulfate protects against inflammatory response and oxidative damage in rat placenta of intrahepatic cholestasis of pregnancy. It effectively reduces IL-1β, tumor necrosis factor-α (TNF-α) and interferon-gamma (IFN-γ) levels, and improves growth of offspring in this animal model (Han et al., 2018).

3.2. Neurological and mental disease

In neurological system, magnesium is considered as a neuroprotective agent (Saver and Starkman, 2011). A study of about 16,000 individuals in Germany has demonstrated that hypomagnesemia (low serum magnesium) is common, accounting for approximately 14.5% of the total unselected research population (Schimatschek and Rempis, 2001). People with migraine may excrete excess magnesium due to stress, and develop a magnesium deficiency, indicating that migraine is associated with low magnesium level in the brain (Ramadan et al., 1989) and cerebrospinal fluid (Jain et al., 1985). Magnesium supplementation is suggested as a therapeutic approach in all migraine suffers (Mauskop and Varughese, 2012). For a part of patients, intravenous injection of 2 g magnesium sulfate over 1–2 h is a cost-effective first-line therapy for status migrainosus, especially for patients who initially present with lower pain intensity (Xu et al., 2019). Additionally, magnesium sulfate is also a highly promising neuroprotective drug for stroke (Saver, 2010; Saver and Starkman, 2011; Saver et al., 2015). Continuous cisternal irrigation with magnesium sulfate solution containing 5 mM of Mg^{2+} at 20 ml/h decreases the occurrence rate of cerebral vasospasm in patients with aneurysmal subarachnoid hemorrhage (Yamamoto et al., 2016). In fact, there is evidence for the contact of magnesium with depression and anxiety in subjects (Serefko et al., 2013). Magnesium-depletion leads to the enhanced depression- and anxiety-related behaviors in mice (Singewald et al., 2004). Antidepressant drugs such as amytriptiline and sertraline, increase intracellular magnesium concentrations, which positively correlates with the antidepressant action in patients with major depression (Nechifor, 2009).

N-methyl-D-aspartate (NMDA) receptors are a vital class of receptors in emotion, learning and memory. In the process of synaptic transmission, the activation of NMDA receptors requires the participation of non-NMDA receptors, mainly α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) (Nechifor, 2011; Watt et al., 2004). When the stimulation reaches a certain intensity, glutamic acid released by the presynaptic membrane acts on AMPA receptors. And the ion current through AMPA receptors channel is enhanced. Thus, the post-synaptic membrane adjacent to NMDA receptors is locally depolarized. At this time, the binding of glutamic acid to NMDA receptors can open the channel (Watt et al., 2004). Therefore, dysregulation of NMDA receptors may play an important role in the development of neuropathic pain and memory (Miyashita et al., 2012; Noh and Ismail, 2020; Wu et al., 2007). Magnesium as a physiological non-competitive antagonist of NMDA receptors blocks the channel in a dose-dependent manner. The results from the *in vitro* and *in vivo* studies have shown that magnesium inhibits presynaptic release of excitatory neurotransmitters, and non-competitively blocks NMDA receptors (Hou et al., 2020; Miyashita et al., 2012). Of note, magnesium can diminish the frequency of pain paroxysms and improve the emotional component of behavior in patients suffering from neuropathic pain (Pickering et al., 2011). Magnesium enhances analgesia induced by opioids, general and local anesthetics in animal models of pain (Gomes et al., 2020; Mendonça et al., 2020; Savić Vujović et al., 2019). The main mechanism by which magnesium produces analgesic effect is blockage of the calcium channel associated with NMDA receptors (Decollogne et al., 1997; Na et al., 2011; Nechifor, 2011) (Fig. 2). Therefore, the non-competitive binding of magnesium to NMDA receptors may also be a potential molecular mechanism for the prevention and treatment of neurological and mental diseases.

3.3. Digestive system disease

Clinically, oral magnesium solution is often used to treat constipation. Magnesium oxide is effective for the management of chronic functional constipation in children. The frequency of defecation in children receiving 30 mg/kg magnesium oxide of body weight per day, is effectively improved, and the stool consistency is significantly decreased at the fourth week (Pickering et al., 2011). Recent research has further proven that oral magnesium supplementation (800 mg magnesium oxide daily) prevents the postoperative complications of cardiac surgery, including nausea, vomiting and constipation in patients from the admission to discharge from hospital (Moradian et al., 2017). The data from a clinical trial including a total of 259 patients with gallbladder cancer, 701 patients with gallstones, and 851 population-based controls in Shanghai, China, have demonstrated that serum magnesium level is inversely related to gallbladder disease (Lee et al., 2020). Aquamin is a natural product rich in magnesium and calcium. Aquamin can reduce total bile acid levels and increase short-chain fatty acid acetate levels in stool samples from healthy subjects, however, calcium or placebo treatment shows no change in bile acids or short-chain fatty acids (Aslam et al., 2020). Magnesium sulfate is also used as an adjuvant analgesic drug for stomach surgery. Before sedation, intravenous magnesium sulfate at 50 mg/kg decreases analgesic requirements both during and after endoscopic submucosal dissection for gastric neoplasm without adverse effects in patients (Kim et al., 2015). These observations suggest that magnesium supplementation may play a major role in digestive system diseases.

Experimentally, magnesium sulfate at 100 or 200 mg/kg prevents a massive bridging fibrosis around the portal and central vein induced by bile duct ligation in rats (Eshraghi et al., 2015). It remarkably decreases serum alkaline phosphatase (ALP), alanine aminotransferase (ALT), aspartate aminotransferase (AST) and γ-glutamyltransferase (GGT) levels, increases liver superoxide dismutase (SOD) and catalase in this animal model. Subsequently, magnesium sulfate ameliorates bile duct ligation-induced liver fibrosis, bile duct hyperplasia, hepatocyte necrosis and inflammation in rats (Eshraghi et al., 2015).

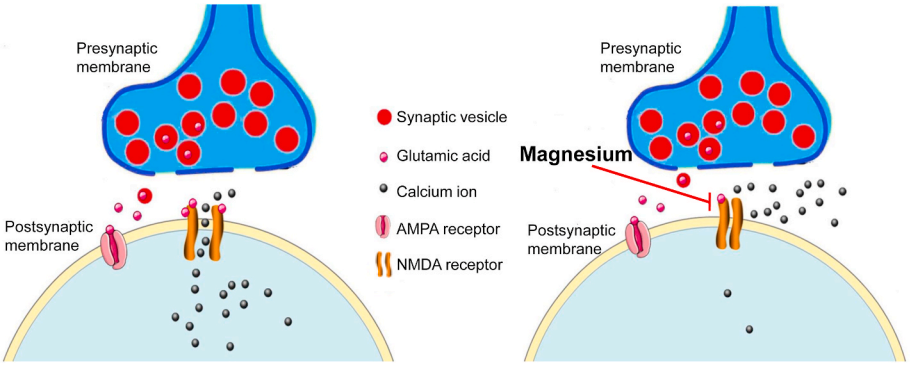

Fig. 2. Scheme demonstrating the function of magnesium sulfate in analgesia: NMDA receptors are associated with neuropathic pain. When the stimulation reaches a certain intensity, glutamic acid released by the presynaptic membrane acts on AMPA receptors, and calcium ion current through AMPA receptors channel is enhanced, thus, the post-synaptic membrane adjacent to NMDA receptors is locally depolarized. Magnesium sulfate suppresses NMDA receptors through non-competitive binding, and inhibits calcium ion outflow, exerting analgesic effects.

3.4. Cardiovascular system disease

It has long been known that magnesium deficiency causes an increased incidence of cardiovascular diseases, including hypertension and atherosclerosis (Saris et al., 2000; Seelig, 1994). As mentioned above, magnesium has a good effect on hypertension during pregnancy (Alexander et al., 2006; Kreepala et al., 2018). Oral magnesium supplementation (300 mg/kg magnesium oxide daily) for 1 month effectively decreases systolic, diastolic and mean arterial blood pressure in patients with essential hypertension at home (Banjanin and Belojevic, 2018). Magnesium chelate supplementation (600 mg/kg) daily for 6 months, is associated with better blood pressure control. It improves cardiovascular endothelial function and ameliorates subclinical atherosclerosis in thiazide-treated hypertensive women (Cunha et al., 2017). A strategy with the magnesium therapy (10 mM, a total of 2.47 g magnesium sulfate infused daily for 3 days) after cardiac surgery is effective in reducing the risk of atrial fibrillation (Osawa et al., 2018), which is also demonstrated by corresponding systematic review and meta-analysis (Gu et al., 2012; Shepherd et al., 2008). A possible explanation might be that magnesium regulates cardiac enzymatic and metabolic pathways, and stabilizes cellular membranes (Romani and Scarpa, 1990). Of note, the strategy of magnesium supplementation in clinical practice cannot be unified. In patients who have cardiothoracic surgery, the strategy of a 10 mmol bolus of magnesium sulfate followed by a continuous infusion of 3 mmol/h over 12 h delivers a sustained and moderately elevated magnesium concentration, with greater time-weighted magnesium plasma level than a single 20 mmol bolus (Osawa et al., 2018). In the protection of heart, further research is needed to assess whether extending the duration of the continuous infusion can continue to provide high but stable magnesium level, maintaining safety.

Magnesium supplementation can lower blood pressure, inhibit smooth muscle contraction and prevent cardiovascular diseases (Eshraghi et al., 2015; Kim et al., 2015) mainly through the following molecular mechanisms. Magnesium has similar property as calcium antagonist, and is considered a physiological calcium blocker (Altura et al., 1987). It is known that the concentration of calcium is a major determinant of vascular smooth muscle cell contractile activity and vascular tone. The main action of magnesium on vascular smooth muscle is to decrease intracellular calcium by the inhibition of calcium influx as well as the blockage of calcium release from the sarcoplasmic reticulum, resulting in the inactivation of calmodulin-dependent myosin light chain kinase activity and the reduction of vascular contraction-induced arterial relaxation (Altura et al., 1987). Furthermore, magnesium induces membrane hyperpolarization and promotes the outflow of calcium ion by activating potassium channel, which initiates the relaxation of smooth muscle cells (Ko et al., 2008; Zhang et al., 1993) (Fig. 3). Magnesium contributes to blood pressure regulation partly via its vasodilator action and sympatholytic property. Using the perforated whole-cell patch clamp method to nerve growth

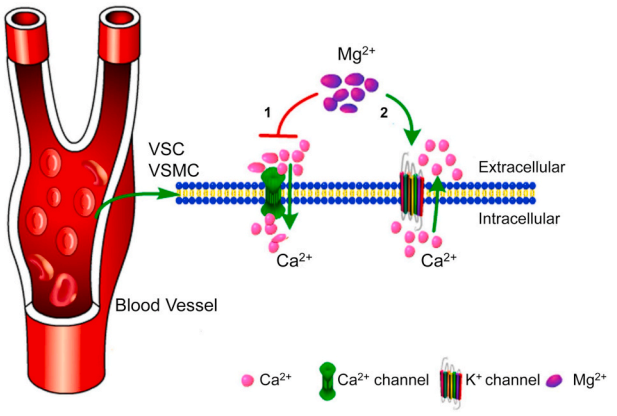

Fig. 3. Mechanism of magnesium sulfate in relaxing blood vessels and lowering blood pressure: Magnesium is considered as a physiological calcium blocker. Magnesium activates potassium channels, induces membrane hyperpolarization and promotes the outflow of calcium ions, initiating the relaxation of smooth muscle cells.

factor-treated PC12 cells, magnesium is found to block voltage-gated calcium currents in a concentration-dependent manner. Most of the voltage-gated calcium currents are carried through N-type calcium channels. Magnesium blocks mainly N-type calcium channels at nerve endings, and then inhibits norepinephrine release, which decreases

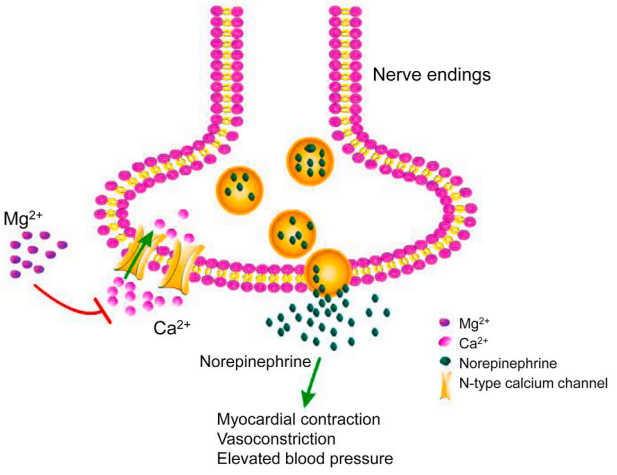

Fig. 4. Magnesium inhibits norepinephrine release in post-sympathetic neurons and adrenergic nerve endings: Mg^{2+} blocks mainly N-type Ca^{2+} channels at nerve endings, and then inhibits norepinephrine release, resulting in the reduction of blood pressure independent of its direct vasodilating action.

blood pressure independent of its direct vasodilating action (Shimosawa et al., 2004) (Fig. 4). On the other hand, magnesium can affect the synthesis of nitric oxide (NO). It increases NO level in serum, playing an important cause of vascular smooth muscle cells relaxation and blood pressure reduction especially in patients with gestational hypertension, but the specific mechanism is still unclear (Teragawa et al., 2002; Wang et al., 2019).

3.5. Kidney injury

Magnesium shows the preventive effect on cisplatin-induced acute kidney injury in patients (Hamroun et al., 2019; Solanki et al., 2014, 2015). A retrospective analysis of 3828 patients has demonstrated that magnesium sulfate supplement, as a co-adjuvant drug during the period of major laparoscopic abdominal surgery, reduces a risk of postoperative acute kidney injury (Oh et al., 2019). Magnesium deficient diet for 2 weeks before cisplatin-induced acute kidney injury, significantly increases renal damage characterized by high plasma levels of urea nitrogen and creatinine in female mice, with the enhanced oxidative stress and increased expression of inflammatory factors IL-6, TNF-α and IL-1β in kidney (Solanki et al., 2014).

3.6. Diabetes

In fact, magnesium deficiency is a common problem in diabetic patients (Kachhawa et al., 2019; Kumar et al., 2019; Mather and Levin, 1979). Magnesium deficiency increases the risk of poor glycemic control and diabetic retinopathy in a cross-sectional study including 250 diabetics in North India (Kumar et al., 2019). A continuous infusion of magnesium sulfate at 15 mg/kg/h produces a better-controlled effect on blood glucose level in patients with diabetes mellitus undergoing cardiac surgery (Soliman and Nofal, 2019). Oral magnesium supplementation (jamieson magnesium tablet, containing 250 mg elemental magnesium) daily for 3 months reduces insulin resistance and improves glycemic control indicators among type 2 diabetes patients (Elderawi et al., 2018).

3.7. Cancer

Recent study suggests that increasing intake of magnesium-containing foods may help reduce the incidence and mortality of primary liver cancer (Zhong et al., 2020). One case report shows that the subcutaneous administration of magnesium in a syringe pump can reduce repeated hospital admissions for patients with recurrent symptomatic hypomagnesaemia like the patients with advanced ovarian cancer (Fenning et al., 2018). Higher magnesium intake in the diet is associated with a lower risk of colorectal tumors (Wark et al., 2012). Prior research has demonstrated that high dietary magnesium intake may reduce the prevalence of chemotherapy-induced peripheral neuropathy and severity in patients with colorectal cancer (Wesselink et al., 2018). Thus, eating magnesium-rich foods may be a new strategy for cancer prevention.

Table 2 summarizes the treatment of magnesium supplementation for the various diseases in recent basic researches and clinical trials.

4. The possibility of the use of magnesium supplementation in the prevent and treatment of COVID-19

COVID-19 has spread globally with severe epidemics (Table 3). SARS-CoV-2 gene sequence has a very high similarity to severe acute respiratory syndrome coronaviruses (SARS-CoV) broke out in 2003, and the Middle East respiratory syndrome coronavirus (MERS-CoV) epidemic in 2012 (Wu et al., 2020a, 2020c). SARS-CoVs-2, a previously unknown beta-coronavirus, is listed as the 7th member of the coronaviruses family that infects humans (Zhu et al., 2020). In addition to respiratory damage, clinical evidences show that a relatively high proportion of patients with COVID-19 has different damage degrees of important organ and tissue such as liver, kidney, and heart (Escalera-Antezana et al., 2020; Guan et al., 2020; Yang et al., 2020). Moreover, patients with ARDS may be accompanied by cytokine storm, which increases multiple organ damage and makes the treatment of COVID-19 more difficult (Guo et al., 2020; Mehta et al., 2020).

4.1. Respiratory system

Most COVID-19 patients develop pneumonia accompanied with respiratory tract symptoms, including cough, sore throat, sputum production, hemoptysis, nasal congestion, dyspnea and shortness of breath (Escalera-Antezana et al., 2020; Guan et al., 2020; Wang et al., 2020a; Young et al., 2020; Zhang et al., 2020). COVID-19 patients admitted to intensive care unit have more severe respiratory symptoms. Among 1300 patients with available respiratory support data, 1287 (99%) require respiratory support, and a large part of patients need positive end-expiratory pressure. But there is still a high mortality rate of 26% in intensive care unit (Grasselli et al., 2020). The pathological features of COVID-19 show bilateral diffuse alveolar injury with cellular fibromyxoid exudates. Right lung sample displays obvious desquamation of pneumocytes and hyaline membrane formation, indicating ARDS, whereas, the left shows pulmonary oedema with hyaline membrane formation. And the bilateral lung tissue exhibits obvious inflammatory infiltration in COVID-19 patients (Grasselli et al., 2020). The elderly and people with underlying diseases are susceptible to infection and prone to serious outcomes even death, which may be associated with ARDS. ARDS can induce inflammatory response and cytokine storm following heavily release of proinflammatory cytokines IFN-γ, TNF-α, interleukin and chemokines, which increase organ damage and accelerate the deterioration of the disease status (Guo et al., 2020; Mehta et al., 2020). Magnesium sulfate as a calcium antagonist is commonly used to inhibit bronchial smooth muscle contraction and promote bronchodilation (Hirota et al., 1999; Landon and Young, 1993; Torres et al., 2012). It also decreases inflammatory response and oxidative stress, as well as improves lung inflammation possibly by inhibiting IL-6 pathway, NF-κB pathway, and L-type calcium channels (Güzel et al., 2019; Kao et al., 2011). Therefore, magnesium sulfate has a good application prospect in controlling pulmonary symptoms.

4.2. Prevention of syndromes in reproductive system

As the epidemic spreads, the number of infected pregnant women is also increased. Human coronavirus infection is an important reason of mortality among pregnant women (Alfaraj et al., 2019). The SARS-CoV and MERS-CoV epidemics are especially grave, with about a third of infected pregnant women dying (Alfaraj et al., 2019; Wong et al., 2004). According to the outcomes of pregnant women and neonates reported (D. Chen et al., 2020; Dashraath et al., 2020; Schwartz, 2020; Zaigham and Andersson, 2020), there are no enough exact evidence to rule out the possibility of vertical transmission because of less case existing. Pregnant women and their fetuses are high-risk populations during COVID-19 outbreak, which will cause newborns to be more prone to complications such as fetal distress, premature delivery, respiratory distress and thrombocytopenia (Dashraath et al., 2020; Liu et al., 2020). Pregnant women are at increased risk for more severe clinical symptoms and complications especially in respiratory system due to high metabolic level and high oxygen consumption (Karimi-Zarchi et al., 2020). Unfortunately, there is little experience with SARS-Cov-2 infections at current stage. Many drugs are restricted during pregnancy according to pregnancy drug category of Food and Drug Administration (FDA). Commonly used antiviral drugs ganciclovir, lamivudine, and compound of lopinavir/ritonavir, belong to C category according to the FDA risk classification, which largely limits the use and also makes the treatment of pregnant women more difficult. But magnesium sulfate belonging to B category formulated by FDA, is safe and non-teratogenic. Magnesium

Table 2
Representative clinical trial of magnesium for the treatment of the diseases.

Diseases	Study	Country	Treatment	Dosage	Outcomes/Conclusion
Reproductive system disease	Kreepala et al. (2018)	Thailand	Magnesium sulfate infusion	4 g of magnesium sulfate intravenously, then 1.0, 1.5, and 2.0 g/h of magnesium sulfate, is given based on the obstetric physician's decision of their perception on patient's somatotype, respectively	Magnesium maintenance infusion at 2.0 g/h is capable of preventing seizure by optimizing the therapeutic magnesium level (4.8–8.4 mg/dL) and shortening the hypertensive episode in preeclampsia.
	Masoumeh et al. (2014)	Iran	Magnesium sulfate infusion	4 g of magnesium sulfate dissolved in 100 mL of normal saline solution for 20 min to reach loading dose, then 2 g of magnesium sulfate dissolved in 100 mL of normal saline by infusion/h until 24 h after complete cessation of uterine contractions	Magnesium sulfate increases the active phase of labor up to 77%, and reduces the risk of respiratory distress syndrome significantly, without any adverse pregnancy outcomes.
Neurological diseases	Xu F et al. (2019)	USA	Magnesium sulfate infusion	Intravenous magnesium sulfate (2 g diluted with 50–100 ml of normal saline) is administered over 1–2 h	Intravenous magnesium therapy results in clinically significant pain relief without the need for intramuscular pain medications, and may be useful as a cost-effective first-line parental therapy for status migrainosus, especially for patients who initially present with lower pain intensity.
	Yamamoto et al. (2016)	Japan	Magnesium sulfate infusion	Continuous infusion of magnesium sulfate solution containing 5 mM of $Mg2^{+}$ is performed at 20 ml/h from Day 4 until Day 14 through the cisternal to spinal drainage	Continuous cisternal irrigation with magnesium sulfate solution decreases the occurrence rate of cerebral vasospasm in patients with aneurysmal subarachnoid hemorrhage.
Digestive diseases	Kim et al. (2015)	Korea	Magnesium sulfate infusion	Intravenous magnesium sulfate of 50 mg/kg over 10 min before the start of sedation	Intravenous magnesium sulfate reduces analgesic requirements both during and after endoscopic submucosal dissection for gastric neoplasm without adverse effects.
	Moradian et al. (2017)	Iran	Oral magnesium supplementation	800 mg magnesium oxide (2 tablets each of them containing 240 mg elemental magnesium) daily	Magnesium supplementation improves less atrial fibrillation, nausea, vomiting, and constipation in patients undergoing cardiac surgery.
	Pickering G et al. (2020)	Japan	Oral magnesium supplementation	30 mg/kg magnesium oxide of body weight per day	Magnesium supplementation exhibits significant improvement in defecation frequency and decrease in stool consistency in young children with functional chronic constipation.
Cardiovascular diseases	Osawa et al. (2018)	Australia	Magnesium sulfate infusion	The before period consisted of a single 20 mmol of magnesium sulfate bolus administered over 1 h. The after period comprised a 10 mmol magnesium loading dose over 1 h followed by a continuous infusion at 3 mmol/h for 12 h	Magnesium sulfate bolus achieves a more sustained and reduced the risk of atrial fibrillation after cardiac surgery.
	Banjanin et al. (2018)	Serbia	Oral magnesium oxide supplementation	300 mg of oral magnesium oxide supplementation product for 1 month	Systolic pressure, diastolic pressures, systemic vascular resistance index left cardiac work index are significantly decreased in patients with essential hypertension.
	Cunha et al. (2017)	UK	Oral magnesium supplementation	600 mg of magnesium chelate orally twice a day for 6 months	Magnesium supplementation is associated with better blood pressure control, improves endothelial function and amelioration of subclinical atherosclerosis in thiazide-treated hypertensive women.
Kindey injury	Barbosaet al. (2016)	Brazil	Magnesium infusion	Daily a daily infusion of 48 mEq magnesium diluted in 250 ml narmal saline during 3 days	Magnesium supplementation decreases the incidence of acute kidney injury, and has a significant impact upon hospital mortality even after adjustment for confounders.
	Qka et al. (2019)	Korea	Magnesium sulfate infusion	A mixture of 50 mg/kg of magnesium sulfate in 100 mL isotonic saline is infused over 15 min during the induction of anesthesia, and the infusion rate is adjusted throughout the surgery using the reference rate of 15 mg/kg/h based on the patient's vital signs	Intravenous magnesium sulfate infusion is associated with a reduced risk of postoperative acute kidney injury until postoperative Day 3 for patients who undergo laparoscopic major abdominal surgery.
Diabetes	Derawiet et al. (2018)	Palestine	Oral magnesium supplementation	250 mg/day of elemental magnesium for three months	Magnesium supplementation reduces insulin resistance and improves glycemic control indicators among type 2 diabetes patients.
	Soliman and Nofal (2019)	Egypt	Magnesium sulfate infusion	A continuous infusion of magnesium sulfate (without a loading dose) at 15 mg/kg/h	Magnesium sulfate produces a better-controlled effect on blood sugar level, and decreases the requirement of insulin infusion and minimizes the changes in blood potassium level.
Cancer	Fenning et al. (2018)	UK	Magnesium sulfate infusion	20 mmol intravenous magnesium sulfate in 500 mL normal saline infused at various rates, ranging from 6 to 12 h in a syringe pump	Magnesium sulfate mitigates recurrent symptomatic hypomagnesaemia in advanced ovarian cancer.
	Zhong et al. (2020)	USA	Magnesium supplementation	Magnesium intake at 100 mg/day from diet and supplement is evaluated through a food frequency questionnaire in 1 year	A high magnesium intake is associated with decreased risk of primary liver cancer incidence and mortality in a nonlinear dose-response manner.

(*continued on next page*)

Table 2 (*continued*)

Diseases	Study	Country	Treatment	Dosage	Outcomes/Conclusion
	Wark et al. (2012)	Netherlands	Magnesium supplementation	Dietary 100 mg magnesium intake per day	Higher dietary magnesium is associated with lower risk of colorectal tumors; every 100 mg/day increase in magnesium intake is associated with 13% lower risk of colorectal adenomas and 12% lower risk of colorectal cancer.

Table 3
Data from Center for Systems Science and Engineering (CSSE) at Johns Hopkins University (JHU) by July 30, 2020. (Countries with more than 80,000 confirmed cases).

Country	Accumulated confirmed patients	Number of cured patients discharged	Death toll	Cure rate (%)	Mortality rate (%)
US	4,424,806	1,389,425	150,676	31.401	3.405
Brazil	2,552,265	1,922,802	90,134	75.337	3.532
India	1,531,669	988,029	34,193	64.507	2.232
Russia	827,509	619,204	13,650	74.827	1.650
South Africa	471,123	297,967	7497	63.246	1.591
Mexico	408,449	314,538	45,361	77.008	11.106
Peru	395,005	280,044	18,612	70.896	4.712
Chile	351,575	324,557	9278	92.315	2.639
United Kingdom	303,058	1438	46,046	0.474	15.194
Iran	298,909	259,116	16,343	86.687	5.468
Spain	282,641	150,376	28,441	53.204	10.063
Pakistan	276,288	244,883	5892	88.633	2.133
Saudi Arabia	272,590	228,569	2816	83.851	1.033
Colombia	267,385	136,690	9074	51.121	3.394
Italy	246,776	199,031	35,129	80.652	14.235
Bangladesh	232,194	130,292	3035	56.113	1.307
Turkey	228,924	212,557	5659	92.850	2.472
France	221,077	81,443	30,226	36.839	13.672
Germany	208,546	191,279	9135	91.720	4.380
Argentina	178,996	77,855	3288	43.495	1.837
Iraq	118,300	83,461	4603	70.550	3.891
Canada	117,357	101,992	8962	86.907	7.637
Qatar	110,153	106,849	169	97.001	0.153
Indonesia	104,432	62,138	4975	59.501	4.764
Egypt	93,356	37,025	4728	39.660	5.064
China	87,117	80,591	4658	92.509	5.347
Kazakhstan	86,192	56,638	793	65.711	0.920
Philippines	85,486	26,996	1962	31.579	2.295
Ecuador	83,193	35,572	5623	42.758	6.759

sulfate is a commonly used drug in obstetrics, for its effective prevention and control of preterm labor, gestational hypertension, preeclampsia, and eclampsia with few side effects (Alexander et al., 2006; Damron, 2007; Kreepala et al., 2018; Magee and von Dadelszen, 2018). Besides, magnesium sulfate is utilized for fetal neuroprotection in preterm birth, its maternal administration prior to anticipated preterm delivery decreases cerebral palsy in survivors possibly by the anti-inflammatory action (Bachnas et al., 2019; Kao et al., 2011; Ozen et al., 2020; Rouse et al., 2008). In view of the beneficial effects of magnesium sulfate on pregnancy-induced hypertension, preeclampsia, and eclampsia, we strongly recommend that magnesium sulfate with fetal neuroprotection can be the treatment of choice for pregnant women infected with SARS-CoV-2 timely.

4.3. Control of cardiovascular symptoms

Coronary heart disease and hypertension are common coexisting disorders in COVID-19 patients. In China, a total of 1099 COVID-19 patients, 27 (2.5%) coexist coronary heart disease and 164 (14.9%) coexist hypertension (Guan et al., 2020). In Italy, of 1591 COVID-19 patients admitted to intensive care unit, the number of patients coexisting with hypertension or cardiovascular disease are 509 (49%) and 223 (23%), respectively (Grasselli et al., 2020). A report of 72,314 cases from the China shows that mortality rate is elevated among those with coexisting disorders −10.5% for cardiovascular disease, 6.0% for hypertension, compared with overall case-fatality rate of 2.3% (Wu and McGoogan, 2020). Besides, COVID-19 outbreak leads to severe ventricular dysfunction, even without obvious symptoms and signs of interstitial pneumonia (Escalera-Antezana et al., 2020). Magnesium inhibits smooth muscle contraction and decreases systolic, diastolic and mean arterial blood pressure (Banjanin and Belojevic, 2018; Shimosawa et al., 2004), possibly by the inhibition of calcium release from the sarcoplasmic reticulum, as well as the promotion of the outflow of calcium ion via activating potassium channel (Altura et al., 1987; Ko et al., 2008; Shimosawa et al., 2004; Zhang et al., 1993), or increasing endothelium-derived NO level (Teragawa et al., 2002) and blocking N-type calcium channel to inhibit norepinephrine release (Shimosawa et al., 2004). Magnesium supplementation therapy can lower blood pressure, reduce the risk of atrial fibrillation, ameliorate subclinical atherosclerosis and prevent other various cardiovascular diseases (Banjanin and Belojevic, 2018; Osawa et al., 2018; Shimosawa et al., 2004). These results indicate that while controlling respiratory symptoms, magnesium also takes the control of cardiovascular symptoms in a large number of patients with cardiac complications or comorbidities.

4.4. Improvement of other coexisting disorders

What cannot be ignored is coexisting disorders in COVID-19 patients, mainly including nervous system disease, cardiovascular and cerebrovascular disease, kidney diseases, diabetes, and cancer, corresponding ratio in representative research are summarized in Table 4. Hypertension and diabetes mellitus are the most common diseases in COVID-19 patients (Wang et al., 2020b; Wu et al., 2020b; Zhang et al., 2020; Zhou et al., 2020). Of note, case-fatality rate is increased among COVID-19 patients with preexisting comorbid conditions such as acute kidney injury, diabetes, hypertension, and cancer (Cheng et al., 2020; Wu and McGoogan, 2020). Of 701 COVID-19 patients, 43.9% patients with proteinuria, 26.7% patients with hematuria, and 5.1% patients with acute kidney injury have a significantly higher risk of death in hospital (Cheng et al., 2020). Diabetes is suggested to a risk factor for mortality in patients infected with SARS and MERS-CoV (Alanazi et al., 2020; Yang et al., 2006). Patients with diabetes have an increased risk of developing infection with SARS-CoV-2 (Gupta et al., 2020; Muniyappa and Gubbi, 2020). The mortality rate of COVID-19 patients with diabetes is 7.3%, which is significantly higher than the total mortality rate of 2.3% (Wu and McGoogan, 2020). Magnesium deficiency is found in patients with chronic medical illnesses, including kidney disease, and diabetes (Gröber et al., 2015; Kachhawa et al., 2019; Mather and Levin, 1979; Mauskop and Varughese, 2012). Thus, magnesium deficiency may be one of the reasons for the further deterioration of COVID-19 patient's condition. Magnesium supplementation plays a beneficial role in improving acute kidney injury (Barbosa et al., 2016; Hamroun et al., 2019; Solanki et al., 2015), controlling blood glucose in diabetic patients (Soliman and Nofal, 2019). Therefore, we recommend that serum magnesium level in COVID-19 patients with other coexisting disorders should be monitored. Magnesium supplementation should be given in a timely manner for COVID-19 patients to prevent from worsening and ensure the patients to have good prognosis.

Table 4
Summary of common comorbidities in COVID-19 patients and corresponding ratio in representative research.

Coexisting disorder-No. (%)	Guan W et al., 2020 N = 1099	Giacomo et al., 2020 N = 1591[b]	Zhang J et al., 2020 N = 140	Korean[d],2020 N = 54[e]	Wu C et al., 2020 N = 201	Zhou F et al., 2020 N = 191	Wang D et al., 2020 N = 138	Wang Z et al., 2020 N = 69
Pulmonary disease	12 (1.1) [a]	42 (4) [a]	4 (2.8)	7 (13.0)	5 (2.5)	6 (3.1)	4 (2.9)	6 (8.7)
Nervous system disease	-	-	3 (2.1)	10 (18.5)	7 (3.5)	-	-	-
Cardiovascular and cerebrovascular disease	42 (3.9)	223 (21)	15 (10.7)	32 (59.3)[f]	8 (4.0)	15 (7.9)	27 (19.6)	8 (11.6)
Hypertension	165 (15.0)	509 (49)	42 (30)	-	39 (19.4)	58 (30.4)	43 (31.2)	9 (13.0)
Liver disease	23 (2.1)	28 (3)	8 (5.7)	2 (3.7)	7 (3.5)	-	4 (2.9)	1 (1.5)
Kidney disease	8 (0.7)	36 (3)	2 (1.4)	5 (9.3)	2 (1.0)	2 (1)	4 (2.9)	-
Diabetes	81 (7.3)	180 (17)[c]	17 (12.1)	16 (29.6)	22 (10.9)	36 (18.8)	14 (10.1)	7 (10.1)
Malignancy	10 (9.1)	81 (8)	-	7 (13.0)	1 (0.5)	2 (0.5)	10 (7.2)	4 (5.8)
Other comorbidities	-	393 (38)	-	-	-	-	-	-

NOTE: [a] Chronic obstructive pulmonary disease (COPD); [b] 1591 patients requiring treatment in an intensive care unit (ICU) in Italy; [c] Diabetes, type 2; [d] Korean Society of Infectious Diseases and Korea Centers for Disease Control and Prevention; [e] 54 mortality cases of COVID-19 in the Republic of Korea; [f] including hypertension, other heart disease such as myocardial infarction.

4.5. The dilemma in the treatment

The drugs recommended for COVID-19 therapy are mainly antiviral drugs, such as lopinavir/ritonavir, ribavirin, and chloroquine phosphate, but no specific antiviral drugs have been approved for the treatment of COVID-2019 due to lack of definite clinical evidence (Du and Chen, 2020). Remdesivir as antiviral drug can incorporate into nascent viral RNA chain to inhibit RNA polymerase and stop viral replication eventually (Warren et al., 2016). Recently, a COVID-19 patient in the United States recovers after intravenous injection remdesivir (Holshue et al., 2020). Remdesivir, as compassionate-use currently, is a lack of further evidence to prove the safety and effectiveness. The treatment with lopinavir-ritonavir (400 and 100 mg, respectively) in 99 COVID-19 patients fail to show a significant difference in the time to clinical improvement, compared to standard care comprised supplemental oxygen, noninvasive and invasive ventilation, renal-replacement therapy, antibiotic agents, vasopressor support, or extracorporeal membrane oxygenation as necessary. In the process of treatment, lopinavir and ritonavir are used to treat COVID-19, because of having inhibitory activity against SARS-CoV and MERS-CoV *in vitro* (Chu et al., 2004). However, these antiviral drugs may cause organ damage and other harmful effects (such as dyslipidemia, hepatotoxicity and elevated transaminases) (Benson et al., 2002; Meraviglia et al., 2004; Patel et al., 2018). Magnesium supplements can decrease serum levels of ALP, ALT, AST and GGT, ameliorate liver fibrosis and injury (Eshraghi et al., 2015). Moreover, magnesium supplementation (magnesium gluconate) enhances antioxidant enzyme activity, reduces blood levels of total cholesterol, triglyceride, and low-density lipoprotein cholesterol, and improves dyslipidemia in high-fat diet-fed rats (Zhang et al., 2018). Therefore, reasonable magnesium supplementation may alleviate hepatotoxicity and dyslipidemia induced by lopinavir-ritonavir. The malaria medication chloroquine (or its chemical cousin hydroxychloroquine) is also suggested to treat COVID-19 for reducing viral load in nasal swabs (Gautret et al., 2020), but it might actually do more harm than good due to its cardiac toxicity (Chatre et al., 2018; Yogasundaram et al., 2014) and neuromyotoxicity (Meyerowitz et al., 2020; Stein et al., 2000). Magnesium supplement can prevent various cardiovascular diseases by lowering blood pressure and inhibiting smooth muscle contraction (Eshraghi et al., 2015; Kim et al., 2015), as well as stabilizing cardiac enzymes and metabolic pathways (Romani and Scarpa, 1990). Additionally, magnesium can bind to NMDA receptors competitively as a neuroprotective agent to reduce the neuromyotoxicity of chloroquine (Hou et al., 2020; Miyashita et al., 2012; Saver and Starkman, 2011). These observations indicate that magnesium supplement may alleviate chloroquine-induced cardiac toxicity or neuromyotoxicity.

Taken together, the available clinical data of the above drugs to treat COVID-19 are limited. Their various side effects cannot be ignored, which would accelerate the progression of turning from mild to severe illness, and easily lead to poor clinical outcome, such as organ failure and death. In the special period, all efforts of approved drugs in drug design and clinical trials for COVID-19 therapy are creditable and worthy. As mentioned in this paper, magnesium sulfate can relieve lung symptoms, protect nervous system, improve cardiovascular function, ameliorate liver and kidney injury, and control blood glucose level by the inhibition of inflammation, oxidative stress, and smooth muscle contraction (Gomes et al., 2020; Johnson et al., 2020).

4.6. Safety, clinical recommendation and expected effectiveness of magnesium supplementation for COVID-19 therapy

Generally, magnesium is a necessary cation in the body. Its serum concentration range in healthy adults is approximately 0.75–0.96 mmol/L (Arnaud, 2008). Magnesium sulfate is a cheap, safe and readily available medication in the treatment of several diseases, and its safety window is large enough. However, its megadose therapy is debatable. The most common symptoms of excess magnesium are nausea, vomiting, and diarrhea, the others include hypotension, confusion, slowed heart and respiratory rates, coma, cardiac arrhythmia, deficiency of other minerals, as well as death from cardiac arrest (McGuire et al., 2000; Kontani et al., 2005; Kutsal et al., 2007; Ajib and Childress, 2020). The first warning of imminent toxicity is the loss of knee tendon reflex when magnesium concentration is between 3.5 and 5 mmol/L (Sibai, 1990). Respiratory paralysis occurs between 5 and 6.5 mmol/L (Winkler et al., 1942). Cardiac conduction change occurs above 7.5 mmol/L, and cardiac arrest can be expected when magnesium concentration exceeds 12.5 mmol/L (McCubbin et al., 1981). Clinically, the use of magnesium sulfate is relatively mature. On the other hand, chronically low serum magnesium levels are associated with metabolic syndrome, fasciculation, diabetic and hypertension, etc (Nadler et al., 1995). Therefore, under the premise of monitoring blood pressure, knee tendon reflex, magnesium, other cofactors and modulators, magnesium can be used as an adjuvant drug to treat COVID-19 patients, who occur adverse reactions or have no improvement of conditions after the recommended treatment.

Of note, except magnesium, other metal ions (sodium, potassium, calcium, etc) and anions (phosphate, chloride etc.) are fundamental constitutive cofactors and modulators of endless physiological functions. This includes numerous cellular enzymes, ion channels, transport, motor function, signal transduction, transmission, activation, synthesis and more. A standard physiological concentration level of each cofactor is essential in maintaining normal homeostasis. Any long term imbalance in extracellular, intracellular and/or serum levels of any of these cofactors due to lack of external supply, diseases modulator and/or drug-induced loss or accumulation often is detrimental both in diseases associated and even in normal healthy subjects. Thus, in any critically ill

surgical or diseases patients, it is crucial to address and stabilize cofactor imbalance, and is a prerequisite even before any therapeutic intervention.

Under pathological conditions, more than one electrolyte disorder often occurs. Increasing epidemiological studies have shown that insufficient or excessive electrolyte is closely related to the development of diseases such as hypertension, diabetes, chronic kidney disease, coronary heart disease, and stroke, etc (Adrogué and Madias, 2007; Hill Gallant and Spiegel, 2017; S. C. Palmer et al., 2011). Magnesium deficiency (serum magnesium less than 0.5 mmol/L) can result in multiple symptoms including tremor, poor coordination, muscle spasms, loss of appetite, personality change, and nystagmus (William, 2018). Of note, magnesium ion transport critically depends on the extracellular sodium concentration. High intracellular sodium concentration normally inhibits this ion transport (Tashiro et al., 2005). In fact, low magnesium (hypomagnesemia) is often associated with hypocalcemia and hypokalemia (Krämer and Endemann, 2000; William, 2018). In patients undergoing peritoneal dialysis, 29% of patients with hypokalemia are accompanied by hypomagnesemia (Hamad et al., 2019). Thiazide diuretic therapy is the first-line treatment of hypertension, which often causes hypokalemia, and 40% of patients are accompanied by hypomagnesemia (Krämer and Endemann, 2000). And when hypomagnesemia coexists, it is usually difficult to compensate for hypokalemia (Whang et al., 1992). A study shows that 93% of severe and critically ill COVID-19 patients have hypokalemia, which may be due to continuous renal potassium loss caused by ACE2 degradation, however, the change in magnesium concentration was not monitored in this study (H. Chen et al., 2020). Thus, hypocalcemia or hypokalemia occurs, clinicians should be alert for the occurrence of hypomagnesemia. When magnesium deficiency is detected, it should be supplemented according to the actual clinical situation to prevent serious incidents. We estimate that, in patients with moderate and severe COVID-19, most of them accompany hypomagnesemia.

Recent studies have suggested that serum magnesium level of critically ill patients deserves attention (Bani et al., 2020; Browne et al., 2020; Iotti et al., 2020)]. Hypomagnesemia is common in all hospitalized patients, especially in critically ill patients with coexisting electrolyte abnormalities (Hansen and Bruserud, 2018). In a study on the clinical management of Ebola virus disease in the United States and Europe, 90% of patients had hypomagnesemia before admission, and almost all patients received electrolyte supplementation therapy (Uyeki et al., 2016). A clinical trial of allogeneic human dental pulp stem cells for the treatment of patients with severe COVID-19 included magnesium concentration in the indicators of liver and kidney function tests (Ye et al., 2020). Moreover, some studies have mentioned that trace elements including magnesium, vitamins and other nutrients play an important and complementary role in supporting the immune system and combating COVID-19 (Calder et al., 2020; Wallace, 2020).

Together all, we gave our clinical recommendations on the administration method of magnesium supplementation. According to the 2015–2020 Edition of the Dietary Guidelines for Americans, we recommend daily oral magnesium supplementation 310–320 mg or 400–420 mg for COVID-19 adult women or men patients with mild symptoms, respectively, especially in patients with mild magnesium deficiency (serum magnesium concentration range from 0.5 to 0.75 mmol/L). For children, oral magnesium supplement needs to be reduced referring to the guide for details (Ayuk and Gittoes, 2014; Institute of Medicine Committee to Review Dietary Reference Intakes for Vitamin and Calcium, 2011). For COVID-19 patients with respiratory symptoms such as mild breathing difficulties, we speculate orally receiving 340 mg daily (twice a day) of magnesium supplementation (Kazaks et al., 2010) for adults, and 150 mg nebulised magnesium supplementation treatment for children (Powell et al., 2012; Wongwaree and Daengsuwan, 2019), which may have a good effect on relieving lung inflammation response and oxidative stress, as well as inhibiting bronchial smooth muscle contraction and promoting bronchodilation. SARS-CoV-2 infection during pregnancy is associated with an increased risk of preterm delivery (Browne et al., 2020). Thus, for pregnant women with COVID-19, magnesium sulfate maintenance infusion at 2.0 g/h is capable of preventing seizure by optimizing the therapeutic magnesium level (4.8–8.4 mg/dL) and shortening the hypertensive episode in preeclampsia (Kreepala et al., 2018). When uterine contraction occurs, it can be solved by intravenous fluid hydration and intravenous magnesium sulfate for uterine contraction (4 g intravenous bolus and 2 g/h) (Browne et al., 2020). COVID-19 presents high risk to elderly individuals and causes devastating morbidity and mortality, while mainly induces mild to moderate symptoms in younger individuals (Akbar and Gilroy, 2020; Applegate and Ouslander, 2020). A cohort study shows that the combined oral treatment of combination magnesium (150 mg daily), vitamin D (1000 IU daily) and vitamin B12 (500 mcg daily) significantly reduces the proportion of older COVID-19 patients with clinical deterioration requiring oxygen support and/or intensive care support (Tan et al., 2020). Actually, magnesium sulfate-extended infusion could be an adjunctive treatment for complicated COVID-19 infected critically ill patients (Bani et al., 2020).

Magnesium has a wide range of effects, and supplementation effectively prevents the development of the disorders or diseases within the safe blood concentration range. Accordingly, we believe that, under the premise of reasonable use and detection of serum magnesium concentration as well as control of fundamental constitutive cofactors and modulators, timely supplementation of magnesium will benefit COVID-19 patients, with few side effects occurrences. Of course, in the special period of COVID-19 outbreak, more clinical evidences are needed in the future research whether magnesium sulfate combined with other recommended treatment drugs is more beneficial to the COVID-19 patient's condition.

5. Outlook

The COVID-19 epidemic with a relatively high mortality rate is still spreading quickly, and has brought great challenge to the world. It is very important to implement effective treatment programs actively. Magnesium supplementation protects organs and tissues from damage through multiple mechanisms including anti-inflammation, anti-oxidation, immune-regulation. It is worth noting that magnesium sulfate can be a drug of choice in supportive treatment of COVID-19 especially critically ill patients with promising crucial beneficial medical effects (Bani et al., 2020). The evidence from this review preliminarily supports the expected efficacy of magnesium supplementation in the prevention and treatment of COVID-19 patients, especially pregnant women, as well as subjects with hypertension and diabetes. Therefore, magnesium supplementation is expected to play an active role in clinical practice in the prevention and treatment of COVID-19. However, more clinical studies are necessary to provide true representation of beneficial role of magnesium in light of other essential physiologically linked cofactors in COVID-19 and non-COVID-19 state.

Author's contributions

L.K provided writing ideas of this article. L.K and C.T built the framework. C.T and H. D were responsible for data collection and collation. C.T and L.K were responsible for article writing. C.T, H. D and R.J organized the figures, tables and the format of this paper. L.K and X. W viewed the manuscript. L.K approves final version of manuscript.

CRediT authorship contribution statement

Chuan-Feng Tang: Methodology, Formal analysis, Investigation, Data curation, Writing - original draft, Investigation. **Hong Ding:** Formal analysis, Data curation, Writing - original draft, Investigation. **Rui-Qing Jiao:** Methodology, Data curation. **Xing-Xin Wu:** Writing - review & editing. **Ling-Dong Kong:** Conceptualization, Writing - review

& editing, Supervision, Project administration, Funding acquisition.

Declaration of competing interest

The authors declare no conflict of interest.

Acknowledgement

This paper was supported by grants from the Grants from National Key R&D Program of China (2019YFC1711000) and Special Funding for Emergency Research on COVID-19 in Nanjing University (No. 020814380135).

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