

## REVIEW ARTICLE

# Long COVID: The roles of magnesium and angiotensin-converting enzyme 2

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## Abstract

The functions of magnesium (Mg) and angiotensin-converting enzyme 2 (ACE2) in lowering blood pressure are well known; however, their roles in long COVID (LC) remain unclear. This review proposes a hypothetical model that mechanistically links symptoms of LC to: (i) deficiencies in essential ACE2-dependent neutral amino acids, including tryptophan and methionine; (ii) altered Mg-dependent one-carbon metabolism; (iii) altered Mg-dependent autophagy; and (iv) altered Mg-dependent mechanistic target of rapamycin (mTOR) signaling, potentially modulated by rapamycin. Mg and vitamin D deficiency are linked to LC. All forms of vitamin D, including its cutaneous precursor, are Mg-dependent. Accordingly, Mg is proposed as an essential factor in the prevention and/or attenuation of LC. The SARS-CoV-2 virus targets ACE2-expressing cells, leading to the downregulation of ACE2 function. ACE2 and sodium-dependent neutral amino acid transporter are required for the absorption of tryptophan, methionine, and branched-chain amino acids, all of which are low in LC. Loss of ACE2 negatively impacts the Mg-dependent serotonin pathway, the Mg-dependent indole pathway, and the methionine-dependent one-carbon metabolism. Autophagy and mTOR kinase are Mg-dependent. Additionally, individuals carrying the methylenetetrahydrofolate reductase 677T allele—which is prevalent in many populations—may exhibit further impairment in one-carbon metabolism. Gut dysbiosis, present in almost 75% of long haulers, may enable *Candida* overgrowth. Candidalysin has been shown to upregulate mTOR and inhibit autophagy, similar to mechanisms employed by several viruses, including SARS-CoV-2, and may contribute to chronic fatigue. Although numerous linkages are outlined, this mechanistic model is hypothetical, and causal relationships require validation through clinical studies.

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## 1. Introduction

Long COVID (LC) remains poorly understood, characterized by a wide range of seemingly unrelated symptoms. Given the ongoing massive, global, economic, and personal impact of LC, a half-decade of research into etiology and therapeutic solutions has surprisingly found limited success. No unifying theory has yet emerged; however, the gut may provide important clues. Cellular invasion by the SARS-CoV-2

virus disrupts angiotensin-converting enzyme 2 (ACE2) function.<sup>1</sup> Enterocytes are rich in ACE2, and long haulers report persistent mucosal SARS-CoV-2 spike (S) protein. Magnesium (Mg) is recognized as a central player in the vast majority of known human metabolic functions.<sup>2</sup> Mg deficiency (MgD) is also global, and many experts in the field point to outdated lower limits for laboratory reference ranges.

## 2. Angiotensin-converting enzyme 2, sodium-dependent neutral amino acid transporter, and mechanistic target of rapamycin

Persistent spike (S) protein has been detected in the intestinal mucosa of many long haulers.<sup>3</sup> Via its spike (S) protein, SARS-CoV-2 enters ACE2-bearing cells, compromising ACE2 function. ACE2 interacts with the sodium-dependent neutral amino acid transporter (B<sup>0</sup>AT1) to facilitate the cellular entry of non-polar or neutral amino acids.<sup>4,5</sup> Any decrease in ACE2 function corresponds to a decrease in B<sup>0</sup>AT1 function. B<sup>0</sup>AT1, encoded by *SLC6A19*, is the primary transporter for transcellular absorption of tryptophan, methionine, and branched-chain amino acids, such as leucine, isoleucine, and valine.<sup>6-8</sup> Branched-chain amino acids are critical to immune function,<sup>9</sup> muscle repair, and provision of energy during exercise.<sup>10</sup> These deficiencies are associated with LC symptoms, such as fatigue, muscle atrophy,<sup>11</sup> and impaired immune function.<sup>12</sup> Long haulers are deficient in branched-chain amino acids.<sup>13</sup>

The mechanistic target of rapamycin (mTOR) has been called “the brain of the cell.” It is an Mg-dependent kinase that, when activated (in an anabolic state), regulates cell growth, proliferation, and metabolism, and suppresses autophagy. Autophagy involves recycling “intracellular debris,” suppressing cancer cells, and eliminating pathogens. This Mg-dependent kinase (mTOR) is suppressed under conditions of nutrient deprivation, such as essential amino acid deficiency. In a catabolic state, Mg-dependent autophagy is correspondingly upregulated. However, adenosine monophosphate-activated protein kinase, another Mg-dependent kinase, suppresses mTOR during energy stress (i.e., low cellular adenosine triphosphate)<sup>14</sup> and upregulates autophagy.<sup>15</sup> Mg enhances mTOR activity, while rapamycin suppresses mTOR activity. Paradoxically, both have been associated with longevity.<sup>16,17</sup> They both stimulate autophagy<sup>15,18</sup> and may exert complementary effects.<sup>19</sup> Both may hold therapeutic potential for individuals with LC (Figure 1).<sup>20,21</sup>

Since rapamycin induces a relative catabolic state, there is concern for sarcopenia in the elderly.<sup>15</sup> However, Mg may

help avert this, especially in the elderly, who are not only more likely to be Mg-deficient but also more likely to have increased mTOR activity and autophagy suppression.<sup>22</sup> In short, there is a delicate, complex balance among multiple Mg-dependent kinases that dynamically determine optimal mTOR activity, which depends on nutritional status, energy needs, the inflammatory state, and age.<sup>15</sup>

Magnesium deficiency and mTOR hyperactivity compromise autophagy, enabling the spread of pathogens. Viruses have evolved mechanisms to avoid autophagy. *Candida albicans* has likewise evolved and can deploy candidalysin to upregulate mTOR and inhibit autophagy.<sup>23</sup> SARS-CoV-2 may persist in individuals with MgD due to ineffective autophagy and may further manipulate intracellular mTOR via hyperactivation to suppress autophagy.<sup>22</sup>

Angiotensin-converting enzyme and B<sup>0</sup>AT1 promote anabolic signaling by mTOR,<sup>24</sup> which downregulates autophagy and upregulates intestinal antimicrobial peptides, microbiome homeostasis, and intestinal barrier integrity.<sup>24</sup> Low tryptophan downregulates mTOR activation.<sup>25</sup> This reduction may result from impaired absorption due to disruption of the ACE2/B<sup>0</sup>AT1 partnership or from increased indoleamine dioxygenase (IDO)-mediated catabolism of tryptophan (Figure 2).<sup>26</sup> Accordingly, early downregulation of mTOR signaling in LC may reflect low tryptophan levels.<sup>25</sup> However, in later or chronic stages of LC, mTOR signaling may become dysregulated and relatively hyperactivated in the context of persistent systemic inflammation, profound fatigue, and post-exertional myalgia.<sup>27</sup>

In contrast, persistence of intracellular virus may directly trigger hyperactivation of mTOR,<sup>27</sup> a mechanism distinct from the disrupted ACE2/B<sup>0</sup>AT1 pathway for tryptophan absorption.<sup>27</sup> This hyperactivation of mTOR suppresses autophagy, thereby protecting the virus. This overactivation of mTOR is also linked to type 2 diabetes mellitus,<sup>28</sup> hypertension,<sup>27</sup> LC,<sup>29</sup> chronic fatigue syndrome,<sup>30</sup> and post-acute infection syndrome.<sup>27</sup> Respiratory syncytial virus and coronaviruses upregulate mTOR,<sup>31</sup> similar to the influenza virus,<sup>32</sup> hepatitis B virus,<sup>33</sup> Epstein-Barr virus (EBV),<sup>34</sup> Zika virus,<sup>35</sup> cytomegalovirus,<sup>36</sup> herpes simplex,<sup>37</sup> human immunodeficiency virus,<sup>38</sup> and Lyme disease.<sup>39</sup> Many of these are linked with chronic fatigue. Not surprisingly, mTOR activity is directly linked to mitochondrial dysfunction.<sup>40</sup> Mg is a mitochondrial antioxidant, and MgD disrupts mitochondrial function on many levels.<sup>41</sup> Hyperactivation of Mg-dependent mTOR may consume Mg and eventually exhaust existing stores, further disabling autophagy. These linkages are hypothetical and do not establish causation.

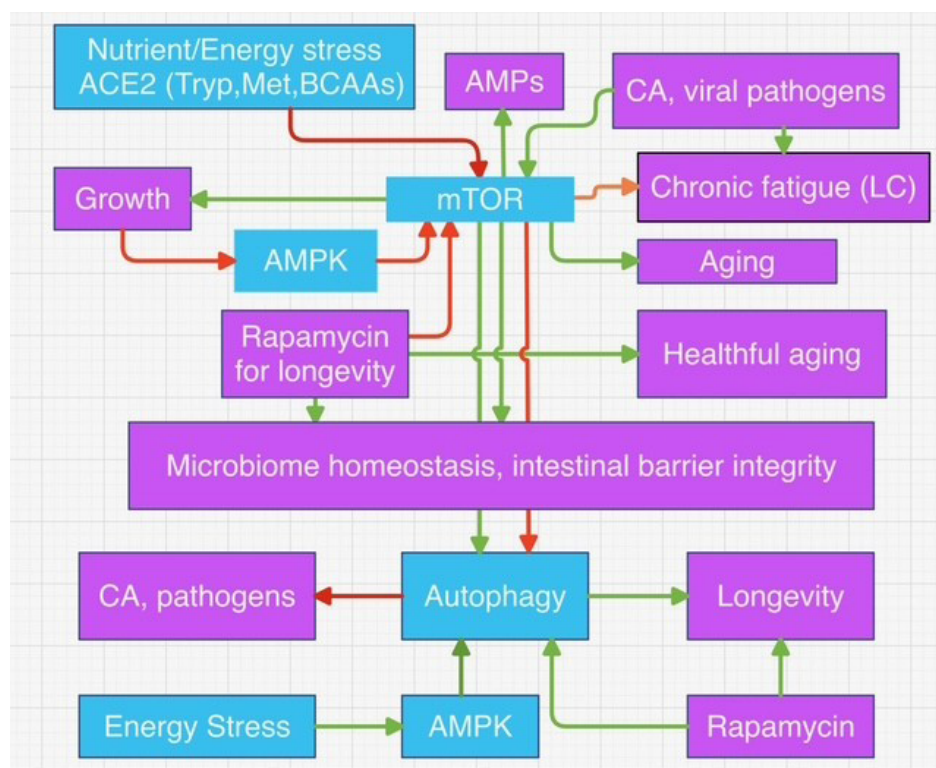


**Figure 1.** Role of magnesium (Mg) and rapamycin in longevity. Adenosine monophosphate-activated protein kinase (AMPK) and mechanistic target of rapamycin (mTOR) are Mg-dependent kinases. Blue boxes denote Mg-dependent pathways. Tryptophan (Tryp), methionine (Met), and branched-chain amino acids (BCAAs) are neutral essential amino acids. Green arrows indicate activation, red arrows indicate inhibition, and orange arrows denote hyperactivation. The central node is mTOR, illustrated in its “Goldilocks” zone (green arrows up and down). Mg deficiency and loss of angiotensin-converting enzyme 2 (ACE2) (nutrient stress) suppress Mg-dependent mTOR and Mg-dependent autophagy (which are otherwise promoted). Cancer (CA) and intracellular pathogens promote hyperactivity of mTOR and suppress autophagy (promoting their replication). With aging, mTOR regulation becomes impaired, leading to persistent suppression of autophagy and contributing to non-lethal cellular senescence, as reflected in phenotypes such as hair graying and skin wrinkling. Image created using Flowchart Designer 3 (<https://lightgraphics.ltd/flowchart3/index.html>). Abbreviation: AMP: Antimicrobial peptide.

*Candida* overgrowth can also activate mTOR with a negative impact on CD8<sup>+</sup> T cell function.<sup>42</sup> Rapamycin, an mTOR inhibitor,<sup>43</sup> is reportedly beneficial in LC, and clinical trials evaluating its efficacy are currently ongoing. As an inducer of autophagy, rapamycin has been studied for potential anticancer effects and may also exhibit antifungal activity, including against *Candida* species.<sup>44,45</sup> Rapamycin may also help offset some of the detrimental consequences associated with dysregulated mTOR signaling under conditions of low mTOR activity, including gut microbiome homeostasis<sup>46</sup> and intestinal barrier integrity.<sup>47</sup> Rapamycin may not only inhibit mTOR hyperactivation but also, as an inducer of autophagy, limit *Candida* overgrowth and thereby indirectly influence IDO-mediated tryptophan metabolism. Such effects may, in turn, modulate IDO-mediated immunosuppressive signaling.<sup>26</sup> The physiology of mTOR is complex, and IDO may represent an important interacting component within this network.

### 3. Long COVID and tryptophan metabolism

The gut microbiota do not require ACE2 or B<sup>0</sup>AT1 to access luminal tryptophan. Supplemental tryptophan and nicotinamide improve symptoms in ACE2 knockout mice and may rebalance the gut microbiome and upregulate antimicrobial peptides in the apical mucus layer.<sup>48</sup> Most, if not all, microbial tryptophan metabolites, i.e., indole derivatives that promote longevity, require Mg-dependent activated B vitamins, especially B2, B3, B5, B6, and some Mg-dependent cytochrome P450 enzymes. These reduce intestinal permeability and alleviate inflammation (Figure 2).<sup>49</sup> In the host, tryptophan-dependent nicotinamide adenine dinucleotide helps slow cognitive decline (Figure 2).<sup>50</sup>

Recent research in long haulers reported low levels of tryptophan, but no increments were observed in the kynurenine pathway metabolites (Figure 3), suggesting that the kynurenine to tryptophan ratio (K/T) elevation in long

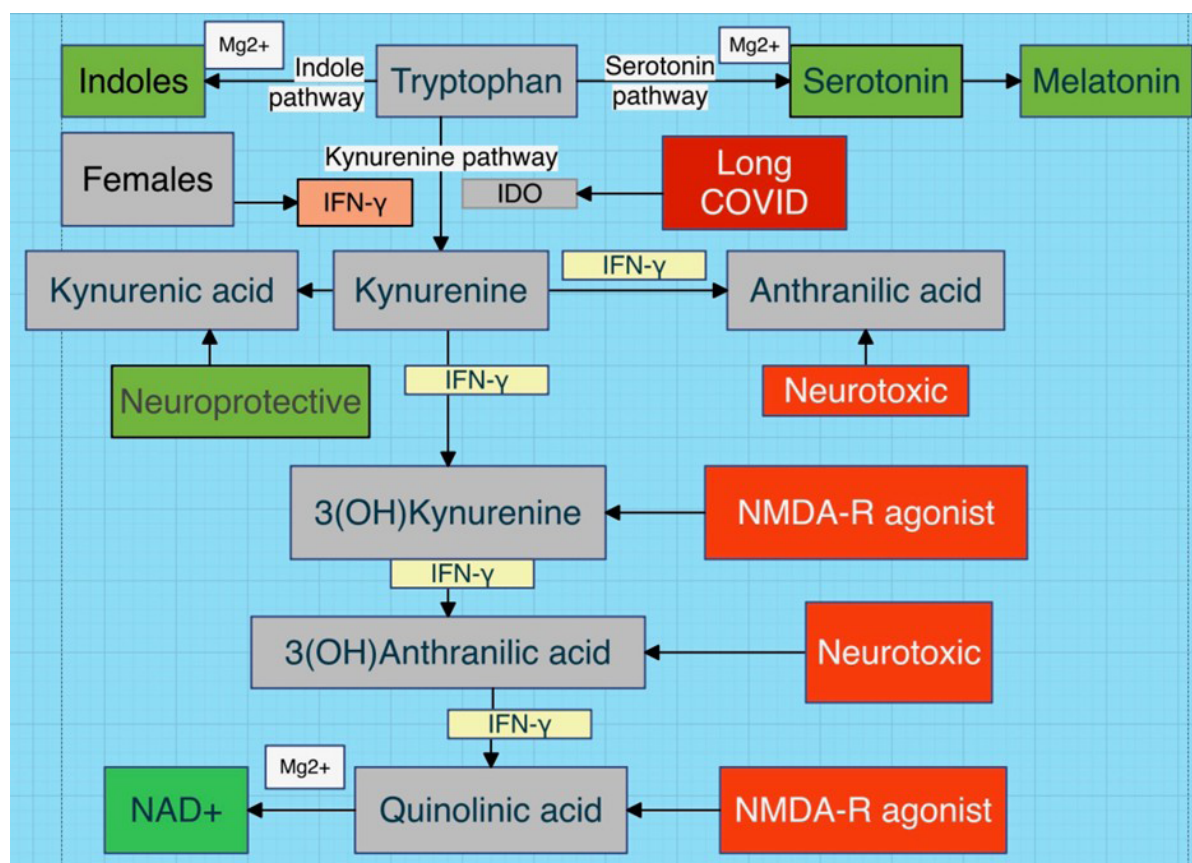


**Figure 2.** Role of magnesium ions ( $Mg^{2+}$ ) in all three tryptophan metabolism pathways. Elevated indoleamine dioxygenase (IDO) and interferon gamma ( $IFN-\gamma$ ) characterize long COVID (LC) and *Candida* overgrowth. Mg deficiency downregulates nicotinamide adenine dinucleotide ( $NAD^+$ ) production, the serotonin pathway, and the microbial indole pathway, linked to longevity. Image created using Flowchart Designer 3 (<https://lightgraphics.ltd/flowchart3/index.html>).

Abbreviation: NMDA-R: N-methyl-D-aspartate receptor.

hauliers may be due more to low tryptophan than elevated kynurenines.<sup>51</sup> However, if elevation of K/T persists and kynurenine pathway metabolites increase, long-term risks for cancer, autoimmune disease, cardiovascular disease, dementia, and obesity would also increase.<sup>52</sup> Low tryptophan is negatively linked to cardiovascular disease,<sup>53</sup> dementia,<sup>54</sup> chronic fatigue syndrome, fibromyalgia,<sup>55</sup> and cancer risk,<sup>56</sup> while elevated kynurenine metabolites have been implicated in similar conditions. LC has been reported to be associated with increased IDO<sup>57</sup> and interferon gamma activity (Figures 1 and 2).<sup>58</sup> Similar immune-metabolic alterations have also been described in the context of *Candida* overgrowth.<sup>59,60</sup> These overlapping immunometabolic features may be relevant to the observed sex differences in LC prevalence.

#### 4. Serotonin

Two 2025 studies<sup>61</sup> reported a link between LC and increased galanin, a neuropeptide, and increased alpha-

amino-3-hydroxy-5-methylisoxazole-4-propionic acid receptor (AMPA) density. One study revealed increased galanin system activation and insulin resistance in the majority of long hauliers.<sup>61</sup> Galanin, via its receptor GR1, is a potent inhibitor of serotonergic neurotransmission,<sup>62-64</sup> while GR2 promotes serotonergic neurotransmission.<sup>65</sup> A substantial proportion of individuals with LC responded well to selective serotonin reuptake inhibitors,<sup>66</sup> which have also been proposed as potentially preventive or modulatory agents in LC.<sup>67</sup> Mg enhances serotonin receptor function and promotes serotonin signaling.<sup>68</sup>

Insulin resistance is inversely linked to  $Mg^{69}$  and may contribute to altered metabolic signaling. It has also been linked to increased galanin expression in the context of elevated fasting blood glucose.<sup>70</sup> Insulin resistance is a primary determinant of chronic fatigue in LC.<sup>71</sup> Moreover, obesity increases galanin<sup>72</sup> and is a common feature of long hauliers.<sup>73</sup> Galanin in obese women may exceed that observed in non-obese men and women, and is reported

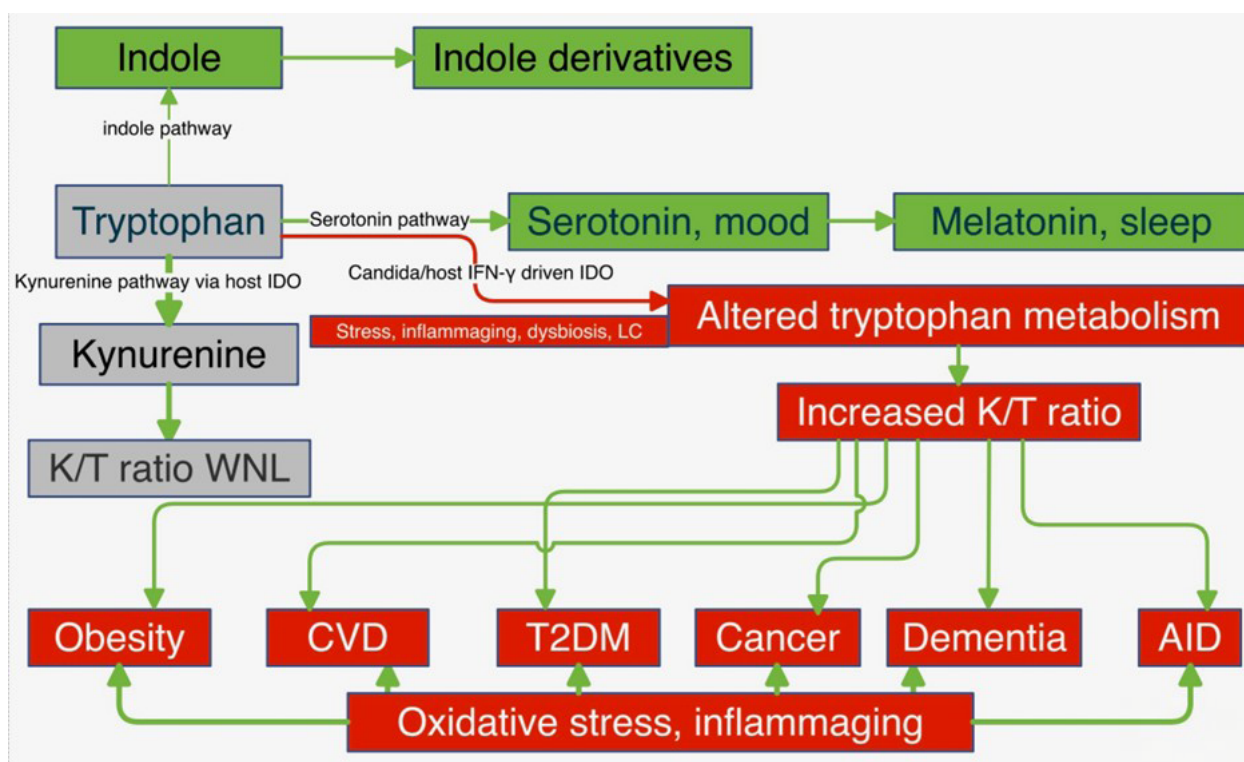


**Figure 3.** The three pathways available for tryptophan metabolism. Red arrows/boxes indicate inhibition or negative effects; green arrows/boxes indicate activation or positive effects. Image created using Flowchart Designer 3 (<https://lightgraphics.ltd/flowchart3/index.html>). Abbreviations: AID: Autoimmune disease; CVD: Cardiovascular disease; IDO: Indoleamine dioxygenase; IFN: Interferon; K/T: Kynurenine to tryptophan; LC: Long COVID; T2DM: Type 2 diabetes mellitus; WNL: Within normal limits.

to be higher in premenopausal women,<sup>74</sup> who are more susceptible to LC. Surprisingly, galanin (and tryptophan<sup>59</sup>) suppresses hyphal morphogenesis in *Candida albicans*, and *Candida* overgrowth can upregulate galanin production.<sup>75</sup>

A recent study by Japanese researchers revealed that AMPAR density is directly linked to cognitive impairment in LC.<sup>76</sup> The ratio of AMPARs to N-methyl-D-aspartate receptors is very high in the dorsal raphe nucleus,<sup>77</sup> the brain's major serotonin-producing center, suggesting that serotonin depletion may increase AMPAR levels.<sup>78</sup>

## 5. Long COVID and one-carbon metabolism

Methionine is critical to one-carbon metabolism, which in turn affects methylation (Figure 3). Methylation is dependent on Mg, zinc, and some B vitamins, all of which require Mg-dependent phosphorylation (B1,2,3,5,6,7) or methylation (B9, 12) for activation.

Abnormal methylation has been proposed as central to many LC symptoms, such as fatigue, memory complaints, and sleep disturbance.<sup>79</sup> A reduction in methionine could also compromise one-carbon metabolism (Figure 4). Furthermore, methionine synthase connects the folate and methionine cycles (Figure 4). Acetaldehyde produced by

*Candida albicans* generates reactive oxygen species that can compromise B12, a cofactor required for methionine synthase.

Homocysteine levels, which are associated with cognitive decline, were found to be persistently elevated following COVID-19 infection.<sup>80</sup> Elevated levels are also associated with the *MTHFR* 677T variant,<sup>81</sup> which is common among Americans. The *MTHFR* 677T variant has been associated with COVID-19 susceptibility<sup>82</sup> and severity.<sup>83</sup> In addition, homocysteine levels—which are influenced by *MTHFR* activity—have been implicated across COVID-19 infection, severe COVID-19, and LC. Deficiencies of Mg-dependent B9 and B12 aggravate this linkage, which predisposes to LC.<sup>84,85</sup>

Transmembrane serine protease 2 is a key facilitator for SARS-CoV-2 entry and disease progression. Mg has been reported to induce differential DNA methylation of *TMPRSS2* genes, thereby preventing viral entry.<sup>86</sup> This is particularly relevant in the context of LC, where a tendency toward global DNA hypermethylation has been reported.<sup>87,88</sup> Hypermethylation and hyperhomocysteinemia, associated with skeletal muscle dysfunction and fatigue,<sup>89</sup> may be mechanistically linked. Increased methylation activity

may reflect greater reliance on the betaine–homocysteine methyltransferase pathway (Figure 4),<sup>90</sup> which serves as an alternative to the main folate-dependent pathway when methylenetetrahydrofolate reductase function is impaired. Elevated homocysteine may further drive flux through this pathway. This betaine homocysteine methyltransferase pathway is also linked to multiple sclerosis,<sup>91</sup> a condition that has been reported to share clinical and mechanistic features with LC, particularly in the context of low vitamin D (VD) status.<sup>92</sup> Hyperhomocysteinemia can, in turn, increase K/T (Figure 3).<sup>93</sup> However, these linkages are hypothetical and do not establish causality.

## 6. Microbial and host determinants of long COVID

Gut dysbiosis is an imbalance in the gut microbiome that may arise from frequent antibiotic use or a poor diet. Periodontitis, a marker of gut dysbiosis, may increase the risk of LC,<sup>94</sup> a risk that is aggravated by MgD,<sup>95</sup> leading to *Candida* overgrowth. *Candida albicans* produces its own IDO,<sup>59</sup> which degrades tryptophan and may create an optimal environment for LC progression. Tryptophan also inhibits hyphal morphogenesis,<sup>59</sup> and reduced absorption should favor *Candida*'s role as a pathobiont. Candidalysin hyperactivates mTOR and suppresses autophagy.<sup>23</sup> The hypothesis that *Candida* overgrowth may contribute to the etiology of chronic fatigue syndrome has been proposed for over three decades.<sup>96</sup> Indeed, it may re-emerge as a co-conspirator with SARS-CoV-2 in LC.<sup>97,98</sup> Alcohol and refined carbohydrates are known to promote the growth of the commensal fungus *Candida albicans*. It has been hypothesized that *Candida* overgrowth may play an intermediary role in modulating galanin levels. In addition, *Candida* may sequester intestinal Mg<sup>2+</sup>, potentially further compromising Mg absorption in already deficient states.<sup>99</sup>

Over 60% of those who recover from COVID-19 have persistent gastrointestinal symptoms.<sup>100</sup> Small intestinal mucosa is rich in ACE2 receptors, and many long haulers report the presence of mucosal spike (S) protein.<sup>101</sup> Persistent fecal viral RNA shedding<sup>102</sup> has been associated with gut dysbiosis, which has been reported in up to 75% of individuals with LC.<sup>103</sup> Dysbiosis may contribute to increased intestinal permeability and subsequent translocation of microbial products, potentially promoting systemic inflammation and elevated autoimmune risk. In addition, the LC-associated microbiome is characterized by a shortage of butyrate-producing bacteria.<sup>104</sup>

Persistent circulating spike protein has also been reported in LC.<sup>105</sup> One proposed mechanism involves infection of ACE2-expressing CD8<sup>+</sup> T cells, in which spike-dependent, ACE2-mediated signaling may facilitate

immune escape.<sup>106</sup> The role of EBV reactivation in COVID-19 remains unclear, with ongoing debate as to whether it is incidental or contributory.<sup>107</sup> Individuals with LC have been reported to have high EBV titers.<sup>108</sup> Although EBV invades B lymphocytes, the primary immune response to EBV is a striking proliferation of EBV-specific CD8<sup>+</sup> T cells.<sup>109</sup> In long haulers, the presence of spike (S) protein in CD8<sup>+</sup> T cells may herald reactivation of EBV.<sup>110</sup> Mg is essential for CD8<sup>+</sup> T cell signaling, augmenting T cell activation and function.<sup>111</sup> In addition, CD8<sup>+</sup> T cells play a role in controlling *Candida* overgrowth and inhibiting hyphal morphogenesis.<sup>112</sup>

Estrogen can promote CD8<sup>+</sup> T cell dysfunction and exhaustion.<sup>113</sup> Recent research on over 12,000 individuals has underscored the gender predilection for LC.<sup>114</sup> Interferon gamma is considered the most potent IDO-activating cytokine,<sup>115</sup> which drives the increase in K/T (Figure 2). Females have been reported to exhibit stronger interferon gamma responses, which play important roles in host defense and pro-inflammatory signaling.<sup>116</sup> However, when sustained, elevated interferon gamma activity may dysregulate the innate immune response by reducing the alternative complement response to *Candida* overgrowth.<sup>117</sup>

## 7. Long COVID and magnesium

Long COVID represents a sustained pro-inflammatory state,<sup>118</sup> and the spike protein of SARS-CoV-2 is the primary mechanism underlying its pathogenesis.<sup>3</sup> VD is widely regarded as essential to overall health, particularly for preventing LC. Mg is essential for VD metabolism (Figure 5).<sup>119–121</sup> MgD is an inflammatory agent<sup>122–124</sup> and is particularly linked to deterioration in brain health.<sup>125</sup> SARS-CoV-2 invasion triggers ACE2-mediated activation of nuclear factor kappa B, which increases the levels of tumor necrosis factor alpha, interleukin (IL)-1 $\beta$ , IL-6, and high-sensitivity C-reactive protein.<sup>126</sup> Mg supplementation has been shown to decrease circulating levels of high-sensitivity C-reactive protein, tumor necrosis factor alpha, and IL-6.<sup>95</sup> Moreover, Mg is vital for immune regulation and helps downregulate chronic inflammation, infectious diseases, and cancer.<sup>127</sup>

About 60% of adults do not achieve the average dietary intake for Mg, and 45% of Americans are MgD.<sup>2</sup> However, the true burden may be underestimated. A typical laboratory reference range for serum magnesium is 0.75–0.95 mmol/L (1.8–2.3 mg/dL), yet individuals within the lower half of this range have been associated with increased risks of insulin resistance,<sup>128</sup> migraines, premenstrual syndrome, and depression.<sup>129,130</sup> This condition, previously termed normo-magnesemic MgD, is now known as chronic latent

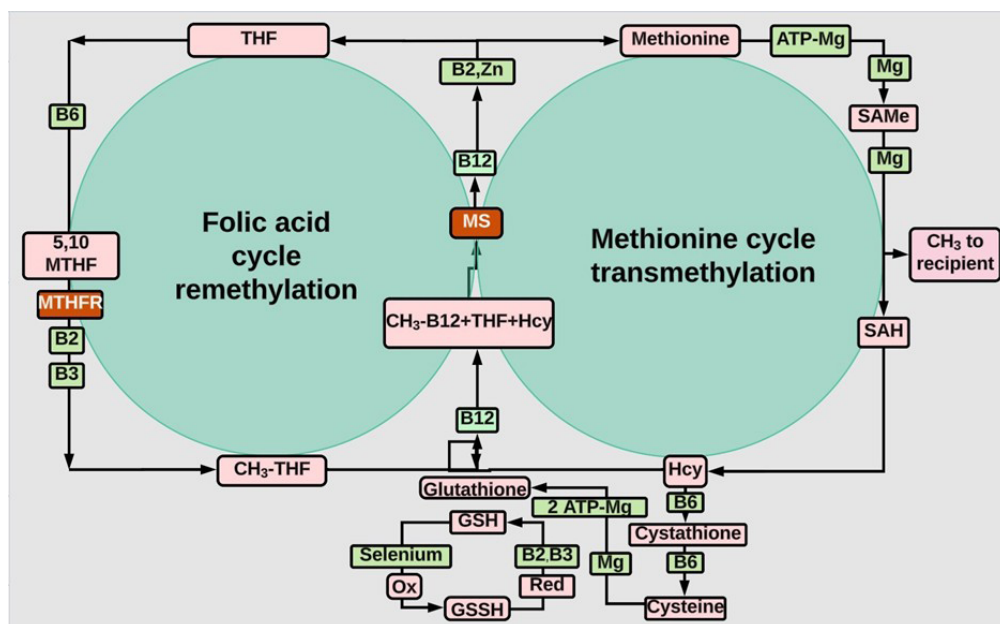


**Figure 4.** Role of magnesium (Mg) in the folate and methionine cycles. Enzymes and cofactors are depicted in green, while substrates are depicted in pink. Image created using Lucidchart (<https://www.lucidchart.com/pages>).

Abbreviations: ATP: Adenosine triphosphate; BHMT: Betaine homocysteine methyltransferase; DMG: Dimethylglycine; GNMT: Glycine-N-methyltransferase; GSH: Reduced glutathione; GSSH: Oxidized glutathione; Hcy: Homocysteine; MS: Methionine synthase; MTHF: Methyltetrahydrofolate; SAH: S-adenosylhomocysteine; SHMT: Serine hydroxymethyltransferase; THF: Tetrahydrofolate; TMG: Trimethylglycine (aka betaine); ZN: Zinc.

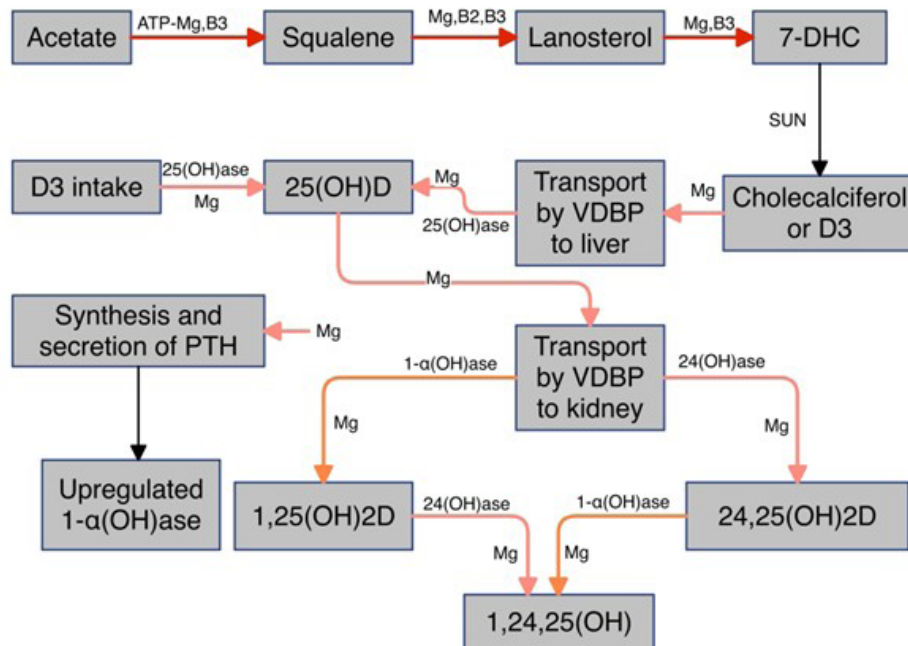


**Figure 5.** Role of magnesium (Mg) across the three forms of vitamin D (VD). All enzymatic steps involved in the conversion of VD3 to its active form, 1,25-dihydroxyvitamin D3 (1,25[OH]<sub>2</sub>D<sub>3</sub>), including vitamin D binding protein interaction, parathormone (PTH) synthesis, and PTH secretion, are Mg-dependent. Many enzymes and cofactors involved in the synthesis of 7-dehydrocholesterol (7-DHC) from acetate are also Mg-dependent. Image using Flowchart Designer 3 (<https://lightgraphics.ltd/flowchart3/>).

Abbreviations: ATP: Adenosine triphosphate; VDBP: Vitamin D-binding protein.

MgD. Calcium competes with Mg for the same receptors, and a dietary intake ratio of approximately 2:1 (Ca:Mg) has traditionally been recommended.<sup>131</sup> However, data from the National Health and Nutrition Examination Survey indicate that the average intake ratio in the United States has exceeded 3:1 since 2000.<sup>132</sup>

Magnesium is required for multiple steps in VD metabolism, including processes related to 7-dehydrocholesterol, the substrate for cutaneous VD<sub>3</sub> synthesis, as well as the conversion to 25-hydroxyvitamin D (25[OH]D) and its activation to 1,25-dihydroxyvitamin D (1,25[OH]<sub>2</sub>D). Deficiencies in both VD and Mg have been associated with increased symptom severity in LC (Figure 5).<sup>119</sup>

Furthermore, Mg is critical for the synthesis and secretion of parathyroid hormone (PTH).<sup>121</sup> MgD can therefore contribute to refractory hypocalcemia. Although this phenomenon is most clearly observed when serum Mg approaches 0.5 mmol/L, one must also consider the effect of MgD (0.5–0.75 mmol/L) on intestinal absorption and renal tubular reabsorption. These processes involve the calcium-sensing receptor and the transient receptor potential melastatin 7 channels. The calcium-sensing receptor is a Mg-dependent G-protein-coupled receptor, whereas the transient receptor potential melastatin 7 channel functions via the adenosine triphosphate–Mg complex. Together, these pathways suggest a graded spectrum of Mg-related dysregulation rather than a strict threshold effect.

Vitamin D also increases serotonin by repressing serotonin reuptake and degradation.<sup>133</sup> In addition to the synthesis of VD, Mg facilitates the activation of all eight B vitamins, vitamins A, E, and K, all cytochrome P450 enzymes,<sup>129</sup> and all ATP-dependent reactions. Over 80% of known metabolic functions are Mg-dependent.<sup>2</sup>

This raises two practical questions: how to assess Ca:Mg balance, and how to correct potential imbalances. The French physiologist, founder of the International Society for Research on Magnesium in 1971, recommended a 2:1 Ca:Mg intake by weight.<sup>131</sup> Under steady-state conditions, dietary intake may loosely relate to physiological ionized Ca:Mg (unbound forms) in mmol/L. Interactions between elements occur through both molar and electrochemical mechanisms.

When applying laboratory reference ranges for serum Mg, the ratio of ionized to total Mg approximates 70% at both the lower and upper limits. However, for calcium, the ionized fractions are close to 50% at both the lower and upper limits. When expressed in molar terms (calcium  $\approx$  40 mg/mol; Mg  $\approx$  24 mg/mol) and considering physiologically

active (ionized) fractions, these values broadly align with the historically proposed dietary Ca:Mg intake ratio of approximately 2:1, using mean serum concentrations (calcium: 8.5–10.5 mg/dL; Mg: 1.8–2.2 mg/dL).

If red blood cell Mg is assumed to be approximately 6.0 mg/dL,<sup>134</sup> which is about three times the mean serum Mg, then extrapolations from total body distributions of calcium and Mg in whole blood ( $\sim$ 5 L) suggest a dietary intake ratio closer to 3:2 in healthy adults. This assumes equivalent absorption rates, which are highly dependent on VD levels (Figure 5).

A joint American/Chinese study recommended a balanced Ca:Mg ratio of 1.7–2.63 (weight-to-weight),<sup>135</sup> with increased risks of morbidity and mortality outside this range. This is especially important for COVID-19, where reported Ca:Mg ratios were higher among hospitalized patients, higher still in intensive care unit patients (4–5), and highest among non-survivors ( $>5$ ).<sup>136</sup> The implications for LC should not be underestimated.

When Ca:Mg is elevated, and VD is considered sufficient (over 30 ng/mL), calcium intake should be reduced before increasing Mg intake. A 2018 study showed that when Ca:Mg intake exceeds 3.5 and 25(OH)D exceeds 30 ng/mL, increasing Mg intake may suppress VD. At 30 ng/mL, the additional Mg may further suppress PTH and VD (Figure 6).<sup>137</sup>

As previously discussed, many are familiar with the physiologic needs and role of Mg in optimal health, suggesting that the lower limit of the laboratory reference range for serum magnesium be raised from 0.75 mg/dL to 0.85 mg/dL. If the Ca:Mg is then recalculated, the optimal range reduces from 1.7–2.6 to 1.7–2.3, bracketing Durlach's recommendation of 2:1 Ca:Mg intake (weight-to-weight). The slope of the upper line in Figure 6 would be much flatter, and the area of optimal Ca:Mg balance would be smaller. To directly link the two balanced ratio ranges, i.e., Ca:Mg weight-to-weight and ionized Ca:Mg mmol to mmol, one must assume equivalent absorption. With VD deficiency, calcium absorption may drop to 10–15%, whereas Mg absorption is approximately equivalent to 35% when 25(OH)D<sub>3</sub> is about 30 ng/mL. In summary, Mg is a calcium channel blocker; Ca and Mg both compete for the same receptors, such as transient receptor potential melastatin 7 and calcium-sensing receptor (both are Mg-dependent). PTH secretion is likewise regulated by both calcium and Mg, with calcium serving as the primary physiological driver and Mg modulating this response. Accordingly, the physiological effects of calcium, Mg, and VD are interdependent and cannot be meaningfully evaluated in isolation.

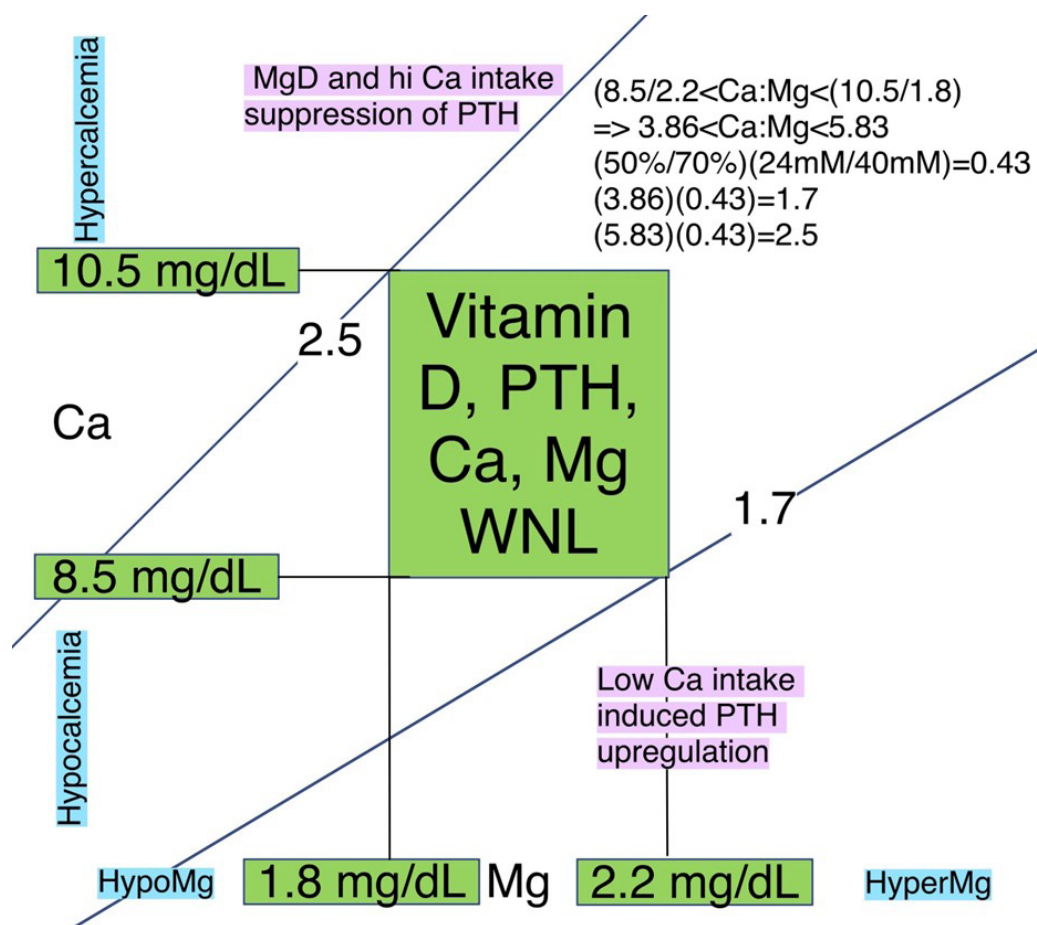


**Figure 6.** The interlinkage of calcium (Ca) and magnesium (Mg). It is an approximation based on specific laboratory reference ranges (derived from healthy adults) that may differ slightly by region. Lines represent the upper and lower limits of a balanced serum Ca:Mg, where  $1.7 < \text{Ca:Mg} < 2.5$ . Mean Ca:Mg on a Western diet (hypercalcemia) has been over 3:1 since 2000.<sup>132,138</sup> Image created using Flowchart Designer 3 (<https://lightgraphics.ltd/flowchart3/index.html>).

Abbreviations: PTH: Parathormone; WNL: Within normal limits.

## 8. Conclusion

Numerous studies have hypothesized that the pathogenesis of LC involves dysfunction of the ACE2/B<sup>0</sup>AT1 axis, leading to reduced tryptophan absorption.<sup>139-141</sup> Others have proposed hyperactivation of mTOR and suppression of autophagy. The proposed hypothesis combines and expands on these to include:

- (i) ACE2/B<sup>0</sup>AT1-mediated reductions in the availability of tryptophan and other essential neutral amino acids, e.g., methionine.
- (ii) the biochemical impact of methionine deficiency on one-carbon metabolism.
- (iii) the physiologic impact of reduced tryptophan availability, causing underactivation of mTOR, reduced antimicrobial peptide production, and increased intestinal permeability.
- (iv) the underactivation of mTOR and the upregulation of

Mg-dependent autophagy during nutrient stress, i.e., low essential neutral amino acids.

- (v) the deleterious impact of persistent intracellular SARS-CoV-2 directly causing overactivation of mTOR, independent of ACE2/B<sup>0</sup>AT1, which may be potentially modulated by rapamycin.
- (vi) the importance of Mg in maintaining Ca:Mg balance and modulating susceptibility to LC.
- (vii) the central role of Mg in one-carbon metabolism, tryptophan metabolism, mTOR function and signaling, autophagy, and VD synthesis.
- (viii) the possibility that gut dysbiosis in LC may enable *Candida* overgrowth, with candidalysin contributing to mTOR upregulation.<sup>23,94</sup>

Symptoms of LC vary significantly across patients. This may be due to the widely disparate predisposing factors that affect its pathogenesis, including persistent spike S load in enterocytes, MgD, VD deficiency, ACE2/

B<sup>0</sup>AT1-mediated neutral amino acid deficiencies, the 677T *MTHFR* variant, and estrogen-induced gut dysbiosis. Many studies examining serotonin levels and the efficacy of selective serotonin reuptake inhibitors in long haulers address this proposed ACE2/B<sup>0</sup>AT1-mediated mechanism. In conclusion, deficiencies of Mg and Mg-dependent VD not only further exacerbate LC but also compromise general health.

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## Conflict of interest

The author declares he has no competing interests.

## Author contributions

This is a single-authored article.

## Ethics approval and consent to participate

Not applicable.

## Consent for publication

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## Availability of data

Not applicable.

## Further disclosure

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