Magnesium Switch Key of COVID.19 Morbidity , Mortality and Treatment

Book · August 2021

CITATIONS
0

READS
210

1 author:

Mosab Nouraldein Mohammed Hamad
Elsheikh Abdallah Elbadri University
560 PUBLICATIONS **167** CITATIONS

SEE PROFILE

These findings support the hypothesis of influence of Cadmium and Lead in mutation of Influenza virus and emergence of novel corona virus COVID 19, as exposure to Cd leads to disturbances in Mg metabolism in the organism, while Mg supplementation has an adverse effect on Cd absorption, accumulation and toxicity. According to the available results, which indicate a protective role of Mg against Cd toxicity, comprehensive observations suggest that exposure to Cd and Pb mixtures produces more pronounced effects compared to the response observed after exposure to single metal solutions. A study showed that the potential protective effect of influenza vaccination in SARS-CoV-2-positive patients against adverse outcomes of COVID 19. Significant findings favoring influenza vaccination mitigating the risks of sepsis, stroke, deep vein thrombosis (DVT), emergency department (ED) & Intensive Care Unit (ICU) admissions suggest a potential protective effect that could benefit populations without readily available access to SARS-CoV-2 vaccination.

Mosab Nouraldein Mohammed Hamad, BSC(honors), MSC, MRSB.
Head of Research Unit, Banoon Fertility Center, Khartoum, Sudan.
Head of Medical Parasitology Phylum, Medical Laboratory Department, Faculty of Health Sciences, Elsheikh Abdallah Elbadri University, Berber, Sudan.

9 7 8 6 1 3 6 6 1 6 8 8 9

Mosab Nouraldein Mohammed Hamad

Magnesium Switch Key of COVID 19 Morbidity, Mortality and Treatment

LAP LAMBERT Academic Publishing

Mosab Nouraldein Mohammed Hamad

Magnesium Switch Key of COVID 19 Morbidity, Mortality and Treatment

Mosab Nouraldein Mohammed Hamad

Magnesium Switch Key of COVID 19 Morbidity, Mortality and Treatment

LAP LAMBERT Academic Publishing

Imprint

Cover image: www.ingimage.com

Publisher:
LAP LAMBERT Academic Publishing
is a trademark of
Dodo Books Indian Ocean Ltd., member of the OmniScriptum S.R.L Publishing group
str. A.Russo 15, of. 61, Chisinau-2068, Republic of Moldova Europe
Printed at: see last page
ISBN: 978-613-6-61688-9

Magnesium Switch Key of COVID.19 Morbidity , Mortality and Treatment

Mosab Nouraldein Mohammed Hamad

Research Unit, Banoon Fertility Center , Khartoum , Sudan

Faculty of Health Sciences , Elsheikh Abdallah Elbadri University, Berber, Sudan

August,2021

List of content

Dedication :

To the soul of my father
To my Mother
To my sisters
To my wife and my kids
To the soul of my teacher:
Dr. Ahmed Mohammed Abdelhalim

Acknowledgement:

I am grateful to my friend Yasir Ibrahim for support and encouragement during my research and study about the COVID.19 pandemic.

Introduction

Magnesium is the eighth most widespread element in the layer of the Earth. The most abundant source of biologically accessible magnesium, though, is the hydrosphere (i.e. oceans and rivers). In the sea, the concentration of magnesium is ~55 mmol/L and in the Dead Sea—as an extreme example—the concentration is documented to be 198 mmol/L magnesium. Magnesium salts easily dissolved in water and are much more soluble than the respective calcium salts. As a result, magnesium is readily obtainable to organisms. It plays a significant role in vegetation and animals alike. In plants, magnesium is the vital ion of chlorophyll. In vertebrates, magnesium is the fourth most abundant cation and is essential, especially within cells, being the second most frequent intracellular cation after potassium, with both these elements being fundamental for numerous physiological tasks.

It is a Group 2 (alkaline earth) element within the periodic table and has a relative atomic mass of 24.305 Da, a specific gravity at 20°C of 1.738, a melting point of 648.8°C and a boiling point of 1090°C. In the dissolved state, magnesium binds hydration water tighter than calcium, potassium and sodium. Thus, the hydrated magnesium cation is hard to dehydrate. Its radius is ~400 times larger than its dehydrated radius. This difference between the hydrated and the dehydrated state is much more prominent than in sodium (~25-fold), calcium (~25-fold) or potassium (4-fold). Consequently, the ionic radius of dehydrated magnesium is small but biologically relevant. This simple fact explains a lot of magnesium's peculiarities, including its often antagonistic behavior to calcium, despite similar chemical reactivity and charge. For instance, it is almost impossible for magnesium to pass through narrow channels in biological membranes that can be readily traversed by calcium because magnesium, unlike calcium, cannot be easily stripped of its hydration shell. Steric constraints for magnesium transporters are also far greater than for any other cation transport system.

The body of most animals contains ~0.4 g magnesium/kgThe total magnesium content of the human body is reported to be ~20 mmol/kg of fat-free tissue. In other words, total magnesium in the average 70 kg adult with 20% (w/w) fat is ~1000 to 1120 mmol. In comparison, the body content of calcium is ~1000 g (i.e. 42 times

greater than the body content of magnesium) . About 99% of total body magnesium is located in bone, muscles and non-muscular soft tissue [1].

Magnesium (Mg^{2+}) has several functions in the human body. It acts as a cofactor for more than 300 enzymes, regulating a number of fundamental functions such as muscle contraction, neuromuscular conduction, glycemic control, myocardial contraction, and blood pressure. Moreover, magnesium also plays a vital role in energy production, active transmembrane transport for other ions, synthesis of nuclear materials, and bone development [2].

Magnesium metabolism

As an essential mineral the amount of magnesium within an organisms must be continuously regulated and distribution to single cells must be guaranteed. The medicinal use of magnesium in the form of magnesium rich mineral waters, goes back into ancient times but it was in the 17th century, when magnesium sulphate was discovered to be the cathartic agent in mineral water (Epsom salt). The essentiality of magnesium to animals was first described by Leroy (1926). The first description of clinical depletion in humans was published 1934. In the 1950th magnesium deficiency was described for various pathological conditions in humans and from then on the importance of magnesium in physiological processes and medicine has gained widespread attention. The functions and regulation of magnesium in living cells, however, have been discovered only within the last few decades as new analytical techniques became available .

In spite of the importance of magnesium to various physiological and biochemical processes there is no indication that magnesium homeostasis is under specific tight hormonal control. The usual need could be relatively simply fulfilled by absorption from the gut, distribution of the needed amounts to the cells and excretion of the surplus by the kidney.

About 90% of magnesium is bound and only 10% free. The intracellular free magnesium concentration is about 0.5 mmol/l. Intracellular magnesium is mainly bound to nucleic acids, ATP, negatively charged phospholipids and proteins. According to the distribution of binding sites within the cell the highest magnesium content is found in microsomes containing ribosomes and endoplasmic reticulum, followed by mitochondria and nuclei.

Absorption–secretion:

Intestinal absorption of magnesium in humans takes place primarily in the ileum and jejunum, whereas in some monogastric animals also the colon and caecum maycontribute to magnesium uptake; In man the absorbed amount of magnesium is nearly linear proportional to the magnesium intake, only at low dietary intakes increased fractional absorption was observed. In healthy men consuming a usual

western diet a fractional magnesium absorption of 0.44 has been determined with stable isotopes.

Generally, magnesium is absorbed as an ion; there is no indication of either a directly coupled transport of magnesium with the uptake of other nutrients or of significant absorption of magnesium complexes. Magnesium ions are absorbed by passive and active uptake mechanisms, which seem not to be under hormonal control.

The major part of magnesium is absorbed across the paracellular route, determined by the electrochemical gradient and by solvent drag . Saturable transcellular uptake mechanisms have also been detected which may account for the higher fractional absorption rate at low dietary magnesium intakes. Uptake into brush border cells may be mediated by a magnesium/anion complex; efflux of magnesium across the basolateral membrane may involve sodium/magnesium antiport systems. A gene has been identified that is involved in human magnesium deficiency states and is expressed in intestine and kidney. The gene product encodes for a protein that combines calcium- and magnesium-permeable cation channel properties with protein kinase activity, which might be involved in magnesium absorption.

There are various nutrients that might interact with magnesium absorption. A high fiber diet reduces magnesium absorption by binding of magnesium to phytate. There are some interactions between magnesium and calcium but at dietary intake levels no significant effects of calcium on magnesium absorption was detected. The ability of phosphate to bind magnesium may explain the decreased magnesium absorption in persons on high phosphate diets.

High magnesium content of foods is not connected with any adverse health effects and does not pose any hazard to man. Use of oral magnesium supplements is generally safe and the no-observed-adverse-effects level was considered to be 250 mg for supplemental magnesium. Higher doses of magnesium might induce diarrhea due to the water binding of the non-absorbed part of the administered dose.

After absorption from the gut, magnesium is transported to the tissues where it is taken up only in the case of a magnesium need. Magnesium is taken up into cells until the normal intracellular ionized magnesium concentration is achieved. Intracellular magnesium losses occur, when bound magnesium is released (ATP breakdown, acidosis) leading to an increased intracellular free magnesium concentration, which is normalized by magnesium efflux via a Naþ/Mg2þ antiport system. The intracellular magnesium concentration is subjected to intense regulation, as so many intracellular

systems would be influenced by significant changes of the intracellular concentration that no targeted effect could be achieved.

This is the reason why magnesium cannot work as intracellular second messenger, but may work as a facilitating agent slightly changing the direction of metabolism with only small changes in intracellular concentration.

The kidney excretes any surplus of magnesium in plasma. About 70% of total serum magnesium is ultrafiltrated through the glomerular membrane. Only 10–15% of the filtered magnesium is reabsorbed in the proximal tubule, whereas the major part (60–70%) is reabsorbed in the cortical thick ascending limb of the loop of Henle and another 10–15% in the distal convoluted tubule. In the cortical thick ascending limb of the loop of Henle magnesium is reabsorbed by a paracellular mechanism involving paracellin-1. It could be demonstrated that a mutation of this protein is responsible for the excessive magnesium wasting in patients with hypomagnesaemia/hypercalciuria syndrome.

In the distal convoluted segment magnesium is absorbed by an active transcellular mechanism. This absorption is under the control of special divalent cation sensing receptors; elevated plasma magnesium concentrations inhibit reabsorption of magnesium from the distal convoluted tubule, leading to an increased loss of magnesium from the body . To the current knowledge, this system seems to be the main regulator of the total excretion of magnesium as there is little magnesium reabsorption beyond the distal tubule.

Elevation of plasma magnesium concentration leads to activation of the divalent cation sensing receptor on the peritubular side of the cells of the distal tubule. Activation of this receptor reduces response to hormones such as parathyroid hormone, calcitonin, glucagon and arginine vasopressin on the hormone mediated magnesium uptake into the cells of the distal tubule. Subsequently less magnesium is transported through the cells leading to an increased urinary magnesium excretion.

The main part of body magnesium is located in bone. Part of this magnesium—adsorbed to the surface—is in equilibrium with the extracellular magnesium. At reduced plasma concentrations magnesium can be rapidly released from the bone surface and at increased plasma concentrations magnesium is bound to the surface. In a kinetic model of magnesium metabolism in healthy men based on investigations with the stable isotopes 25Mg and 26Mg it has been determined that 24% of the human total magnesium exchanges rapidly; of this 79% turns over in 115 h,

representing probably the bone surface pool and the remaining part—which may represent serum and easily accessible extracellular space—in less than 9 h. In growing animals magnesium deficiency induced a loss of bone magnesium with few days. Bone magnesium, therefore, represents a magnesium reservoir that buffers extracellular magnesium concentration. In humans this magnesium buffering capacity is reduced with increasing age as over lifetime nearly half of the magnesium content of bone is lost. This might be explained by slight changes in acid–base balance at increasing age. Due to a reduced ability to excrete acid together with an increased nutritional acid load a general loss of minerals from the skeleton occurs with increasing age. The usual amount of magnesium in the diet seems not to be high enough to avoid this magnesium loss from the bones that are also accompanied by calcium losses and reduced bone mineral density. This might be of importance for the development of osteoporosis. Animal experiments and human studies showed a positive effects of supplementing magnesium on bone density and bone absorption parameters.

The normal range of plasma magnesium concentration is 0.75–1 mmol/l. Supplying low dietary amounts of magnesium can induce magnesium deficiency in animals and humans. In growing rats very low plasma magnesium concentrations occur within few days after feeding a magnesium deficient diet. In adult humans, however, low plasma magnesium concentrations are observed only after prolonged ingestion of food with low magnesium content. The risk of magnesium deficiency in children, however, might be higher. Low serum magnesium concentrations have been detected in a high percentage of children in central Europe. The plasma magnesium concentration is kept constant over longer periods of time even at reduced magnesium intake by decreasing the renal magnesium excretion and by release of magnesium bound to bones. During experimental magnesium depletion in humans, magnesium in the urine decreases to very low levels within 3–4 days with only small changes in plasma magnesium concentration. A magnesium concentration below the reference range is expression of a marked magnesium deficiency, a plasma magnesium concentration within the reference range, however, does not exclude a suboptimal magnesium supply as intracellular magnesium might have been released shortly before blood sampling or due to a slight acidosis magnesium had been released from bone surface: both conditions artificially increase circulating magnesium content. Generally, hypomagnesaemia may arise from various disorders of the gastrointestinal tract

leading to reduced magnesium absorption or from conditions that affect renal handling of magnesium. In humans severe magnesium deficiency has been observed in families with rare genetic disorders.

The symptoms of magnesium deficiency are variable and associated with nonspecific clinical signs. Very often neuromuscular hyperexcitability, cardiac arrhythmias, increased muscle tension, muscle cramps, increased stress susceptibility, and headaches are observed but also paresthesias, irritability, decreased attention span, mental confusion and dizziness might occur.

The main effects of magnesium deficiency are caused by changes in extracellular magnesium concentrations due to direct membrane effects of magnesium and magnesium/ calcium interactions.

Because of the magnesium buffering capacity of bone and the regulation of magnesium excretion by the kidney a considerable reduction of plasma magnesium can be avoided over prolonged periods. However, additional losses of magnesium or renal effects of certain drugs may lead to overt magnesium deficiency in already depleted subject.

Magnesium control Sodium and Potassium balance

Both sodium and potassium are minerals essential to regulate the body's water balance and maintain healthy bones, nerves and muscle function. The function together to regulate healthy cell signaling in the body. potassium is an anion (a negatively charged ion), because having more electrons than protons makes it carry a negative charge.

Sodium is the opposite; it's known as a cation because it has more protons than electrons and carries a positive charge. A healthy level of potassium inside of the cells and sodium outside the cells, is necessary for proper cell signaling in the nervous system.

Magnesium's role in the balance of sodium and potassium is as an intermediary. Potassium can't cross the cell membrane on its own, and needs magnesium to move across the cell membrane.

Once the cell membrane is open, the cell can absorb all of the potassium it needs to function properly. This process of achieving sodium and potassium balance accounts for 20 to 40 percent of the resting energy the body uses [4].

Magnesium deficiency is always followed by a disturbed electrolyte homeostasis. it causes a lot of deficiency symptoms according to its many-fold relations in the organism and should be considered in many diseases and clinical situations, sufficient magnesium supply is important for maintaining the concentration gradients and the electric potential at the Cell and stabilizes electrolyte homeostasis, it is able to restore the ionic and electric imbalance by reactivating the sodium/potassium pump and by reducing the calcium overload and it is indispensable for potassium substitution and for compensation of a refractory potassium deficiency [5].

Disturbed electrolyte homeostasis known at:

i. Coronary heart disease
ii. Traumatic and surgical events
iii. Dysrhythmias
iv. Postoperative period
v. Angina pectoris

vi. ECC: open heart surgery
vii. Acute myocardial infarction
viii. Burns
ix. Heart valve disease
x. Distress
xi. Hypertension
xii. Latent tetany
xiii. Congestive heart failure
xiv. Cramp in the leg
xv. Diuretic therapy
xvi. Diabetes mellitus
xvii. Digitalis therapy
xviii. Pregnancy
xix. Cardiac arrest
xx. Hormonal dysregulation
xxi. Intensive care
xxii. Alcoholism.

Effects of Lead and Cadmium in Magnesium

The results obtained up to now indicate that increased intake of some heavy metals causes disorder of bioelements metabolism leading to their blood and organs decrease and higher elimination via the urine. As to lead and magnesium, investigations indicated that the reaction is reversible and that increased intake of Mg eliminates Pb via urine. Cadmium lead to statistically significant decrease of blood Mg ($p < 0.001$ after day 16) which was associated with increased Mg elimination via urine ($p < 0.01$). Statistically significant changes were not detected in the tissues, except in the liver where we found enhanced Mg content ($p < 0.05$), while its level in the muscles decreased ($p < 0.01$) [6].

Cadmium is a hormone-disrupting heavy metal that's all-too-common in our modern environment. acquire it from cigarette smoke, water, fertilizers, air pollution, fish, coffee, plastics, and some yellow coloring agents. It has been linked to low progesterone and prolactin levels and lowers testosterone in men.

The nasty thing about cadmium is that one of the places it is stored is the pituitary gland – the master gland that signals to your thyroid, adrenals and ovaries. Because of this cadmium can affect thyroid function and interrupt signalling to the ovaries. Cadmium blocks but also mimics estrogen, which causes fertility problems in both sexes. It also interferes with estrogen. It blocks the binding of estradiol to the ER-alpha estrogen receptor. So even if you are producing enough estradiol, cadmium interferes in it actually acting upon your cells correctly. Cadmium also lowers testosterone production in males, contributing to infertility.

Most concerning is the fact that Cadmium causes more cancers than all the other heavy metals combined. Cadmium increases the risk of prostate cancer, breast cancer and many other types of cancers.

The most common and concentrated source of cadmium is cigarette smoke. Tobacco plants are especially good at absorbing cadmium from the soil, and smoking tobacco releases cadmium directly into the bloodstream. This is the main reason smokers have much higher rates of cancer.

Lead impairs sex hormone production, interfering with menstrual cycles in women, promoting inferility and damaging testicular function in men. Lead can cause period irregularity by lowering progesterone and prolactin production.

High levels of lead reduce estrogen, testosterone and cortisol production. These imbalances can all lead to irregular periods and infertility.

Lead is water-soluble and will readily leach into tap water, which is a big problem for the U.S. Occasionally, lead piping will contaminate the water supply, especially as the country's water infrastructure gets older.

Due to decades of use of leaded gasoline and it's continued use in developing countries, lead persists in the air, soils and water, leaching into our food supply and supplements [7].

Cadmium has been listed as one of the 126 priority pollutants and a category I carcinogen. Carcinogenic effects of cadmium on the lungs, testicles, and prostate are widely recognized, but there has been insufficient research on the effect of cadmium on the thyroid gland. Cadmium has the affinity to accumulate not only in the liver, kidneys, and pancreas but also in the thyroid gland. It has been established that cadmium blood concentration correlates positively with its accumulation in the thyroid gland. Women of fertile age have higher cadmium blood and urine concentrations than men. In spite of its redox inertia, cadmium brings about oxidative stress and damage to the tissue by indirect mechanisms. Mitochondria are considered to be the main intracellular targets for cadmium [8].

Studies suggest that cadmium is associated with several clinical complications, such as renal dysfunction and bone disease, but also some cancers. With

regards to thyroid health, one study showed a positive association between cadmium exposure and thyroid hormones in adults. Another study showed that taking selenium and zinc may have a synergistic role against cadmium-induced thyroid dysfunction . Also there is some evidence that lead exposure can lead to depressed thyroid hormone levels. However, some other studies show no relationship between lead exposure and thyroid health. It is possible that the amount of lead can play a role on how it affects thyroid health.

It's important to understand that while the amount of exposure to a specific heavy metal, or any other toxin, can be important, this isn't the only factor to consider. In other words, different people experience different reactions to certain toxins. For example, someone who is exposed to a small amount of mercury might have a negative reaction, thus triggering an autoimmune response. On the other hand, another person who has a high level of mercury in their tissues might not have any problems. The company Cyrex Labs has a test called the Chemical Immune Reactivity Screen, which helps to identify immune responses to chemicals bound to human proteins. So while most tests detect the levels of toxins, this tests measures the actual immune response to certain toxins [9].

It is becoming a well-known fact that environmental exposure to toxic metals and chemicals can damage the immune system and other cells in the body, leading to dozens of different disorders and symptoms, including autoimmunity.

25% of Americans have some form of heavy metal poisoning, including mercury, lead, arsenic, cadmium, aluminum and nickel. These metal toxins change the chemical structure of DNA and RNA.

Studies have shown that metals such as mercury, cadmium and lead have been associated with the development of the autoimmune diseases scleroderma, lupus, autoimmune hepatitis, multiple sclerosis, Hashimoto's thyroiditis, Graves disease, rheumatoid arthritis, lupus, pernicious anemia, chronic fatigue syndrome, fibromyalgia, and type 1 diabetes [10].

Metal toxicity is a condition in which there is an elevated level of essential minerals or heavy metals in the body. Essential minerals include calcium, potassium, magnesium, manganese, selenium, zinc, copper, molybdenum iron, phosphorus, chromium, vanadium. and boron. Metals classified as heavy metals are lead, arsenic, cadmium, mercury, aluminum, uranium, strontium, and thallium.

Problems which exist with essential minerals can exist in ratios of essential minerals to each other such as copper to zinc, calcium to magnesium, sodium to magnesium, sodium to potassium and calcium to phosphorus. Some toxicity is due to specific disease processes, and others are due to excessive exposure or intake of the mineral. Manganese can be too low or toxic if too high. Problems arise when a specific mineral which needs to be in an exact ratio to another becomes in excess creating imbalances leading to toxicity issues and unwanted symptoms [11]. COVID-19 severity is associated with lower serum concentrations of sodium, potassium and calcium [12]. Researchers say people with high levels of the heavy metal cadmium may also have higher odds of severe disease during the pandemic [13].

According to Dr. Dean , the magnesium content in the modern diet has sunk by about 60%. One hundred years ago , people consumed an average of 500mg of magnesium daily. That number is now about 200mg due to soil erosion and the use of synthetic chemical fertilizers [14] (mostly contain lead and cadmium). Naturally composted fertilizers typically contain healthy amounts of magnesium , which are taken up by the plants.

Dr. Dean added that magnesium deficiency contribute to a myriad of conditions, including heart diseases , high blood pressure, high cholesterol , anxiety, fatigue muscle cramping and inflammation.

Magnesium deficiency also contribute to a higher risk of influenza . Researchers find that lower serum magnesium level independently predicts readmission for chronic obstructive pulmonary disease. Magnesium has also been shown to be calming and can help sleep [14]. Significant decrease of magnesium associated with significant increase of lead [15].

Mr. Mosab Nouraldein hypothesize that Lead and Cadmium mutate influenza virus form COVID.19 [16], and all of them cause depletion of magnesium.

Magnesium and blood pressure

Hypertension is an important public health challenge because of its high prevalence and strong association with cardiovascular disease and premature death. Hypertension is a major cause of CKD, is present in more than 80% of CKD patients, and contributes to CKD progression. Risk factors for hypertension include, but are not limited to, age, race, family history, obesity, physical inactivity, tobacco use, and inadequate intake of minerals such as calcium, potassium, and magnesium. Magnesium is the second most abundant intracellular cation in the human body and plays an important role in insulin and adenosine triphosphate metabolism. Low dietary magnesium intake has been associated with an increased risk of developing hypertension [17].

The effect of magnesium on blood pressure may be direct or through influences on the internal balance of potassium, sodium, and calcium [18].

Magnesium intake of 500 mg/d to 1000 mg/d may reduce blood pressure (BP) as much as 5.6/2.8 mm Hg. However, clinical studies have a wide range of BP reduction, with some showing no change in BP. The combination of increased intake of magnesium and potassium coupled with reduced sodium intake is more effective in reducing BP than single mineral intake and is often as effective as one antihypertensive drug in treating hypertension. Reducing intracellular sodium and calcium while increasing intracellular magnesium and potassium improves BP response. Magnesium also increases the effectiveness of all antihypertensive drug classes. It remains to be conclusively proven that cardiovascular disease such as coronary heart disease, ischemic stroke, and cardiac arrhythmias can be prevented or treated with magnesium intake. Preliminary evidence suggests that insulin sensitivity, hyperglycemia, diabetes mellitus, left ventricular hypertrophy, and dyslipidemia may be improved with increased magnesium intake. Various genetic defects in magnesium transport are associated with hypertension and possibly with cardiovascular disease. Oral magnesium acts as a natural calcium channel blocker, increases nitric oxide, improves endothelial dysfunction, and induces direct and indirect vasodilation [19].

Magnesium and blood sugar

Magnesium is a mineral that plays many important roles in the body, including managing insulin and carbohydrate metabolism. It's involved in body's ability to secrete insulin and may help the cells to use insulin more effectively.
It appears to help manage blood sugar levels among people with diabetes. Also, those who tend to consume less magnesium typically have poorer blood sugar regulation and a higher risk of type 2 diabetes than people who consume higher amounts.
Increasing magnesium intake through food or supplements may help people with diabetes improve their blood sugar regulation. A 12-week study in 54 people with type 2 diabetes found that taking 300 mg of magnesium daily significantly lowered fasting blood sugar levels, as well as post-meal blood sugar levels, compared with taking a placebo pill.
Similarly, in one review of 18 studies, 12 of them including people either with diabetes or at risk of developing diabetes found that taking 250–450 mg of magnesium daily for 6–24 weeks helped significantly reduce fasting blood sugar levels, compared with placebo groups.

In general, studies have found that taking 250–350 mg of magnesium daily appears to benefit people with diabetes. It's best to take magnesium with food to improve absorption .

However, in case of type 2 diabetes, it's important to notify the healthcare provider before taking magnesium. This is because magnesium may increase the risk of hypoglycemia, or low blood sugar, as it may have an additive effect when combined with medication [20].

Type 2 diabetes is frequently associated with both extracellular and intracellular magnesium (Mg) deficits. A chronic latent Mg deficit or an overt clinical hypomagnesemia is common in patients with type 2 diabetes, especially in those with poorly controlled glycemic profiles. Insulin and glucose are important regulators of Mg metabolism. Intracellular Mg plays a key role in regulating insulin action, insulin-mediated-glucose-uptake and vascular tone. Reduced intracellular Mg concentrations result in a defective tyrosine-kinase activity, postreceptorial impairment in insulin action and worsening of insulin resistance in diabetic patients. A low Mg intake and

an increased Mg urinary loss appear the most important mechanisms that may favor Mg depletion in patients with type 2 diabetes. Low dietary Mg intake has been related to the development of type 2 diabetes and metabolic syndrome [21].

The effect of calcium and magnesium ions on glucagon and insulin secretion was studied *in vitro*, using pieces of pancreas from duct-ligaturated rats. Omission of calcium from the incubation media stimulated glucagon release. Addition of barium to the calcium-depleted media did not prevent the stimulation of glucagon release. Omission of magnesium also tended to increase the rate of glucagon secretion. Much higher rates of glucagon release were observed in the concomitant absence of calcium and magnesium, or in calcium-depleted media supplemented with a chelating agent (EGTA). On the other hand, excess of calcium (8 mEq/1) was without effect, and excess magnesium (20 mEq/1) inhibited basal or arginine-induced glucagon release. In these various experimental conditions, except those in which a marked stimulation of glucagon occurred (absence of both cations, presence of EGTA), the rate of insulin secretion followed the patterns documented by previous investigators. It is concluded that calcium and magnesium, in contrast to their effect on the β cell, act synergistically upon the secretory process of the α_2 cell in such a way that glucagon release is stimulated at low levels of both cations [22].

The association between magnesium deficiency and insulin resistance is present during childhood. Serum magnesium deficiency in obese children may be secondary to decreased dietary magnesium intake. Magnesium supplementation or increased intake of magnesium-rich foods may be an important tool in the prevention of type 2 diabetes in obese children [23].

Intracellular magnesium concentration is low in type 2 diabetes mellitus and in hypertensive patients. In patients with type 2 diabetes an inverse association exists between the plasma magnesium and insulin resistance due to intracellular changes. The suppressed intracellular magnesium concentration may result in defective tyrosine kinase activity and modify insulin sensitivity by influencing receptor activity after binding or by influencing intracellular signaling and processing. Intracellular magnesium deficiency may affect the development of insulin resistance and alter the glucose entry into the cell [24].

A tyrosine kinase is an enzyme that can transfer a phosphate group from ATP to the tyrosine residues of specific proteins inside a cell. It functions as an "on" or "off" switch in many cellular functions[25].

The stimulation by Mg^{2+} and the polyamines occurred with and without insulin. These characteristics of the heart insulin receptor provide a mechanism for regulating the activity of the receptor's tyrosine kinase activity by the intracellular free Mg^{2+} concentration and the polyamines in the absence and presence of insulin [26].
Low Mg^{2+} levels result in a defective tyrosine kinase activity, post-receptor impairment in insulin action, altered cellular glucose transport, and decreased cellular glucose utilization, which promotes peripheral insulin resistance in type2diabetes. Magnesium deficiency triggers chronic systemic inflammation that also potentiates insulin resistance. People with type 2 diabetes may end up in a vicious circle in which magnesium deficiency increases insulin resistance and insulin resistance causes magnesium deficiency, that requires periodic monitoring of serum Mg^{2+} levels [27].
A 2015 review in the *World Journal of Diabetes* reports that most, but not all, people with diabetes have low magnesium and that magnesium may play a role in diabetes management.

Magnesium and vitamins

Magnesium is an important mineral, playing a role in over 300 enzyme reactions in the human body. Its many functions include helping with muscle and nerve function, regulating blood pressure, and supporting the immune system.

An adult body contains around 25 gram (g) of magnesium, 50–60% of which the skeletal system stores. The rest is present in muscle, soft tissues, and bodily fluids. Magnesium may improve bone health both directly and indirectly, as it helps to regulate calcium and vitamin D levels, which are two other nutrients vital for bone health [28].

It assists in the activation of vitamin D, which helps regulate calcium and phosphate homeostasis to influence the growth and maintenance of bones. All of the enzymes that metabolize vitamin D seem to require magnesium, which acts as a cofactor in the enzymatic reactions in the liver and kidneys [29].

magnesium supplementation enhanced the anticancer effect of ascorbic acid (vitamin C) by inhibiting the hormetic response at a low dose. Ascorbic acid treatment with magnesium supplementation provided more effective anticancer therapy than AA treatment alone [30].3 months of the Magnesium- melatonin-vitamin B complex supplementation has a beneficial effect in the treatment of insomnia regardless of cause [31].

Magnesium and vitamin E are known to exert multiple beneficial effects, such as anti-glycemic and anti-lipidemic properties. magnesium and vitamin E co-supplementation for 6 weeks in women with gestational diabetes mellitus significantly improved glycemic control and lipid profiles, except for HDL-cholesterol levels [32].

Magnesium and renal function

Magnesium is the fourth most abundant cation and is essential for every cell. This mineral is a cofactor in multiple enzymatic reactions, including those involving energy metabolism as well as DNA and protein synthesis, and it participates in the regulation of ion channels. Magnesium homeostasis is therefore fundamental to the existence of life.

However, the clinical significance of magnesium has only been acknowledged during recent years. In fact, years ago, magnesium was even called 'the forgotten electrolyte'. In this issue of the American Journal of Nephrology, Rebholz et al. report on the correlation between dietary magnesium intake and kidney function decline from a large epidemiological investigation, the HANDLS study. Compared with the upper tertile of dietary magnesium intake, the risk for rapid kidney function decline was roughly doubled in the lower tertile [33].

The kidneys play a central role in the homeostasis of these ions. Gastrointestinal absorption is balanced by renal excretion. When body stores of these ions decline significantly, gastrointestinal absorption, bone resorption, and renal tubular reabsorption increase to normalize their levels. Renal regulation of these ions occurs through glomerular filtration and tubular reabsorption and/or secretion and is therefore an important determinant of plasma ion concentration. Under physiologic conditions, the whole body balance of calcium, phosphate, and magnesium is maintained by fine adjustments of urinary excretion to equal the net intake [34].

Magnesium and blood cells

Recent research has shown that magnesium levels in serum, salivary secretions and red blood cells are reduced in migraine patients with and without aura, both ictally and interictally. This suggests that lower magnesium levels can contribute to the etiopathogenetic mechanisms underlying migraine attacks. It has been suggested that mononuclear magnesium content is a reliable index of magnesium nutritional status, as it is more closely related to the total body stores than other biochemical indices. Therefore we determined mononuclear magnesium content in adult migraine patients with and without aura, in headache-free periods and, in a number of patients, during attacks. Migraine patients with and without aura, assessed in interictal periods, had a reduced mononuclear magnesium content compared to age-matched healthy control subjects. No significant variations were observed between ictal and interictal periods in migraine patients with aura and without aura. The lower magnesium content in mononuclear cells could indirectly indicate the reduction of brain magnesium concentration, which has recently been demonstrated in the course of migraine [35].
A Chinese study showed that; The prevalence of anemia was 18.3% in men and 31.5% in women. Magnesium and iron intakes were positively associated with hemoglobin levels and inversely related to the prevalence of anemia. The risks of anemia were reduced by 26% (P for trend = 0.03) and 52% ($P < 0.01$), respectively, for iron and magnesium intake comparing the fourth quartile with the first with adjustment for potential confounders. The lowest risk of anemia was observed among participants with the highest intakes of magnesium and iron (odds ratio 0.46, 95% confidence interval 0.31–0.68). The inverse association of iron intake and anemia but not the association of magnesium intake and anemia was modified by serum ferritin levels. The observed relations were not appreciably modified by gender. This suggests that magnesium is a potent predictor of anemia in Chinese adults [36].
In fact, magnesium may have a more potent effect on platelet aggregation than calcium. Magnesium infusion has demonstrated encouraging results for hemostasis and the treatment of coagulopathy in cirrhotic patients before liver transplantation and in models of trauma-associated coagulopathy [37].
Inter-dimer chemical cross-linking of spectrin in intact red cell membranes is enhanced if magnesium ions at a concentration of 0.5MM or more are present. On the other hand, the elimination of magnesium from the interior of intact cells causes no

significant change in shear elastic modulus, measured by micropipette assays, nor is there any dependence of membrane filtration rate on intracellular free magnesium concentration in the range 0–1MM. Magnesium-depleted cells are, however, converted into echinocytes within a short period, in which, control cells, exposed to ionophore and external magnesium ions, remain completely discoid. Magnesium-depleted cells also undergo structural, changes on heating below the temperature at which vesiculation sets in. These reveal themselves by the transformation of the cells to a unique characteristic shape, by grossly reduced filtrability, and by extensive agglutination of the cells when treated with a bifunctional reagent. Magnesium ions thus regulate the stability, but not to any measurable extent the gross elasticity, of the red cell membrane [38].

Researchers suggest that; that magnesium supplementation positively influences the performance of training athletes by increasing erythrocyte and hemoglobin levels and no effect in hematocrit levels [39]. Another study found A significant inverse correlation of serum Magnesium with mean platelet volume, There was not significant association of serum Mg and PLT count [40].

Outlined findings from several studies, in vitro and in vivo, that showed the detrimental effects of magnesium deficiency environments on lymphocyte proliferation as well as on the immune related functioning of several kinds of T-cell [41].

Magnesium and inflammatory markers

Animal studies have shown that magnesium deficiency induces an inflammatory response that results in leukocyte and macrophage activation, release of inflammatory cytokines and acute-phase proteins, and excessive production of free radicals. Animal and in vitro studies indicate that the primary mechanism through which magnesium deficiency has this effect is through increasing cellular Ca^{2+}, which is the signal that results in the priming of cells to give the inflammatory response. Primary pro-inflammatory cytokines such as tumor necrosis factor-α and interleukin (IL)-1; the messenger cytokine IL-6; cytokine responders E-selectin, intracellular adhesion molecule-1 and vascular cell adhesion molecule-1; and acute-phase reactants C-reactive protein and fibrinogen have been determined to associate magnesium deficiency with chronic low-grade inflammation (inflammatory stress). When magnesium dietary intake, supplementation, and/or serum concentration suggest/s the presence of magnesium deficiency, it often is associated with low-grade inflammation and/or with pathological conditions for which inflammatory stress is considered a risk factor. When magnesium intake, supplementation, and/or serum concentration suggest/s an adequate status, magnesium generally has not been found to significantly affect markers of chronic low-grade inflammation or chronic disease. The consistency of these findings can be modified by other nutritional and metabolic factors that affect inflammatory and oxidative stress. In spite of this, findings to date provide convincing evidence that magnesium deficiency is a significant contributor to chronic low-grade inflammation that is a risk factor for a variety of pathological conditions such as cardiovascular disease, hypertension, and diabetes . Because magnesium deficiency commonly occurs in countries where foods rich in magnesium are not consumed in recommended amounts, magnesium should be considered an element of significant nutritional concern for health and well-being in these countries [42].

Most Americans consume magnesium at levels below the recommended daily allowance. Individuals with intakes below the recommended daily allowance are more likely to have elevated CRP, which may contribute to cardiovascular disease risk [43].

Subclinical magnesium deficiency caused by low dietary intake often occurring in the population is a predisposing factor for chronic inflammatory stress that is conducive for chronic disease [44].

Magnesium intake was inversely associated with plasma concentrations of CRP , E-selectin , and sICAM-1 [45]. magnesium treatment significantly decreased fasting C-peptide concentrations (change: –0.4 ng/mL after magnesium treatment compared with +0.05 ng/mL after placebo treatment; $P = 0.004$) and appeared to decrease fasting insulin concentrations (change: –2.2 μU/mL after magnesium treatment compared with 0.0 μU/mL after placebo treatment; $P = 0.25$). No consistent patterns were observed across inflammatory biomarkers. Gene expression profiling revealed up-regulation of 24 genes and down-regulation of 36 genes including genes related to metabolic and inflammatory pathways such as C1q and tumor necrosis factor–related protein 9 (*C1QTNF9*) and pro-platelet basic protein (*PPBP*) [46].

A low Mg diet decreased the Mg concentration in the plasma and erythrocytes, which was accompanied by a reduced concentration of eNOs and increased levels of endothelin-1 level in the serum and impaired endothelium-dependent vasodilatation. These effects increased the concentration of proinflammatory molecules, such as VCAM-1, TNF-α, IL-6 and CRP, indicating the development of systemic inflammation and endothelial dysfunction . Two weeks of Mg supplementation partially or fully normalised the ability of the vascular wall to effect adequate endothelium-dependent vasodilatation and reversed the levels of most endothelial dysfunction and inflammatory markers (except CRP) to the mean values of the control group. Mg sulphate had the smallest effect on the endothelin-1, TNF-α and VCAM-1 levels. Mg N-acetyltaurate was significantly more effective in restoring the level of eNOS compared to all other studied compounds, except for Mg oxybutyrate. Taken together, the present findings demonstrate that all Mg compounds equally alleviate endothelial dysfunction and inflammation caused by Mg deficiency. Mg sulphate tended to be the least effective compound [47].

Magnesium and vitamin D each have the possibility of affecting the immune system and consequently the cytokine storm and coagulation cascade in COVID-19 infections. Vitamin D is important for reducing the risk of upper respiratory tract infections and plays a role in pulmonary epithelial health. While the importance of vitamin D for a healthy immune system has been known for decades, the benefits of magnesium has only recently been elucidated. Indeed, magnesium is important for activating vitamin D and has a protective role against oxidative stress. Magnesium deficiency increases endothelial cell susceptibility to oxidative stress, promotes endothelial dysfunction, reduces fibrinolysis and increases coagulation. Furthermore,

magnesium deficient animals and humans have depressed immune responses, which, when supplemented with magnesium, a partial or near full reversal of the immunodeficiency occurs. Moreover, intracellular free magnesium levels in natural killer cells and CD8 killer T cells regulates their cytotoxicity. Considering that magnesium and vitamin D are important for immune function and cellular resilience, a deficiency in either may contribute to cytokine storm in the novel coronavirus 2019 (COVID-19) infection [48].

Magnesium deficiency primes phagocytes, enhances granulocyte oxidative burst, activates endothelial cells and increases the levels of cytokines, thus promoting inflammation. Consequently, a low magnesium status, which is often underdiagnosed, potentiates the reactivity to various immune challenges and is implicated in the pathophysiology of many common chronic diseases [49].

Researchers hypothesize that that a low Mg status, which is rather common, might foment the transition from mild to critical clinical manifestations of the disease [50]. Constant monitoring of ionized magnesium status with subsequent repletion, when appropriate, may be an effective strategy to influence disease contraction and progression [51].

Mg deficiency could be a risk factor for multi-organ dysfunction in COVID-19 infection. Mg supplementation improves functions of the immune, cardiovascular, nervous, urinary, and respiratory systems through different mechanisms. Suppression of cytokine storm, bronchodilation, antithrombotic function, a decrease of arterial blood pressure, preventing electrolyte imbalance, increase stress resistance are some of the related mechanisms. These findings may provide a reference regarding the possible beneficial effects of the Mg supplement as an inexpensive, safe, and easily available drug for supportive treatment in COVID-19 patients [52]. Reduced magnesium (Mg) intake is a frequent cause of deficiency with age together with reduced absorption, renal wasting, and polypharmacotherapy. Chronic Mg deficiency may result in increased oxidative stress and low-grade inflammation, which may be linked to several age-related diseases, including higher predisposition to infectious diseases. Mg might play a role in the immune response being a cofactor for immunoglobulin synthesis and other processes strictly associated with the function of T and B cells. Mg is necessary for the biosynthesis, transport, and activation of vitamin D, another key factor in the pathogenesis of infectious diseases [53]..

magnesium modulates cellular events involved in inflammation. Experimental magnesium deficiency in the rat induces after a few days a clinical inflammatory syndrome characterized by leukocyte and macrophage activation, release of inflammatory cytokines and acute phase proteins, excessive production of free radicals. Increase in extracellular magnesium concentration, decreases inflammatory response while reduction in the extracellular magnesium results in cell activation. Because magnesium acts as a natural calcium antagonist, the molecular basis for inflammatory response is probably the result of modulation of intracellular calcium concentration. The priming of phagocytic cells, the opening calcium channel and activation of *N*-methyl-D-aspartate (NMDA) receptors, the activation of nuclear factor-kappa B (NFκB) have been considered as potential mechanisms. Moreover, magnesium deficiency induces a systemic stress response by activation of neuro endocrinological pathways. As nervous and immune systems interact bidirectionally, the roles of neuromediators have also been considered. Magnesium deficiency contributes to an exaggerated response to immune stress and oxidative stress is the consequence of the inflammatory response. Inflammation contributes to the pro-atherogenic changes in lipoprotein metabolism, endothelial dysfunction, thrombosis, hypertension and explains the aggravating effect of magnesium deficiency on the development of metabolic syndrome [54].

Magnesium and loss of smell and taste

Magnesium helps the body to regulate its zinc levels, though it should be noted that high intake of zinc can be detrimental to magnesium absorption and reduce magnesium balance [55].

The common cold is frequently associated with anosmia. A significant portion of COVID-19 patients has been reported to have anosmia and taste dysfunction.
A recent study from Germany found that among confirmed COVID-19 patients 47% had anosmia with a mean duration of anosmia of 8.9 days as well as an association with dysgeusia in 85% of cases.
There are multiple proposals for the pathogenesis of anosmia during COVID-19 including the direct and indirect toxic effect of SARS-CoV-2 on neuronal cells and toxicity to non-neuronal supportive cells such as olfactory epithelium sustentacular cells, microvillar cells and olfactory bulb pericytes.
Zinc (Zn) is an essential micronutrient and is the second most abundant metal in the human body, with 2 to 4 grams distributed throughout the whole body. Zinc is generally taken in through food or breast milk, is absorbed via several intestinal Zn transporters, and is released into the bloodstream. It is required for cell growth, differentiation, and survival and approximately 10% of the entire human genome can potentially bind Zn through Zn-finger motifs.
Zinc deficiency is well known to cause anosmia and taste dysfunction. This is because one of the enzymes critical to maintain taste and smell function is a zinc dependent metalloenzyme called carbonic anhydrase (CA) . Interestingly, different formulations of intranasal Zn have also been shown to cause anosmia, but the mechanisms for toxicity are complex, including oxidative stress, ATP depletion, cytoskeletal changes and apoptosis of olfactory neuronal cells, and is affected by many factors, such as concentration of zinc tested, the length of exposure, the cell type, and the presence of other toxic chemicals [56].

Loss of smell is a relatively common occurrence as people progress through adulthood. In one large epidemiological study of US adults, 25% had a measurable olfactory impairment. Similarly, 19% of Swedes were found to have hyposmia or anosmia. Many times, the ability to smell diminishes gradually over time, making self-reported olfactory impairment substantially underestimated. Patients frequently

do not discuss their olfaction difficulties; however, the loss of smell can lead to depression and a lower quality of life.

The most common known etiologies for anosmia are nasal/sinus congestion, upper respiratory tract infection, current smoking, head trauma, stroke, and epilepsy**.** Some investigators theorize that olfactory declines may be a consequence of autoimmune mechanism or neurodegenerative diseases. The prognosis of olfactory dysfunction is influenced by certain demographic and clinical factors. Over time, regaining the sense of smell is more likely in females, younger persons, those with lesser severity of initial olfactory loss.

Two cases are presented in which the sense of smell was substantially diminished but was regained, presumably through the supplementation of vitamin D3. Both cases presented with similar complaints of depression, fatigue, and muscle aches, all of which have been previously associated with vitamin D deficiency. A link between hypovitaminosis D and a diminished sense of smell was noted in these 2 individuals [57], but I suggest the probable reason of anosmia is magnesium deficiency which is needed to activate vitamin D.

It was previously reported that magnesium ion inhibited carbonic anhydrase. Studies with partially purified carbonic anhydrase from spinach (Spinacia oleracea L.) chloroplasts show that the effect was the result of the chloride counterion and not the magnesium ion [58].

Magnesium and Sleep

Magnesium is required for enzymes used in neurotransmitter synthesis, and is involved in cholinergic, monoaminergic, and amino acid transmitter function. Magnesium blocks the N-methyl-D-aspartate (NMDA) receptor and is an agonist of the γ-amino butyric acid (GABA) receptor. Heightened activation of the NMDA receptor may cause poor sleep architecture, while augmentation of the GABA receptor may improve sleep architecture. Thus, it is not surprising that magnesium deficiency has been associated with sleep disorders, which magnesium supplementation alleviated. Magnesium deficiency may contribute to the inflammatory stress that can result in pathological changes such as diabetes mellitus and cardiovascular disease associated with sleep deprivation or poor-quality sleep. Based on recent survey data, magnesium deficiency such that it would affect sleep quality in humans may be a common occurrence, especially in older adults, obese individuals, and alcohol abusers [59].

Insomnia is a common sleep disorder where you have difficulty falling asleep, staying asleep, or both. People with insomnia experience a lack of energy and don't feel refreshed in the morning. They may also struggle with excessive daytime sleepiness, irritability, anxiety, or depression.

Research shows that magnesium may help improve insomnia symptoms. In a study of elderly patients with insomnia, taking 500 mg of magnesium daily for eight weeks improved many subjective and objective measures of insomnia. The patients:

i. Fell asleep faster and slept longer

ii. Increased their sleep efficiency, meaning they spent more time sleeping while they were in bed

iii. Woke up later and reduced early morning awakening

iv. Experienced increased concentrations of melatonin, a sleep hormone, and serum renin which plays a role in regulating blood pressure

v. Experienced decreased concentrations of serum cortisol, the (stress hormone) [60].

Magnesium and depression

Magnesium ions regulate calcium ion flow in neuronal calcium channels, helping to regulate neuronal nitric oxide production. In magnesium deficiency, neuronal requirements for magnesium may not be met, causing neuronal damage which could manifest as depression. Magnesium treatment is hypothesized to be effective in treating major depression resulting from intraneuronal magnesium deficits. These magnesium ion neuronal deficits may be induced by stress hormones, excessive dietary calcium as well as dietary deficiencies of magnesium. Case histories are presented showing rapid recovery (less than 7 days) from major depression using 125–300 mg of magnesium (as glycinate and taurinate) with each meal and at bedtime. Magnesium was found usually effective for treatment of depression in general use. Related and accompanying mental illnesses in these case histories including traumatic brain injury, headache, suicidal ideation, anxiety, irritability, insomnia, postpartum depression, cocaine, alcohol and tobacco abuse, hypersensitivity to calcium, short-term memory loss and IQ loss were also benefited. Dietary deficiencies of magnesium, coupled with excess calcium and stress may cause many cases of other related symptoms including agitation, anxiety, irritability, confusion, asthenia, sleeplessness, headache, delirium, hallucinations and hyperexcitability, with each of these having been previously documented. The possibility that magnesium deficiency is the cause of most major depression and related mental health problems including IQ loss and addiction is enormously important to public health and is recommended for immediate further study. Fortifying refined grain and drinking water with biologically available magnesium to pre-twentieth century levels is recommended [62].

Researchers found that magnesium was generally effective for the treatment of depression as well as anxiety, irritability and insomnia, which are also symptoms of bipolar disorder [63].

Magnesium and Migraines

Magnesium is an important natural mineral that our bodies need for various cellular functions. It helps maintain stable blood pressure, keeps the heart healthy, and is involved in building bone, DNA, and proteins. Research has shown that increasing the level of magnesium in the blood may help prevent or treat migraines.

Dr. Alexander Mauskop, a leading researcher in migraines, has helped shed light on the role of magnesium deficiency in the occurrence of migraines. In one of his studies, Mauskop observed that people who did not get relief from a popular and effective migraine medication had low levels of magnesium in the blood. After increasing these levels, the individuals found relief.

In another study, people who were deficient in red blood cell (RBC) magnesium and received magnesium infusions for their migraine attacks also found relief. In comparison, those that experienced migraine attacks but weren't deficient in RBC magnesium did not find relief [64].

Magnesium and fertility

Years ago the women had to face society's blame due to their childless marriages. The problem of infertility has increasingly been extended to anomalies in the male partner. Male fertility may also have various causes: reduced volume of ejaculate, decreases number and motility of sperms and increased proportion of abnormal (injured) sperms. It was found that as a result of ATP and cAMP supply in vitro in demembranated models the length of time of the sperms' motility grew thirtyfold (122.0 min) compared to the control (4.2 min). This is made possible by the fact that the energy required for the motion of sperms is released from the ATP by the ATPase. The motility of sperms needs the joint presence of cAMP and Mg ATP. It was found that the formation of ATP, as well as, cAMP is a magnesium intensive process [65].

Magnesium , COVID.19 Clinical manifestations and laboratory parameters

Headache:

Having a headache is a very common symptom of COVID-19 for all age groups, is a potential symptom of COVID-19 and may often feel similar to a migraine attack. While we're still learning more about COVID-19 and headache, researchers have noticed that a headache due to COVID-19 is often:

i. moderate to severe in intensity.

ii. characterized as having a pulsing or pressing pain.

iii. felt on both sides of the head (bilateral).

iv. worse with physical activity or when moving the head.

v. difficult to ease with over-the-counter (OTC) pain medications such as acetaminophen (Tylenol) or ibuprofen (Advil, Motrin).

vi. typically occurs early on in the infection but may be associated with worsening illness when it appears later in infection.

COVID-19 headache may *feel* like a migraine attack [66], and researchers noticed low level of magnesium between migraine patients[64].

Anosmia:

Anosmia was present in half of our European COVID-19 patients and was often associated with dysgeusia. 47%) with confirmed COVID-19 reported anosmia [67]. the possible cause of anosmia is magnesium insufficiency which is required to activate vitamin D, and needed to regulate zinc concentration which play significant in maintenance of smell and taste through zinc dependent carbonic anhydrase.

Dysgeusia:

It is of particular significance that dysgeusia (with or without olfactory symptoms) has been reported as an early or lone symptom of COVID-19 before involvement of the lungs or other organs. We hypothesize that changes in localized cellular zinc

homeostasis in oral gustatory cells resulting from immune responses to SARS-CoV-2 viral replication may result in dysgeusia, which may or may not be accompanied by hypozincemia [68]. Dysgeusia is linked to vitamin D Deficiency [69].

Sore throat:

A sore throat is pretty common, as far as symptoms of illness go. Sore throat can be caused by illnesses ranging from the non-serious to the dangerous. It is also a common symptom of the disease caused by the novel coronavirus [70]. Magnesium at low dose decreases sore throat and pain severity more effectively [71].

Fatigue:

fatigue is one of the most persistent and debilitating symptom of COVID.19, we define fatigue *as* the decrease in physical and/or mental performance that results from changes in central, psychological, and/or peripheral factors due to the COVID-19 disease *and propose a model to explain potential factors contributing to post-COVID-19 fatigue [72]. One of the first signs of magnesium deficiency is often fatigue [73].*

Digestive symptoms:

Some people with COVID-19 develop gastrointestinal symptoms either alone or with respiratory symptoms.

Recently, researchers at Stanford University found that a third of patients they studied with a mild case of COVID-19 had symptoms affecting the digestive system.

Another recent study published by researchers in Beijing found that anywhere from 3 to 79 percent of people with COVID-19 develop gastrointestinal symptoms.

Diarrhea:

It is commonly occurs in people with COVID-19. One study published in the American Journal of Gastroenterology examined 206 patients with a mild case of COVID-19. They found 48 people had only digestive symptoms and another 69 had both digestive and respiratory symptoms.

Of the combined total of 117 people with gastric distress, 19.4 percent experienced diarrhea as their first symptom.

Vomiting:

The research from Beijing found that vomiting is more common in children with COVID-19 than adults.

The researchers analyzed all the COVID-19 clinical studies and case reports related to digestive issues published between December 2019 and February 2020. They found that 3.6 to 15.9 percent of adults experienced vomiting, compared with 6.5 to 66.7 percent of children.

Loss of appetite :

Many people who develop COVID-19 report losing their appetite, often alongside other gastrointestinal symptoms.

According to the same study from Beijing, about 39.9 to 50.2 percent of people experience a loss of appetite.

Several other digestive symptoms have been reported by people with COVID-19. According to the study from Beijing:

i. 1 to 29.4 percent of people experience nausea
ii. 2.2 to 6 percent experience abdominal pain
iii. 4 to 13.7 percent experience gastrointestinal bleeding [73].

Magnesium deficiency cause nausea , vomiting , loss of appetite [74] , digestive trouble and constipation [75] , diarrhea [76], also it may leads to leaky gut [77].

Leaky gut:

Leaky gut, also known as increased intestinal permeability, is not a recognized medical diagnosis. Because of this, there's limited clinical data about the condition, including how long it takes to recover from it.

For example, a 2005 study from the University of Manitoba studied people with celiac disease(attributed to low magnesium concentration), which is often associated with intestinal permeability.

The gastrointestinal tract, includes over 4,000 square feet of intestinal epithelial lining that controls what gets into your bloodstream.

Low magnesium makes, this lining "leaky" with holes or cracks that allow bacteria, toxins, antigens, and partially digested food to penetrate the tissues beneath it.

That can trigger inflammation and changes in the gut flora (normal bacteria), which could lead to problems within your digestive tract and beyond.

It is not recognized by mainstream medical professionals as a condition, it's generally recognized as a symptom.

According to a 2014 study, the proponents of leaky gut syndrome claim it can cause many health problems, including:

i. Allergies

ii. Chronic fatigue syndrome

iii. Depression

iv. Fibromyalgia

v. Skin disorders

Occurrence of leaky gut more frequent in the presence of the following medical disorders:

i. Celiac disease

ii. HIV

iii. Inflammatory disease

iv. Irritable bowel syndrome

v. Crohn's disease.

vi. Multiple sclerosis

vii. Rheumatoid arthritis

viii. Type 1 diabetes.

Symptoms of leaky gut may vary depending on the underlying cause. For example:

i. Celiac disease can cause abdominal pain, diarrhea or constipation, fatigue, nausea and vomiting, bloating and gas, and weight loss.

ii. IBD can cause abdominal pain, severe diarrhea, weight loss, fatigue, fever, and bloody stools.

iii. IBS can cause abdominal pain, bloating, cramping, constipation or diarrhea, mucus in stools, and excess gas [77].

Leaky gut besides Poor nutrition and Medications that deplete magnesium (such as antibiotics and diuretics) is a known cause of magnesium deficiency [78].

Sleep trouble:

Research has found magnesium supplementation helped improve all the major physiological markers associated with insomnia. For instance a neurotransmitter, GABA is key in the body's regulation of its sleep system, and GABA receptors in the brain need magnesium to function properly.

Throughout the COVID-19 pandemic, various studies have documented increased rates of insomnia and mental health disorders. Prior to the pandemic, about 24% of people suffered from sleep maintenance insomnia, or difficulty staying asleep. During the pandemic, that increased to 40%. Among individuals with sleep onset insomnia, or difficulty falling asleep in the first place, the prevalence jumped from 15% to 42%. Overall, experts estimate the number of people with any form of insomnia has increased 37% from pre-pandemic levels.

People's sleep habits have also changed during the pandemic. People are spending less time sleeping at night and napping more during the day[13]. They're also pushing back their bedtimes and wake times, by as much as 39 and 64 minutes, respectively. As a result, sleep quality has suffered.

Patients with COVID-19 are most likely to report sleep problems, due to symptoms of the illness that make rest difficult, such as breathing and coughing. 75% of patients have reported trouble sleeping [79].

Low thyroid hormone levels:

Magnesium deficiency is often an overlooked factor when it comes to those dealing with thyroid problems. Magnesium is an essential component to the production of thyroid hormones [78]. FT3 concentration was significantly lower in patients with severe COVID-19 than in non-severely ill patients [80]. Magnesium convert the inactive thyroid hormone T4 into the active thyroid hormone T3. Without this conversion, cells do not receive the more potent form of thyroid hormone. Therefore, when magnesium levels are low, our thyroid is not able to function correctly [81].

Skin and hair health:

Post Covid, many people are struggling with extreme hair loss and persistent skin problems [82]. A study in Poland showed that those with skin allergies saw substantial improvements in their skin with magnesium supplementation [78].

Even though our hair is dead outside, there's a lot of work going on inside the hair follicles to build hair. Since magnesium takes part in making protein as well as the growth of cells, adequate supply of magnesium ensures that our hair is growing

stronger and thicker and there's no interruption in the hair cycle to cause premature hair fall [83].

Poor memory:

Research done at MIT found that magnesium is key in regulating brain receptors that are necessary to learning and memory function, and that supplementing with magnesium helped clear so-called brain fog. Magnesium also supports the brain's lifelong function of adapting, healing and adding new neural pathways. Getting enough magnesium may lead to slowed down and reversal of cognitive decline [78]. A 28-year-old woman who was diagnosed with COVID-19. After resolution of her acute symptoms, she continued to experience retrosternal discomfort, shortness of breath, poor memory and severe myalgia [84], all these clinical features may result from magnesium shortage.

Weak bones:

In two studies published in the American Journal of Clinical Nutrition a strong correlation between magnesium deficiency and low bone density was found. Low bone density increases one's risk of osteoporosis and fractures.

When supplemental magnesium (300 mg) was taken for one year by participants in a randomized controlled study bone mineral content increased [78]. Post-Covid complications in bones, joints and infections in the bone are reported in Covid recovered patients who were treated with steroids, remdesivir and tocilizumab. Patients are coming back to hospitals in 60 to 90 days with pain in the hip, joints, shoulders and also inability to walk and a limp [85].

Premature aging:

The death of human endothelial cells and fibroblasts at a rapid pace contributes to early aging and age-related diseases. Being deficient in magnesium is indicated in the acceleration of these processes [78]. Fibroblasts in secondary lymphoid organs, or fibroblastic reticular cells (FRC), are gate-keepers of immune responses [86].

Endothelial cells are a constitutive part of the heart and vasculature and form a crucial link between the cardiovascular system and the immune system [87]. People who survive severe covid-19 appear to end up with a prematurely-aged immune system and other persistent immunological problems [88].

Muscle cramps and spasms:

Spontaneous spasms, cramps in your muscles or "charley horses" are not really random —they are the most common sign of magnesium deficiency [78].

Twenty years ago, Brian McArdle discovered a disorder of muscle-energy metabolism (later identified as phosphorylase deficiency) in a young man with exertional muscle cramps [89].

Data from millions of ZOE COVID Symptom Study app contributors has shown that unusual muscle pains can be a symptom of COVID-19.

COVID-related muscle pains can range from being mild to quite debilitating, especially when they occur alongside fatigue [90]

Attention deficit hyperactivity disorder (ADHD):

COVID-19 is still spreading worldwide and posing a threat to individuals' physical and mental health including problematic internet use (PIU). A potentially high-risk group for PIU are those with symptoms of attention deficit and hyperactivity (ADHD symptoms), because of restrictions in their physical activity levels and engagement in computer diversions requiring only short attention spans.

The prevalence of PIU was high during COVID-19, and those people with ADHD symptoms and other mental illness symptoms appear to be at higher risk of PIU. Regular exercise may reduce that PIU risk and hence should be recommended during the COVID-19 pandemic [91]. Study suggest that an inverse relationship between serum magnesium deficiency and ADHD exists [92].

Adrenal fatigue:

The adrenals are two small glands that sit on top of the kidneys and produce several hormones, among them, cortisol. When under stress, we produce and release short

bursts of cortisol into the bloodstream. The adrenal fatigue theory suggests that prolonged exposure to stress could drain the adrenals leading to a low cortisol state. The adrenal depletion would cause brain fog, low energy, depressive mood, salt and sweet cravings, lightheadedness, and other vague symptoms [93].

Research showed that the association between high serum total cortisol concentrations and mortality from COVID-19. showed that cortisol concentrations in patients with COVID-19 were significantly higher than in those without COVID-19 [94].

Depression or anxiety:

Magnesium is one of the most essential mineral in the human body, connected with brain biochemistry and the fluidity of neuronal membrane. A variety of neuromuscular and psychiatric symptoms, including different types of depression, was observed in magnesium deficiency [95].

Magnesium works in the brain to calm down the excitatory NMDA receptor. Without it, calcium and glutamate activate NMDA unchecked, which can lead to depression and anxiety [78].

Research showed that More than one third of patients had underlying disease. Overall, 97.2% of patients with COVID-19 had some degree of depression[96].

Asthma

Researchers are suggesting that those who do not include enough magnesium-rich foods in their diet have a higher rate of asthma. One reason could be that magnesium may facilitate healthy bronchodilation [78].

Coronavirus disease 2019 (COVID-19) pandemic is creating concern and uncertainty for many people around the globe, including those with asthma. The disease can affect the nose, throat, and lungs, cause an asthma attack, and possibly lead to pneumonia and acute respiratory disease [97].

A patient with confirmed COVID-19 combined with asthma. It took 41 d from disease onset to discharge to obtain two negative tests for this coronavirus. This case

indicates the dynamic clinical characteristics, laboratory and computed tomography findings and adjustment of treatment, and the possible relationship between glucocorticoid therapy and coronavirus clearance [98].

level of LDH, CRP, ALT and NEU can be used to predict the result of COVID-19 test, these parameters increased in COVID.19 positive cases [99]. compared to low white blood cell count , low serum albumin lymphopenia low T. cell count and increased IL-6 [99,100].
Magnesium deficiency usually associate with increased IL.6 [42], High CRP [43], Lymphopenia , low T. cell count [41].

Summary

This findings support the hypothesis of influence of Cadmium and Lead in mutation of Influenza virus and emergence of novel corona virus, COVID.19 , as Exposure to Cd leads to disturbances in Mg metabolism in the organism, while Mg supplementation has an adverse effect on Cd absorption, accumulation and toxicity. According to the available results, which indicate a protective role of Mg against Cd toxicity [101]. Comprehensive observations suggest that exposure to Cd and Pb mixtures produces more pronounced effects compared to the response observed after exposure to single metal solutions [102]. A study showed that the potential protective effect of influenza vaccination in SARS-CoV-2-positive patients against adverse outcomes of COVID.19. Significant findings favoring influenza vaccination mitigating the risks of sepsis, stroke, deep vein thrombosis (DVT), emergency department (ED) & Intensive Care Unit (ICU) admissions suggest a potential protective effect that could benefit populations without readily available access to SARS-CoV-2 vaccination [103].

Sharing of many clinical features between Cadmium and Lead toxicity and COVID.19 , antagonism of cadmium and lead to magnesium[101,104] and protective effect of influenza vaccine against COVID.19 syndrome , give more strength to the hypothesis of Man Made Pandemic: Lead and Cadmium Mutate Influenza Virus Produce: SARS COV-2 [16], and I attribute the mortality of delta variant of COVID.19 to the highest cadmium blood concentrations among the vegetarians [105] (most Indians are vegans).

Monitoring of magnesium level during the COVID.19 era and increase intake of magnesium rich food , beside magnesium supplements will decrease the mortality and morbidity of it.

References:

1. Jahnen-Dechent, Wilhelm, and Markus Ketteler. “Magnesium basics.” Clinical kidney journal vol. 5,Suppl 1 (2012): i3-i14. doi:10.1093/ndtplus/sfr163.

2. Al Alawi AM, Majoni SW, Falhammar H. Magnesium and Human Health: Perspectives and Research Directions. *Int J Endocrinol*. 2018;2018:9041694. Published 2018 Apr 16. doi:10.1155/2018/9041694.

3. Vormann J. Magnesium: nutrition and metabolism. Mol Aspects Med. 2003 Feb-Jun;24(1-3):27-37. doi: 10.1016/s0098-2997(02)00089-4. PMID: 12537987.

4.Ryan Haas, The Effect of Magnesium on Sodium-Potassium Balance, May2, 2018, https://www.livestrong.com/article/530885-the-effect-of-magnesium-on-sodium-potassium-balance/.

5. Armin Schroll, Importance of magnesium for the electrolyte homeostasis - an overview, January 30, 2002, http://mgwater.com/schroll.shtml#:~:text=Sufficient%20magnesium%20supply%20is%20important%20for%20maintaining%20the,sodium%2Fpotassium%20pump%20and%20by%20reducing%20the%20calcium%20overload.

6. Soldatović D, Matović V, Vujanović D, Stojanović Z. Contribution to interaction between magnesium and toxic metals: the effect of prolonged cadmium intoxication on magnesium metabolism in rabbits. Magnes Res. 1998 Dec;11(4):283-8. PMID: 9884986.

7. Magdalena Wszelaki , Top 4 Heavy Metals that Cause Hormone Imbalance, Fatigue, and Weight Gain,Oct 14, 2019, https://hormonesbalance.com/articles/heavy-metals-that-cause-hormone-imbalance-fatigue-weight-gain/.

8. Snezana A. Jancic, Bojan Z. Stosic,Chapter Fourteen - Cadmium Effects on the Thyroid Gland,Editor(s): Gerald Litwack,Vitamins & Hormones,Academic Press,

Volume 94,2014,Pages 391-425,ISSN 0083-6729,ISBN 9780128000953,https://doi.org/10.1016/B978-0-12-800095-3.00014-6.

9. Osansky, The Relationship Between Toxic Metals And Thyroid Health, December 16 2013, https://www.naturalendocrinesolutions.com/articles/the-relationship-between-toxic-metals-and-thyroid-health/.

10. Pete Shuster on, 25% of Americans have some form of heavy metal poisoning, https://www.immunolinktherapies.com/is-it-autoimmune-disease-or-is-it-heavy-metal-toxicity.

11. https://www.ehcd.com/metal-toxicity-and-metal-sensitivity/.

12. Lippi G, South AM, Henry BM. Electrolyte imbalances in patients with severe coronavirus disease 2019 (COVID-19). Ann Clin Biochem. 2020 May;57(3):262-265. doi: 10.1177/0004563220922255. Epub 2020 May 3. PMID: 32266828; PMCID: PMC8173320.

13. HealthDay News, High blood levels of cadmium linked to worse COVID-19, https://www.upi.com/Health_News/2020/12/17/High-blood-levels-of-cadmium-linked-to-worse-COVID-19/9561608158393/..

14. CASE ADAMS, Doctor says Magnesium Fights the Flu, COPD and Insomnia, https://www.realnatural.org/doctor-says-that-magnesium-helps-prevent-influenza-copd-and-improves-sleep/#:~:text=Magnesium%20boosts%20immunity.%20Carolyn%20Dean%2C%20M.D.%20N.D.%20says,the%20modern%20diet%20has%20sunk%20by%20about%2060%25.

15. Mohamed Hussein Abdelazim; Mahmoud Helmy Elsaied & Wesam Abdalsalam Abdalwahab, SERUM LEVELS OF SOME METALS (IRON, MAGNISUM, ZINC AND LEAD) IN PATIENTS WITH CHRONIC OTITIS MEDIA AND ITS ASSOCIATION WITH CHOLESTEATOMA FORMATION, Egypt J. Forensic Sci. Appli. Toxicol.Vol 19 (2), June 2019. https://www.researchgate.net/publication/338954751_Serum_levels_of_Some_metals_iron_magnesium_zinc_and_lead_in_patients_with_chronic_otitis_media_and_its_association_with_cholesteatoma_formation.

16. Mosab Nouraldein Mohammed Hamad, COVID.19 : Man Made Pandemic: Lead and Cadmium Mutate Influenza Virus Produce: SARS COV-2, Lambert Academic Publishing, ISBN: 978-620-3-86941-5, June 2021,

https://www.researchgate.net/publication/352244968_COVID19_Man_Made_Pandemic_Lead_and_Cadmium_Mutate_Influenza_Virus_Produce_SARS_COV-2.

17. Joëlle C. Schutten, Michel M. Joosten, Martin H. de Borst, Stephan J.L. Bakker,

Magnesium and Blood Pressure: A Physiology-Based Approach,

Advances in Chronic Kidney Disease,,Volume 25, Issue 3,2018

18. T Dyckner, P O Wester, Effect of magnesium on blood pressure, Br Med J (Clin Res Ed) 1983; 286 doi: https://doi.org/10.1136/bmj.286.6381.1847 (Published 11 June 1983).

19. Houston M. The role of magnesium in hypertension and cardiovascular disease. J Clin Hypertens (Greenwich). 2011 Nov;13(11):843-7. doi: 10.1111/j.1751-7176.2011.00538.x. Epub 2011 Sep 26. PMID: 22051430.

20.Ryan Raman, Is Magnesium Good for My Blood Sugar Levels If I Have Diabetes?, March 15,2021, https://www.healthline.com/nutrition/is-magnesium-good-for-my-blood-sugar-levels-if-i-have-diabetes.

21. Barbagallo M, Dominguez LJ. Magnesium and type 2 diabetes. World J Diabetes. 2015 Aug 25;6(10):1152-7. doi: 10.4239/wjd.v6.i10.1152. PMID: 26322160; PMCID: PMC4549665.

22. V. LECLERCQ-MEYER, J. MARCHAND, W. J. MALAISSE, The Effect of Calcium and Magnesium on Glucagon Secretion, *Endocrinology*, Volume 93, Issue 6, 1 December 1973, Pages 1360–1370, https://doi.org/10.1210/endo-93-6-1360.

23. Milagros G. Huerta, James N. Roemmich, Marit L. Kington, Viktor E. Bovbjerg, Arthur L. Weltman, Viola F. Holmes, James T. Patrie, Alan D. Rogol, Jerry L. Nadler, Magnesium Deficiency Is Associated With Insulin Resistance in Obese Children Diabetes Care May 2005, 28 (5) 1175-1181; DOI: 10.2337/diacare.28.5.1175.

24**.** Junji Takaya, Hirohiko Higashino, Yohnosuke Kobayashi . Intracellular magnesium and insulin resistance . Magnesium Research. 2004;17(2):126-136.

25. https://en.wikipedia.org/wiki/Tyrosine_kinase.

26. Paxton, R., Ye, L. Regulation of heart insulin receptor tyrosine kinase activity by magnesium and spermine. Mol Cell Biochem **277,** 7–17 (2005). https://doi.org/10.1007/s11010-005-5755-4.

27. Kostov K. Effects of Magnesium Deficiency on Mechanisms of Insulin Resistance in Type 2 Diabetes: Focusing on the Processes of Insulin Secretion and Signaling. Int J Mol Sci. 2019;20(6):1351. Published 2019 Mar 18. doi:10.3390/ijms20061351.

28. https://www.medicalnewstoday.com/articles/286839.

29. Uwitonze AM, Razzaque MS. Role of Magnesium in Vitamin D Activation and Function. J Am Osteopath Assoc. 2018 Mar 1;118(3):181-189. doi: 10.7556/jaoa.2018.037. PMID: 29480918.

30. Cho S, Chae JS, Shin H, Shin Y, Kim Y, Kil EJ, Byun HS, Cho SH, Park S, Lee S, Yeom CH. Enhanced Anticancer Effect of Adding Magnesium to Vitamin C Therapy: Inhibition of Hormetic Response by SVCT-2 Activation. Transl Oncol. 2020 Feb;13(2):401-409. doi: 10.1016/j.tranon.2019.10.017. Epub 2019 Dec 31. PMID: 31901552; PMCID: PMC6940627.

31. Djokic G, Vojvodić P, Korcok D, Agic A, Rankovic A, Djordjevic V, Vojvodic A, Vlaskovic-Jovicevic T, Peric-Hajzler Z, Matovic D, Vojvodic J, Sijan G, Wollina U, Tirant M, Thuong NV, Fioranelli M, Lotti T. The Effects of Magnesium - Melatonin - Vit B Complex Supplementation in Treatment of Insomnia. Open Access Maced J Med Sci. 2019 Aug 30;7(18):3101-3105. doi: 10.3889/oamjms.2019.771. PMID: 31850132; PMCID: PMC6910806.

32. Maktabi M, Jamilian M, Amirani E, Chamani M, Asemi Z. The effects of magnesium and vitamin E co-supplementation on parameters of glucose homeostasis and lipid profiles in patients with gestational diabetes. Lipids Health Dis. 2018 Jul 20;17(1):163. doi: 10.1186/s12944-018-0814-5. PMID: 30025522; PMCID: PMC6053775.

33. Jürgen Vormann, Magnesium and Kidney Health - More on the 'Forgotten Electrolyte', From: American Journal of Nephrology(Vol. 44, Issue 5), Nov. 1, 2016, https://go.gale.com/ps/i.do?id=GALE%7CA636872079&sid=googleScholar&v=2.1&it=r&linkaccess=abs&issn=02508095&p=HRCA&sw=w&userGroupName=anon%7Ef2f8d08c.

34. Judith Blaine, Michel Chonchol, Moshe Levi, Renal Control of Calcium, Phosphate, and Magnesium Homeostasis, CJASN Jul 2015, 10 (7) 1257-1272**;** DOI: 10.2215/CJN.09750913.

35. Gallai, V., Sarchielli, P., Morucci, P. and Abbritti, G. (1994), Magnesium Content of Mononuclear Blood Cells in Migraine Patients. Headache: The Journal of Head and Face Pain, 34: 160-165. https://doi.org/10.1111/j.1526-4610.1994.hed3403160.x.

36. Shi Z, Hu X, He K, Yuan B, Garg M. Joint association of magnesium and iron intake with anemia among Chinese adults. Nutrition. 2008 Oct;24(10):977-84. doi: 10.1016/j.nut.2008.05.002. Epub 2008 Jun 30. PMID: 18586459.

37. Liotta EM, Prabhakaran S, Sangha RS, Bush RA, Long AE, Trevick SA, Potts MB, Jahromi BS, Kim M, Manno EM, Sorond FA, Naidech AM, Maas MB. Magnesium, hemostasis, and outcomes in patients with intracerebral hemorrhage. Neurology. 2017 Aug 22;89(8):813-819. doi: 10.1212/WNL.0000000000004249. Epub 2017 Jul 26. PMID: 28747450; PMCID: PMC5580864.

38. Beaven, G.H., Parmar, J., Nash, G.B. *et al.* Effect of magnesium ions on red cell membrane properties. *J. Membrain Biol.* **118,** 251–257 (1990). https://doi.org/10.1007/BF01868609.

39. Cinar V, Nizamlioglu M, Mogulkoc R, Baltaci AK. Effects of magnesium supplementation on blood parameters of athletes at rest and after exercise. Biol Trace Elem Res. 2007 Mar;115(3):205-12. doi: 10.1007/BF02685995. PMID: 17625241.

40. Rafieian-Kopaie M, Nasri H. Platelet counts and mean platelet volume in association with serum magnesium in maintenance hemodialysis patients. *J Renal Inj Prev*. 2012;1(1):17-21. Published 2012 Jan 1. doi:10.12861/jrip.2012.08.

41. Jahnová E. (1997) Effect of Magnesium Administration on Proliferation and Differentiation of Lymphocytes. In: Theophanides T., Anastassopoulou J. (eds) Magnesium: Current Status and New Developments. Springer, Dordrecht. https://doi.org/10.1007/978-94-009-0057-8_66.

42. Nielsen FH. Magnesium deficiency and increased inflammation: current perspectives. *J Inflamm Res*. 2018;11:25-34. Published 2018 Jan 18. doi:10.2147/JIR.S136742.

43. Stefanie Dimov, Lisa K. Mundy, Jordana K. Bayer, Felice N. Jacka, Louise Canterford, George C. Patton. (2021) Diet quality and mental health problems in late childhood. *Nutritional Neuroscience* 24:1, pages 62-70.

44. Nielsen, Forrest H, Effects of magnesium depletion on inflammation in chronic disease, Current Opinion in Clinical Nutrition and Metabolic Care: November 2014 - Volume 17 - Issue 6 - p 525-530 doi: 10.1097/MCO.0000000000000093.

45. Yiqing Song, Tricia Y Li, Rob M van Dam, JoAnn E Manson, Frank B Hu, Magnesium intake and plasma concentrations of markers of systemic inflammation and endothelial dysfunction in women, *The American Journal of Clinical Nutrition*, Volume 85, Issue 4, April 2007, Pages 1068–1074, https://doi.org/10.1093/ajcn/85.4.1068.

46. Sara A Chacko, James Sul, Yiqing Song, Xinmin Li, James LeBlanc, Yuko You, Anthony Butch, Simin Liu, Magnesium supplementation, metabolic and inflammatory markers, and global genomic and proteomic profiling: a randomized, double-blind, controlled, crossover trial in overweight individuals, *The American Journal of Clinical Nutrition*, Volume 93, Issue 2, February 2011, Pages 463–473, https://doi.org/10.3945/ajcn.110.002949.

47. Maria Kharitonova, Igor Iezhitsa, Anastasia Zheltova, Alexander Ozerov, Alexander Spasov, Anatoly Skalny, Comparative angioprotective effects of magnesium compounds,Journal of Trace Elements in Medicine and Biology,Volume 29, 2015,Pages 227-234,ISSN 0946-672X, https://doi.org/10.1016/j.jtemb.2014.06.026.

48. DiNicolantonio JJ, O'Keefe JH. Magnesium and Vitamin D Deficiency as a Potential Cause of Immune Dysfunction, Cytokine Storm and Disseminated Intravascular Coagulation in covid-19 patients. Mo Med. 2021 Jan-Feb;118(1):68-73. PMID: 33551489; PMCID: PMC7861592.

49. Jeanette A. Maier, Sara Castiglioni, Laura Locatelli, Monica Zocchi, André Mazur, Magnesium and inflammation: Advances and perspectives, Seminars in Cell & Developmental Biology, Volume 115, 2021,Pages 37-44,ISSN 1084-9521, https://doi.org/10.1016/j.semcdb.2020.11.002.

50. Stefano Iotti, Federica Wolf, André Mazur, Jeanette A. Maier. The COVID-19 pandemic: is there a role for magnesium? Hypotheses and perspectives. Magnesium Research. 2020;33(2):21-27. doi:10.1684/mrh.2020.0465.

51. Taylor C. Wallace (2020) Combating COVID-19 and Building Immune Resilience: A Potential Role for Magnesium Nutrition?, Journal of the American College of Nutrition, 39:8, 685-693, DOI: 10.1080/07315724.2020.1785971.

52. Lyly Nazemi , Mamak Shariat , Mohammad Mehdi Soltan Dallal , Sorourolsadat Daneshfar and Zahra Farahani, The possible correlation between magnesium deficiency and SARS-CoV-2 infection, World Journal of Advanced Research and Reviews, 2021, 11(01), 073–080, DOI: https://doi.org/10.30574/wjarr.2021.11.1.0316.

53. Dominguez, L.J.; Veronese, N.; Guerrero-Romero, F.; Barbagallo, M. Magnesium in Infectious Diseases in Older People. *Nutrients* **2021**, *13*, 180. https://doi.org/10.3390/nu13010180.

54.A ndrzej Mazur, Jeanette A.M. Maier, Edmond Rock, Elyett Gueux, Wojciech Nowacki, Yves Rayssiguier, Magnesium and the inflammatory response: Potential physiopathological implications,Archives of Biochemistry and Biophysics,Volume 458, Issue 1,2007,Pages 48-56,ISSN 0003-9861,https://doi.org/10.1016/j.abb.2006.03.031.

55. https://betteryou.com/blogs/health-hub/magnesium-zinc#:~:text=Magnesium%20helps%20your%20body%20regulate%20its%20zinc%20levels%2C,the%20health%20benefits%20of%20taking%20magnesium%20and%20zinc%3F.

56. https://www.oatext.com/proposed-mechanism-for-anosmia-during-covid-19-the-role-of-local-zinc-distribution.php.

57. Kruse RA, Cambron JA. A possible correlation between vitamin D deficiency and loss of smell: 2 case reports. J Chiropr Med. 2011 Dec;10(4):310-5. doi: 10.1016/j.jcm.2011.06.006. PMID: 22654691; PMCID: PMC3315864.

58. Porter MA, Grodzinski B. Regulation of chloroplastic carbonic anhydrase : effect of magnesium. Plant Physiol. 1983 Jul;72(3):604-5. doi: 10.1104/pp.72.3.604. PMID: 16663052; PMCID: PMC1066287.

59. Forrest H. Nielsen, Chapter 31 - Relation between Magnesium Deficiency and Sleep Disorders and Associated Pathological Changes, Editor(s): Ronald Ross Watson, Modulation of Sleep by Obesity, Diabetes, Age, and Diet, Academic Press,

2015, Pages 291-296, ISBN 9780124201682, https://doi.org/10.1016/B978-0-12-420168-2.00031-4.

60.Elise Chahine, How Magnesium Can Help You Sleep, May20,2021, https://www.sleepfoundation.org/magnesium.

61. Marie-Laure Derom, Carmen Sayón-Orea, José María Martínez-Ortega & Miguel A. Martínez-González (2013) Magnesium and depression: a systematic review, Nutritional Neuroscience, 16:5, 191-206, DOI: 10.1179/1476830512Y.0000000044.

62. George A. Eby, Karen L. Eby,Rapid recovery from major depression using magnesium treatment,Medical Hypotheses,Volume 67, Issue 2, 2006,Pages 362-370,

ISSN 0306-9877,https://doi.org/10.1016/j.mehy.2006.01.047.

63. Barbara Aufiero, Magnesium as Treatment for Bipolar Disorder, 05 December, 2018, https://healthfully.com/magnesium-as-treatment-for-bipolar-disorder-6417179.html#:~:text=Researchers%20found%20that%20magnesium%20was%20generally%20effective%20for,severe%20shifts%20in%20mood%20from%20mania%20to%20depression.

64.Max Mugambi, for Migraines: What You Need To Know, March 11, 2021, https://www.mymigraineteam.com/resources/magnesium-for-migraines-what-you-need-to know#:~:text=Some%20suggest%20that%20stress%20caused%20by%20migraines%20leads,migraine%2C%20but%20further%20research%20needs%20to%20be%20conducted.

65. Viski S., Szöllosi J., Kiss A.S., Csikkel-Szolnoki A. (1997) Effects of Magnesium on Spermiogenesis. In: Theophanides T., Anastassopoulou J. (eds) Magnesium: Current Status and New Developments. Springer, Dordrecht. https://doi.org/10.1007/978-94-009-0057-8_69.

66. Jill Seladi, Are Your Migraine Attacks a Symptom of the New Coronavirus?, August 27, 2020, https://www.healthline.com/health/headache/coronavirus-migraines.

67. T. Klopfenstein, N.J. Kadiane-Oussou, L. Toko, P.-Y. Royer, Q. Lepiller, V. Gendrin, S. Zayet, Features of anosmia in COVID-19,Médecine et Maladies Infectieuses, Volume 50, Issue 5,2020,Pages 436-439,ISSN 0399-077X,https://doi.org/10.1016/j.medmal.2020.04.006.

68. Lozada-Nur F, Chainani-Wu N, Fortuna G, Sroussi H. Dysgeusia in COVID-19: Possible Mechanisms and Implications. Oral Surg Oral Med Oral Pathol Oral Radiol. 2020 Sep;130(3):344-346. doi: 10.1016/j.oooo.2020.06.016. Epub 2020 Jun 27. PMID: 32703719; PMCID: PMC7320705.

69. Michael Fink, Vitamin D Deficiency Is a Cofactor of Chemotherapy-Induced Mucocutaneous Toxicity and Dysgeusia ,Journal of Clinical Oncology 2011 29:4, e81-e82 , doi=10.1200/JCO.2010.31.5317.

70. Ken Harris, Is my sore throat COVID.19 or not?, January 22, 2021, https://www.osfhealthcare.org/blog/is-my-sore-throat-covid-19-or-not/.

71. Teymourian H, Mohajerani SA, Farahbod A. Magnesium and Ketamine Gargle and Postoperative Sore Throat. Anesth Pain Med. 2015 Jun 22;5(3):e22367. doi: 10.5812/aapm.5(3)2015.22367. PMID: 26161316; PMCID: PMC4493740.

72. Rudroff T, Fietsam AC, Deters JR, Bryant AD, Kamholz J. Post-COVID-19 Fatigue: Potential Contributing Factors. *Brain Sciences*. 2020; 10(12):1012. https://doi.org/10.3390/brainsci10121012.

73. Daniel Yetman on April 29, 2020, Diarrhea and Other Confirmed Gastrointestinal Symptoms of COVID-19, https://www.healthline.com/health/coronavirus-diarrhea.
74.Cathleen Crichton-Stuart, How can I tell if I have low magnesium? June20,2018, https://www.medicalnewstoday.com/articles/322191.
75.Courtney Sperlazza, Are You Tired, or Is It Low Magnesium? Signs of Magnesium Deficiency, MARCH 30, 2021, https://www.bulletproof.com/supplements/vitamins-minerals/magnesium-deficiency-supplements-causes/.
76. Atli Arnarson, 7 Signs and Symptoms of Magnesium Deficiency, March25,2021, https://www.healthline.com/nutrition/magnesium-deficiency-symptoms.
77.Saurabh Sehti, How Long Does It Take to Heal a Leaky Gut?, September 4,2019, https://www.healthline.com/health/how-long-does-it-take-to-heal-leaky-gut.
78. DR. WILL COLE, The Important Signs Of Magnesium Deficiency + How To Fix It, https://drwillcole.com/functional-medicine/having-enough-magnesium.
79. Alexa Fry, Definition, Symptoms, and Solutions, updated April 14,2021, https://www.sleepfoundation.org/covid-19-and-sleep/coronasomnia.
80. Gao W, Guo W, Guo Y, Shi M, Dong G, Wang G, Ge Q, Zhu J, Zhou X. Thyroid hormone concentrations in severely or critically ill patients with COVID-19. J Endocrinol Invest. 2021 May;44(5):1031-1040. doi: 10.1007/s40618-020-01460-w. Epub 2020 Nov 2. PMID: 33140379; PMCID: PMC7605732.
81. https://www.palomahealth.com/learn/benefits-magnesium-thyroid-health#:~:text=We%20need%20magnesium%20to%20convert%20the%20inactive%20thyroid,our%20thyroid%20is%20not%20able%20to%20function%20correctly.
82. Parmita Uniyal, Post-Covid Skin And Hair Issues You May Face And What To Do About Them, Jun 03, 2021, https://www.onlymyhealth.com/post-covid-skin-and-hair-issues-1622718426.
83. Minaz, How to Use Magnesium to Reduce Hair Fall (A Vital Mineral for Your Hair), https://www.hairbuddha.net/magnesium-for-hair-loss/#:~:text=Since%20magnesium%20takes%20part%20in%20making%20protein%20as,beneficial%20for%20the%20health%20of%20the%20blood%20vessels.
84. Taribagil P, Creer D, Tahir H'Long COVID' syndrome BMJ Case Reports CP 2021;14:e241485.
85. DECCAN CHRONICLE. | KANIZA GARARI, Patients develop bone issues post Covid-19, Aug 7, 2021, https://www.deccanchronicle.com/nation/current-affairs/060821/patients-develop-bone-issues-post-covid-19.html.

86. Matthew B. Buechler, Shannon J. Turley,A short field guide to fibroblast function in immunity, Seminars in Immunology, Volume 35,2018,Pages 48-58,ISSN 10445323,https://doi.org/10.1016/j.smim.2017.11.001.
87. Sturtzel C. Endothelial Cells. Adv Exp Med Biol. 2017;1003:71-91. doi: 10.1007/978-3-319-57613-8_4. PMID: 28667554.
88. Graham Lawton, Premature ageing of the immune system may be one cause of long covid, 12 May 2021 , https://www.newscientist.com/article/mg25033343-000-premature-ageing-of-the-immune-system-may-be-one-cause-of-long-covid/#ixzz73vXrOsMn.

89. Robert B. Layzer, and Lewis P. Rowland, Cramps, N Engl J Med 1971; 285:31-40 ,DOI: 10.1056/NEJM197107012850109.

90. https://covid.joinzoe.com/post/are-muscle-pains-a-symptom-of-covid-19.

91. Zhao Y, Jiang Z, Guo S, Wu P, Lu Q, Xu Y, Liu L, Su S, Shi L, Que J, Sun Y, Sun Y, Deng J, Meng S, Yan W, Yuan K, Sun S, Yang L, Ran M, Kosten TR, Strang J, Lu Y, Huang G, Lu L, Bao Y, Shi J. Association of Symptoms of Attention Deficit and Hyperactivity with Problematic Internet Use among University Students in Wuhan, China During the COVID-19 Pandemic. J Affect Disord. 2021 May 1;286:220-227. doi: 10.1016/j.jad.2021.02.078. Epub 2021 Mar 5. PMID: 33740639.

92. Effatpanah M, Rezaei M, Effatpanah H, Effatpanah Z, Varkaneh HK, Mousavi SM, Fatahi S, Rinaldi G, Hashemi R. Magnesium status and attention deficit hyperactivity disorder (ADHD): A meta-analysis. Psychiatry Res. 2019 Apr;274:228-234. doi: 10.1016/j.psychres.2019.02.043. Epub 2019 Feb 19. PMID: 30807974.

93. Marcelo Campos, Energy & Fatigue, Is adrenal fatigue "real"?, https://www.health.harvard.edu/blog/is-adrenal-fatigue-real-2018022813344.

94. Rimesh Pal, Mainak Banerjee, Sanjay K Bhadada,The Lancet, Diabetes & Endocrinology, Vol 8 October 2020, DOI:https://doi.org/10.1016/S2213-8587(20)30304-1.

95. Anna Serefko, Aleksandra Szopa, Piotr Wlaź, Gabriel Nowak, Maria Radziwoń-Zaleska, Michał Skalski, Ewa Poleszak,Magnesium in depression,Pharmacological Reports,Volume 65, Issue 3,2013,Pages 547-554,ISSN 1734-1140, https://doi.org/10.1016/S1734-1140(13)71032-6.

96. Zandifar, A., Badrfam, R., Yazdani, S. *et al.* Prevalence and severity of depression, anxiety, stress and perceived stress in hospitalized patients with COVID-

19. *J Diabetes Metab Disord* **19,** 1431–1438 (2020). https://doi.org/10.1007/s40200-020-00667-1.

97. RT staff, NIH DEVELOPING ASTHMA-CORONAVIRUS RESEARC, May 5, 2020 | Asthma, Other Infections**,** https://rtmagazine.com/disorders-diseases/chronic-pulmonary-disorders/asthma/nih-asthma-coronavirus-research/**.**

98**.** Liu AL, Xu N, Li AJ. COVID-19 with asthma: A case report. World J Clin Cases. 2020 Aug 6;8(15):3355-3364. doi: 10.12998/wjcc.v8.i15.3355. PMID: 32874993; PMCID: PMC7441254**.**

99. Mardani R, Ahmadi Vasmehjani A, Zali F, Gholami A, Mousavi Nasab SD, Kaghazian H, Kaviani M, Ahmadi N. Laboratory Parameters in Detection of COVID-19 Patients with Positive RT-PCR; a Diagnostic Accuracy Study. Arch Acad Emerg Med. 2020 Apr 4;8(1):e43. PMID: 32259132; PMCID: PMC7130449.

100. Tavakolpour S, Rakhshandehroo T, Wei EX, Rashidian M. Lymphopenia during the COVID-19 infection: What it shows and what can be learned. Immunol Lett. 2020 Sep;225:31-32. doi: 10.1016/j.imlet.2020.06.013. Epub 2020 Jun 20. PMID: 32569607; PMCID: PMC7305732.

101. Matović V, Plamenac Bulat Z, Djukić-Cosić D, Soldatović D. Antagonism between cadmium and magnesium: a possible role of magnesium in therapy of cadmium intoxication. Magnes Res. 2010 Mar;23(1):19-26. doi: 10.1684/mrh.2010.0196. Epub 2010 Mar 12. PMID: 20228012.

102. Spasojevic-Kalimanovska V, Jovanovic M, Boricic N, Wallace D, Bulat Z. Toxic Effect of Acute Cadmium and Lead Exposure in Rat Blood, Liver, and Kidney. Int J Environ Res Public Health. 2019 Jan 18;16(2):274. doi: 10.3390/ijerph16020274. PMID: 30669347; PMCID: PMC6351928.

103. Taghioff SM, Slavin BR, Holton T, Singh D. Examining the potential benefits of the influenza vaccine against SARS-CoV-2: A retrospective cohort analysis of 74,754 patients. PLoS One. 2021 Aug 3;16(8):e0255541. doi: 10.1371/journal.pone.0255541. PMID: 34343191; PMCID: PMC8330918.

104. Priya Ramaswamy, Malathi Kurre, Dominik Muller, Paul Dargan, Evelien Gevers, Jeremy Allgrove, HYPOMAGNESAEMIA DUE TO LEAD POISONING IN THE CONTEXT OF A HETEROZYGOUS CLDN-16 VARIANT, https://www.endocrine-abstracts.org/ea/0039/eposters/ea0039EP100_eposter.pdf.

105. Marica Krajčovičová-Kudláčková, Monika Ursínyová, Vlasta Mašánová, Alžbeta Béderová, Martina Valachovičová, CADMIUM BLOOD CONCENTRATIONS IN RELATION TO NUTRITION, Cent Eur J Publ Health 2006; 14 (3): 126–129,doi 10.21101/cejph.a3385.