UNDERSTANDING THE IMPORTANCE OF MAGNESIUM IN HUMAN BODY AND ITS ORTHOPEDIC APPLICATIONS

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CANDIDATE'S DECLARATION

We, Chetna (2k22/MSCCHE/07) and Ayush Sharma (2k22/MSCCHE/04), students of M.Sc. Chemistry, hereby certify that the work which is being presented in the dissertation entitled **"Understanding the Importance of Magnesium in Human Body and its Orthopedic Applications"**, in partial fulfilment of the requirements for the award of the Degree of Master of Science, submitted to the Department of Applied Chemistry, Delhi Technological University is an authentic record of our own work carried out under the supervision of Dr. Deenan Santhiya.

The matter presented in the dissertation has not been submitted by us for the award of any other degree of this or any other Institute.

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CERTIFICATE

I, hereby certify that the dissertation titled **"Understanding the Importance of Magnesium in Human Body and its Orthopedic Applications"** which is submitted by CHETNA (2K22/MSCCHE/07) and AYUSH SHARMA (2k22/MSCCHE/04) to the Department of Applied Chemistry, Delhi Technological University, Delhi in partial fulfillment of the requirement for the award of Master of Science. This dissertation embodies results of original work, and studies are carried out by the students themselves and the contents of this dissertation do not form the basis for the award of any other degree to the candidates or to anybody else from this or any other University/Institution.

Place: Delhi

DR. DEENAN SANTHIYA
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Date: 30th May 2024

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ABSTRACT

Magnesium is one the most important trace mineral in the human body. It plays a pivotal role in various physiological processes which includes enzymatic reactions, neural activity and muscle function. The significance of magnesium generally gets overlooked which sometimes can result in hypomagnesemia or magnesium deficiency in serum concentrations.

Magnesium like calcium is very good for skeletal health and it takes part in helping in the absorption of calcium onto bones.

This study explores the multifaceted importance of magnesium in human body, with an emphasis on its function in enhancing the bone health. It delves into the orthopedic applications of magnesium and highlights its use in fracture healing, bone density improvement, as a component in biodegradable implants.

We have studied all the recent advancements in magnesium-based biomaterials, discussing their mechanical properties, biocompatibility and their potential to revolutionize orthopedic treatments.

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CHAPTER 1: INTRODUCTION AND LITERATURE SURVEY

1.1 INTRODUCTION

Since ancient times, magnesium has been known to exist as one of the most prevalent ions in the earth's crust. The district of Magnesia in Thessaly, which was a part of ancient Greece, is where the name originated. Magnesium is still prevalent in this area today. Magnesium serves as the primary component of chlorophyll in plants, much like iron does in haemoglobin. One cation that is vital to good health is magnesium. Magnesium sulphate, or MgSO4, was discovered by Dr. Nehemiah Grew in 1697 as the main component of Epsom salt. Epsom salt, which is used to treat cerebral edema, strained muscles, and abdominal pain, was being taken out of a well in Epsom, England. Joseph Black identified magnesium as an element in 1755. [1]

The human body consists of a number of minerals, some of them are major and some are trace minerals. Magnesium is considered to be one of the major minerals and is present in abundance out of which 60 to 65% is found in bone and 27% is located in muscles. [2]

In extracellular compartment i.e., fluids and blood a comparatively low percentage of about 1% is present. [3]

Magnesium impacts excitable permeability of membranes, neuromuscular transmission, and the electrical potential of nerve tissue. It also aids in the formation of bones and teeth and functions as a cofactor for more than 300 enzymes in the human body, including those involved in ATP binding for kinase activities. [4]

1.2 HYPOMAGNESEMIA

According to The Nutrient Requirements Book for Indians, the recommended dietary allowances (RDA) for magnesium is 370 mg for women and 440 mg for men.(5) If taken in lesser amounts than expected, a deficiency of magnesium can take place in the human body, more commonly known as hypomagnesemia. Magnesium deficiency was first reported by Hirschfielder and Haury in 1934. [1] This takes place when a person has lower than normal levels of magnesium in their blood. It is rare in healthy people but, if present, it can be connected to a number of diseases including both physiological and psychological disorders. Magnesium homeostasis in humans involves the kidney, intestines and bones.[5] Magnesium absorption is a complicated process and can depend on the magnesium status of each person.[6]

For magnesium absorption, mainly two pathways are involved, the paracellular pathway and transcellular pathway. In paracellular absorption, passive transport takes place and it is responsible for 80-90% of uptake. The active transport however is carried out by TRPM 6 (or transient receptor potential channel melastatin member 6) and TRPM7 Mg2+ channels. It has been noted that the mechanisms of magnesium absorption by regulatory factors are very unclear because despite intestinal absorption being dependent on magnesium status in the body it is still not directly proportional to dietary intake. In the large intestine, magnesium-specific transporters TRPM6 and TRPM7 will be required for active transcellular absorption in the event of a decreased dietary magnesium intake. Mutations in TRPM6 have been linked to hypomagnesemia in patients with secondary hypocalcemia and familial hypomagnesemia. [7]

Hypomagnesemia is a term that has been used for patients having total serum magnesium concentrations below 0.70 mM or less than 1.7mg/dL whereas hypermagnesemia occurs when concentrations are above 1.1 mM or 2.7mg/dL. Typical hypermagnesemia is quite rare and is commonly caused by overuse of drugs that have high amounts of Mg^{2+}. Whereas, hypomagnesemia is more common and chronic and can have various different causes as given in table 1. [8]

Table 1 Causes of Hypomagnesemia

S.No.	Causes	Examples
1.	Gastrointestinal Losses	Diarrhea, Vomiting, Nasogastric Suction, Proton Pump Inhibitors, Bariatric Surgery
2.	Hereditary	Hypercalciuric Hypomagnesemia, Gitelman-Like Hypomagnesemia, Mitochondrial Hypomagnesemia
3.	Renal Losses	*Familial:* Bartter syndrome, Familial hypomagnesemia with hypercalciuria and nephrocalcinosis *Acquired:* Medications, Alcohol Dependence, Hypercalcemia
4.	Drugs	EGFR Inhibitors, Platinum Derivative, Calcineurin Inhibitors, Cyclosporine, Tacrolimus
5.	Others	Refeeding, Sepsis, Prolonged Vigorous Exercise, Hungry bone syndrome.
6.	Miscellaneous	Proteinuria, Osmotic diuresis, Insulin resistance, Alcoholism, Primary and secondary hyperaldosterone.

1.3 EFFECTS OF HYPOMAGNESEMIA ON HUMAN BODY

Even though magnesium is one of the neglected and the least abundant serum electrolytes in the human body, it is still extremely crucial for a healthy and lasting life. [9] Magnesium helps in the metabolism of Ca, K, Cu, Zn, Fe, P, HCl, nitric oxide (NO) and acetylcholine. It helps in the activation of more than 300 enzymes, for activation of thiamine, for the intracellular homeostasis and therefore, for a very wide spectrum of crucial body functions. Since it is the most needed minerals in the body, its deficiency dangerously affects every function of the body.[10]

Sircus in 2007 said that "*Without a doubt, a magnesium deficiency is a primary cause of sickness. When our bodies aren't getting enough magnesium, there's nothing we can do to improve our condition of health, regardless of what we try to do with our cardiovascular systems, postures, or medical interventions*." [9]

Magnesium helps in the activation of adenosine triphosphate (ATP) which is a molecule that is responsible for energy storage in the body. It also helps in the transportation and production of energy in the human body and to transmit nerve signals and gives assistance to the muscles to relax. Thus, we can say that without magnesium there will neither be life nor movement. [9]

1.3.1. BONE HEALTH

Bone health is mainly dependent on minerals. It has been observed that most of the researchers focus their attention on calcium even though many other nutritional components and minerals can affect the metabolism of bones. In recent years, this attention seems to be shifted towards magnesium which is present in every type of cell in its ionic form i.e., Mg^{+2}. This ion affects the vitality of the cell and has multifaceted effects on the human body. [11]

According to studies done by Rude et al. about the modulation of activities like osteoblastic and osteoclastic, it was seen that the experimental animals shows an increased numbers of osteoclasts if they are given a Mg-deficient diet. [12] Many epidemiological studies have also shown that bone mass reduction and a decrease in BMD is related to a Mg-deficient diet. These results suggest that magnesium deficiency has a vital role in bone homeostasis. [13]

Magnesium deficiency affects the tissue of bone by two ways; direct pathways and indirect pathways. (Figure 1 and 2).

Figure 1 Direct effects of magnesium deficiency

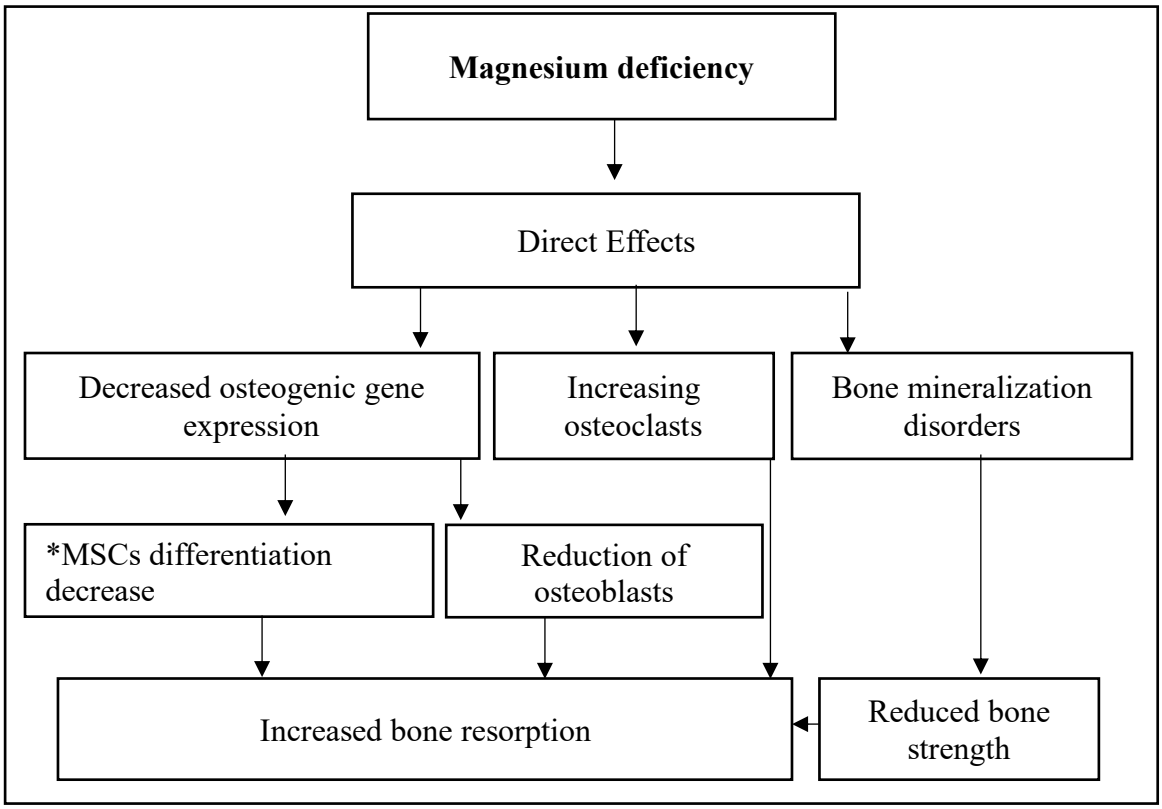
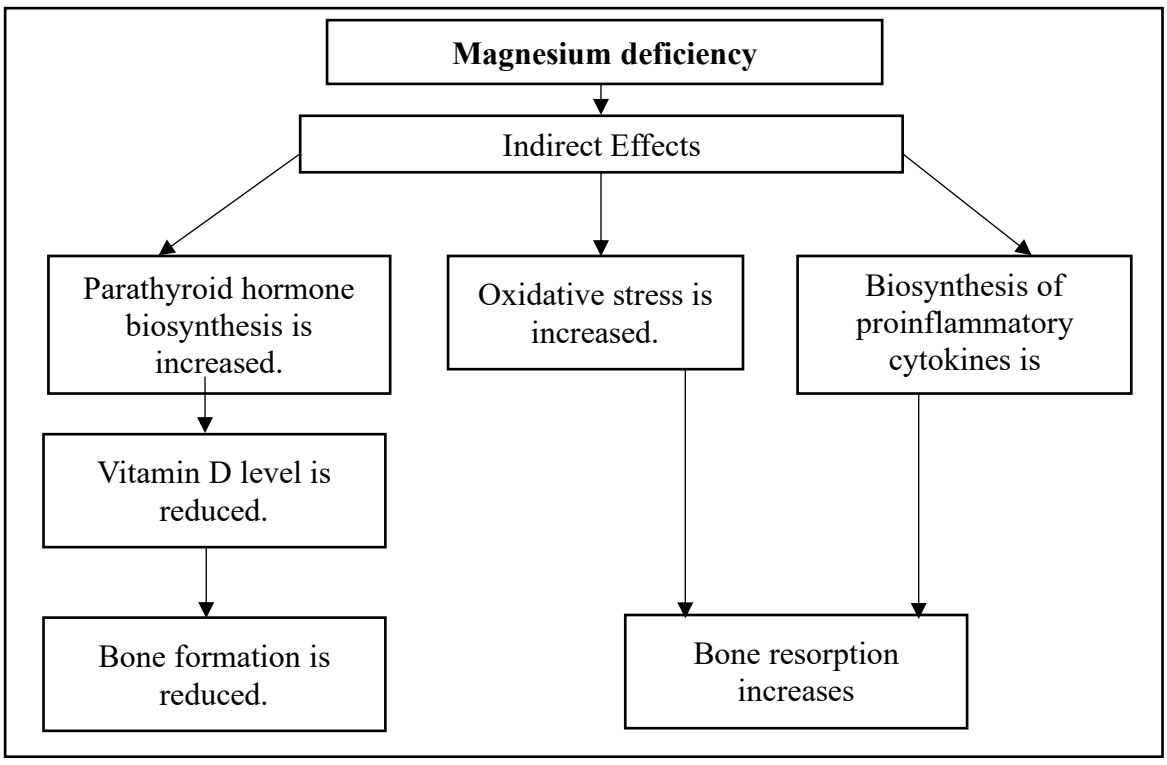


Figure 2 Indirect effects of magnesium deficiency



1.3.2. WOMEN'S HEALTH

Women are far more likely than males to have magnesium deficiencies in their bodies. This is because oestrogen increases the body's usage of magnesium by tissues, and women's hormonal cycles may influence and modify magnesium levels. [14] Frequency of SMD or subclinical magnesium deficiency is highly common even in overall healthy women. This inadequacy of magnesium in body roots from lower than recommended intake i.e. 240 mg/day. [15] This lower intake nowadays can be because of lower magnesium content in packaged food or fast food.

There are a number of biological stages that a woman goes through during her entire life. Some distinctive life events that can be considered are infancy, childbearing age, climacteric period, and elderly years, along with pregnancy and breastfeeding. The requirement for energy and nutrients changes as the stage changes which is also accompanied with hormonal changes in the body. [16] Magnesium deficiency may not have a significant impact on many adults, but it may have a greater one on those in high-risk groups, such as pregnant and menopausal women, who are more susceptible to osteoporosis due to decreased oestrogen output. [14], [15]

Based on research, it appears that pregnant women have a higher need for magnesium due to a combination of increased renal output, changed tissue distribution, and foetus need. Magnesium levels in pregnant women are recommended to be monitored closely because magnesium deficiency is said to be associated with preeclampsia and fetal growth retardation. [17]

Another high risk group is women undergoing menopause. Due to their elderly age, they are at a higher risk of getting bone disorders like osteoporosis or osteoarthritis which have been found to be associated with hypomagnesemia. [18]

1.3.3. EFFECT ON PATIENTS WITH DIABETES

Magnesium plays a vital role in the metabolism of carbohydrates. It may also affect the activity and release of the hormones in the body that are responsible for controlling blood glucose levels. [19] Individuals with type 2 diabetes have been frequently observed to have low blood levels of magnesium. [19] A chronic Mg deficit or clinical hypomagnesemia is common in patients having type 2 diabetes. Insulin and glucose are essential for Mg metabolism. [20]

Patients with type 2 diabetes and hypomagnesemia are at higher risk of developing diabetes-related complications and tend to have increased resistance to insulin. [21] People with insulin resistance are not able to use insulin effectively and they require higher amounts in order to have blood glucose in normal levels. [19]

Both extracellular and intracellular Mg deficits are related to type 2 diabetes.

It has been observed that older patients with diabetes are more prone to hypomagnesemia. In older adults with diabetes, ionized Mg may be used to identify concentrations of magnesium in blood. [20] Plasma Mg ion concentration is regularly observed among patients with T2DM (type 2 diabetes mellitus) and is generally less than those in non-diabetic healthy individuals. Globally, almost 14% to 48% of people with diabetes also have hypomagnesemia. [22]

The poor glycemic control and insulin resistance are also associated with increased CVD (cardiovascular disease) risk. Directly or indirectly, hypomagnesemia may also be responsible for CVD in T2D. [23]

Studies have shown that, patients with T2D who take metformin, glargine insulin or statin are more likely to have hypomagnesemia. [21]

1.3.4. DENTAL HEALTH

Hypomagnesemia can also trigger dental health, the alveolar bone becomes weak, which makes the gum become hypertrophic; if such deficiency takes place during tooth formation, dental eruption gets delayed, and hypoplasia of enamel or dentin may occur. [24]

There is a disease called periodontal disease (PD) which is most commonly responsible for tooth loss. It is a general chronic inflammatory disease that affects humans. Loss or extraction of teeth that can no longer support the functional demands is the final outcome of PD. It causes noteworthy impacts on oral health.

Majorly, PD results in destruction and inflammation of mineralized and non-mineralized tissues that help in supporting the tooth. It has been discovered that a magnesium deficit alters the phenotypic profile of immune cell infiltration, which may indicate that it is in charge of immune-mediated tissue death in PD.

We propose that magnesium insufficiency influences PD and its characteristic bone resorption caused by inflammation, taking into consideration the effects of magnesium consumption on the immune system and bone metabolism. It has been noted that a magnesium shortage might exacerbate inflammatory bone resorption and cause a systemic loss of bone mass. [25]

Magnesium & calcium both have a vital role in bone metabolism and turnover. They both are related to osteoporosis and reduction in bony tooth support which in turn increases the risk of tooth loss.[26]

An optimal calcium-to-magnesium must exist for better human tooth health. Consumption of only calcium and not magnesium results in soft enamel, which results in diminishing of resistance towards acids that may cause decay.

In teeth remineralization process, the role of magnesium is important as it participates in the growth and formation of hydroxyapatite crystals. When experiments are done on guinea pigs and they are fed a magnesium-deficient diet, their teeth fail to calcify normally which leads to discoloration, erosion and eventually breakage of incisors at the gum line. A study done by Danuta and colleagues on the relationship between magnesium content and fluoride in enamel and the depth of etching by perchloric acid showed that the both are interrelated. This finding proves that magnesium enhances resistance of enamel towards erosion. [24]

It is suggested that a diet high in magnesium content can improve periodontal health. Foods like grains, nuts and black chocolate are recommended as they are high in magnesium. [26]

1.3.5. CARDIOVASCULAR EFFECTS

Magnesium has a number of roles in the cardiovascular system, including protecting against stress, controlling potassium transport in myocardial cells, reducing platelet aggregation, and vasodilating both coronary and peripheral arteries. [27]

Heart failure (HF), arrhythmias, atherosclerosis, and stroke are among the disorders grouped under the umbrella term cardiovascular disease (CVD). When the heart is unable to pump sufficient blood to support the body's other organs, two types of heart failure may take place. The first is systolic heart failure (HF) with a reduced ejection fraction (HFrEF), which is caused by inadequate contractile performance. Another type is diastolic heart failure (sometimes referred to as HF with preserved ejection fraction, or HFpEF), which is caused by decreased heart filling during diastole. A new potential treatment for HFpEF has been suggested by recent reports indicating that magnesium (Mg) supplementation significantly protects heart diastolic function.

Diabetes and obesity are two conditions that have been linked to magnesium deficiency and are major risk factors for CVD. Metabolic illnesses have been found to have strong correlations with oxidative stress, inflammation, and hypomagnesemia.

As a result of reduced magnesium intake and increased magnesium loss, hypomagnesemia is common in patients with CVD. In congestive heart failure research, hypomagnesemia affects 38% of patients, while excessive magnesium loss affects 72% of patients. [28]

Reduced dietary magnesium consumption and serum magnesium concentrations have been associated with CVD development and death in a number of observational studies. Due to the uncertainty surrounding the causative association, individuals with other comorbidities are more likely to experience magnesium depletion, hence it is important to interpret these data cautiously. [29]

In those suffering from severe congestive heart failure, oral magnesium supplements have been proposed as a means for enhancing clinical signs and survival rates in comparison to placebo. Elevated magnesium serum levels were shown to correlate with a lower risk of cardiovascular disease, and elevated magnesium intakes through diet were found to be inversely linked with ischemic

heart disease, according to a meta-analysis and systematic review of prospective studies including over 300,000 participants. An additional meta-analysis of prospective studies with 241,378 participants revealed a negative correlation between magnesium consumption and stroke risk. It has been discovered that magnesium sulphate offers protection against stroke in both human and preclinical animals. If administered intravenously soon after the onset of a stroke, magnesium has been reported to have a certain efficacy and a favourable safety record. [30]

1.3.6. MIGRAINES

There is a theory that suggests migraine sufferers temporarily produce low serum magnesium due to stress-induced magnesium excretion during headache episodes. On the other hand, it's feasible that stress leads to the excretion of magnesium, which results in hypomagnesemia and migraines. Low magnesium levels in the CSF (cerebrospinal) fluid have also been linked to migraines, and in vivo 31P nuclear MRS (magnetic resonance spectroscopy) exhibits that low magnesium levels occurs in the brain during attacks and intermittently in certain patients.

Reduced magnesium concentration was seen in the posterior brain, especially the occipital cortex, of individuals with hemiplegic migraine, according to a different study that used 31P MRS imaging. Trend analysis in this study also showed a correlation between the severity of neurologic complaints and reductions in posterior brain Mg^{2+} concentration.

A lack of magnesium has been linked to CSD (cortical spreading depression), platelet aggregation, release of neurotransmitters, and vasoconstriction—all of which are significant aspects of the pathophysiology of migraines that we now understand. Additionally, a lack of magnesium causes the synthesis and release of the substance P, that appears to act on sensory fibres to cause headache discomfort. Therefore, by preventing vasospasm, preventing platelet aggregation, stabilising cell membranes, and lowering the production of inflammatory mediators, external magnesium may help target several elements of the inflammation of neurons that arise during migraine. [31]

Due to changes in neurotransmitter release, activation of CSD, and an increase in platelet aggregation, magnesium shortage plays a crucial part in the

pathophysiology of migraine headaches. The spreading depression, which is characterised by the loss of ion homeostasis, is linked to a brief halt in neuronal activity, is thought to be involved in the pathophysiology of migraines, and requires a release of glutamate. The spread of this process depends critically on N-methyl-D-aspartate receptors. Magnesium inhibits migraines' neurogenic and vascular causes. Because magnesium blocks the NMDA receptor, a receptor known to play a significant role in the transmission of pain, it has also been proposed as a therapy option for migraines. Furthermore, magnesium modifies the release of substance P, regulates the generation of NO, and maintains calcium homeostasis via NMDA receptor binding.

A recent open-trial study's findings demonstrated the effectiveness of tanacetum parthenium, 5-hydroxytryptophan (5-HTP), and magnesium in the prevention of migraines. Aurastop, which was given twice daily for three months and was made of tanacetum parthenium (150 mg of extracted active parthenolide), Griffonia simplicifolia (20 mg of 5-HTP), and magnesium (185 mg of magnesium pidolatum), considerably reduced the frequency of migraine attacks, their duration, and the intensity of their pain in the majority of patients.

A lot of people are searching for a preventive treatment for migraines due to the side effects of these drugs. Magnesium affects voltage-gated calcium channels, connexin channels, NMDA receptors, and other ion channels in the nervous system in a variety of ways. It serves as the backup course of treatment for migraineurs. [32]

1.3.7. MENTAL HEALTH

There is a significant correlation between mental health disorders and concentration of nutrients in the human body. Many disorders might not happen because of a nutrient deficit but can become the reason for it and ultimately affect the physical health and quality of life.

Eating disorders such as binge eating disorder, bulimia nervosa, anorexia nervosa, ARFID & OSFED; they all result in an irregular supply of food and nutrition which then causes a deficiency of minerals, vitamins, fats, protein, water and carbohydrates in the human body.

The microbiome gut-brain axis, endogenous hormones, neuropeptides and neurotransmitters, and the composition, structure, and function of the brain are all affected by dietary profile. These factors collectively play a crucial role in regulating stress and inflammation as well as maintaining cognitive function. Due to their many biological functions, micronutrients (such as minerals and vitamins) and macronutrients (such as fatty acids) supplements can have a number of positive impacts alongside a diet that is balanced and healthy. [33]

The linkage of magnesium deficiency to mental health disorders has been studied extensively.

Neuropathologies are known to be produced by magnesium deficits. Magnesium ions control the passage of calcium ions through neuronal calcium channels, which in turn controls the synthesis of nitric oxide in neurons. Depression may appear as a result of neuronal damage brought on by unfulfilled magnesium requirements in the brain. Treatment with magnesium is thought to be useful in treating serious depression brought on by deficiencies in intraneural magnesium. Stress hormones, too much calcium in the diet, and magnesium deficiency in the diet can all cause these magnesium-induced neuronal deficits. [34]

Additionally, a magnesium-deficient diet is also known for causing anxiety-like behaviors. [33]

A prevalent neurodevelopmental problem, ADHD is linked to deficiencies in certain vitamins and minerals. Although research on children that have ADHD have revealed shortages in specific nutrients, including magnesium and vitamin D, it has not been demonstrated that dietary deficiencies cause ADHD in children.

Magnesium is an important mineral that is linked to cognitive decline and can cause symptoms including anxiety, irritability, exhaustion, and mood changes. Magnesium supplementation was found to considerably reduce clinical symptoms in people with ADHD, according to a study by Baza et al. A meta-analysis by Effatpanah et al. revealed that adolescents and children with ADHD had serum magnesium levels that were significantly lower than those of the control group.

According to one study, blood levels of magnesium in individuals with ADHD were considerably lower than those in both the general population and laboratory references. Consequently, it stands to reason that magnesium supplementation in this patient population can assist alleviate symptoms, considering the role magnesium plays in the neurological system. Supplementing with magnesium has also been demonstrated to improve a number of signs of mental health. When compared with both the control group and the clinical state before supplementation, a randomized clinical trial using supplementation with magnesium (200 mg/day) around six months showed a significant reduction in hyperactivity, regardless of any mental illnesses coexisting with the condition. [35]

Reduced serum levels of magnesium were linked to depressive symptoms in individuals treated in primary care, according to a number of research, which finally supported the use of supplementary magnesium as a therapy. As a result, magnesium may serve as a biomarker of a patient's reaction to pharmacological treatment in the case of mood disorders, as suggested by a prior review. In fact, compared to healthy controls, patients with therapy-resistant depression seem to have decreased central nervous system magnesium levels. A dose of this mineral taken in addition to regular antidepressant treatment may help improve the course of depression in patients with lower levels of magnesium, a target for nutrition therapies. [36]

Magnesium has gamma-aminobutyric acid receptor agonist activity and antagonizes the N-methyl-d-aspartate (NMDA) receptor; both mechanisms could be the reason of the anxiolytic effects or antidepressant action of magnesium seen in animal models. The NMDAR antagonist ketamine, a fast-acting antidepressant, also targets this similar area. [36]

1.3.8. NEUROMUSCULAR EFFECTS

A deficiency in magnesium has been associated with decreased strength due to impaired neuromuscular contractility and metabolic pathways, reduced blood glucose clearance due to disruptions in ion channels as well as transport proteins, and a decreased capacity to maintain elevated oxygen consumption levels due to disruptions in the enzymes involved in aerobic metabolism, transphosphorylation, and oxygen transportation.

The neuron at the junction of the neuromuscular system releases acetylcholine, which, with the help of Mg2+, attaches to a receptor in a synaptic cleft. Through a flow of potassium (K+) and sodium (Na+), this causes the sarcolemma to depolarize. Through the T-tubule system, this action potential travels through the sarcolemma and to the SR. The SR's ryanodine receptors (RyRs) open to permit calcium influx when a shift in Mg2+ is brought about by the polarity of the cells. When the concentration of calcium rises further, it binds to troponin within the thin actin filament, changing the filament's structural composition.

This change results in a crossbridge that connects the actin binding site and the myosin head, where ATP functions to promote the "power stroke" of muscle contraction. Pumping Ca2+ into the SR through particular pumping mechanisms causes muscle relaxation.

According to classical theory, divalent cations such as Na+, K+, and Ca2+ are primarily responsible for controlling muscle contraction. Nevertheless, physiologists have concluded that this is not the full picture since Mg2+ is an essential component of muscular contraction, which ultimately affects efficiency, strength, and endurance. This is due to several in vitro research conducted on animals as well as several recent in vivo investigations conducted on humans. [37]

Numerous researchers have looked into how skeletal muscle is affected by experimental magnesium shortage. The first compositional modifications of skeletal muscle often involve a small decrease in magnesium, an increase in calcium, and an increase in salt and chloride. Serum calcium concentration declines in cases of severe hypomagnesemia, which has been a constant finding. Serum potassium content has typically decreased when magnesium shortage has been present for a long enough duration. Even with persistent deficit, muscle magnesium levels may recover to normal. [38]

1.4 BONE DISORDERS DUE TO MAGNESIUM DEFICIENCY

1.4.1 OSTEOPOROSIS

Osteoporosis is a disease related to reduced bone mass, deteriorated bone structure and fragility fractures. Main symptoms include a stooped posture, back pain, and a bone that breaks more easily than expected. [39]

From an etiological point, osteoporosis is of two types: primary osteoporosis and secondary osteoporosis. The common form of primary osteoporosis in postmenopausal osteoporosis whereas secondary osteoporosis happens as an outcome of medical conditions that might result in decrease of BMD and some particular medications. [40]

It has been observed that magnesium deficiency is closely related to various bone disorders, particularly osteoporosis. Many studies have recognized that individuals with osteoporosis have significantly lower magnesium content in trabecular bone which suggests a direct correlation between magnesium levels and bone health. [41]

Magnesium deficiency can result in osteoporosis through the following mechanisms:

1. Modifications to the hydroxyapatite process may have an impact on bone mineralization, which may then increase bone turnover by promoting osteoclast activity. [42]
2. Disrupting the calcium homeostasis via influencing calcitriol (vitamin D) and parathyroid hormone (PTH), which may result in hypocalcemia.[42]
3. Remodelling and osteopenia are stimulated by inflammation induced by inflammatory cytokines. [42]
4. Encouraging malfunction of the endothelial. [42]

Studies of various human and animal models have confirmed that Mg deficiency is said to be connected with reduced osteoclastic and osteoblastic activity, osteopenia and skeletal fragility. So, it can be said that increasing magnesium intake might have positive effects on patients with osteoporosis. [43]

Deficiency in magnesium has been associated with compromised bone health and increased risk of osteoporosis. By ensuring adequate magnesium levels, supplementation may help support bone density and strength, potentially reducing the risk of fractures associated with osteoporosis. Additionally, magnesium's involvement in inflammation modulation and oxidative stress reduction may contribute to its protective effects on bone health. However, clinical evidence specifically addressing

the impact of magnesium supplementation on osteoporosis prevention or treatment is limited and inconsistent. [44]

1.4.2 OSTEOARTHRITIS

Due to the thick extracellular matrix (ECM) that surrounds the disease, nerves, blood vessels, stem cells, and highly specialized cells known as chondrocytes are sparsely distributed. Osteoarthritis, also referred to as is a multi-factor caused musculoskeletal illness with low self-repairing ability. Age may be one of the greatest predictors of osteoarthritis (OA) among all the risk factors associated with the condition, including non-modifiable systemic risk variables (age, race, ethnicity, and genetics), modifiable systemic risk variables (obesity, unhealthy diets), and local risk variables (muscle weakness, excessive physical activity, injury to the joint, mal-alignment of joint, length of leg inequality, etc.). [45], [46]

Osteoarthritis is said to be linked with Mg deficiency.

The elderly may be deficient in magnesium for a few different causes. First, as people age, their intestinal absorption of magnesium declines. Second, individuals with type 2 diabetic mellitus (T2DM) or individuals on diuretics, an anti-hypertensive drug, frequently exhibit magnesium insufficiency. Two ailments that affect the elderly frequently. Finally, consuming more calcium than recommended for the prevention of osteoporosis exacerbates the magnesium deficiency. A person is more likely to develop cardiovascular illnesses if they have low magnesium and high calcium levels. It should come as no surprise that there is mounting evidence linking a magnesium deficit to a host of age-related conditions, such as osteoporosis, the metabolic syndrome (MetS), a stroke, OA, cognitive impairment, hypertension, and type 2 diabetes.[46]

For MSCs to interact with the extracellular matrix, magnesium is necessary. Multiple divisions of the mesenchymal stem cells (or MSCs) can result in progeny that develop into skeletal tissues including cartilage and bone. It's critical to assess how magnesium affects MSCs because these tissues are crucial to the development of OA. It has been demonstrated that magnesium increases synovial MSC adherence, which in turn encourages cartilaginous matrix construction. The ability of human synovial MSCs, which adhere to slides coated in collagen while magnesium was present, demonstrated that magnesium can improve the adherence to collagen. [45]

Intracellular magnesium (Mg2+) is mostly found in mitochondria, which are organelles that produce energy. It is involved in oxidative phosphorylation as well as the synthesis and activation of adenosine triphosphate (ATP). When magnesium homeostasis is upset, oxidative stress rises, mitochondrial dysregulation is brought on, and eventually cellular senescence is set off. It is well known that human fibroblast and endothelial cells in culture age more quickly when magnesium levels are low. In addition, a diet low in magnesium exacerbates high blood pressure and raises the risk of heart attacks in vivo. Apart from the cells called endothelial cells and fibroblasts, it is uncertain if low magnesium can hasten the senescence of articular chondrocytes and cause osteoarthritis (OA); conversely, magnesium supplementation can eliminate aging chondrocytes and lessen the severity of OA. [45]

Mg2+ might preserve cartilage stem cells' survival and differential potency. By locally administering magnesium ions in the injured cartilage, magnesium becomes a new potential medication in the conservative management of osteoarthritis. The intriguing impact of magnesium on the musculoskeletal system encourages us to investigate the possibility of chondrocyte progenitors or stem cells in cartilage tissues and look for the reason behind these cells' declining capacity to repair cartilage. Determining the precise mechanism behind the magnesium ion curing impact on osteoarthritis would lead to novel discoveries regarding cartilage self-repairing mechanisms and practical treatment approaches for early OA. [45]

1.4.3 HYPOPARATHYROIDISM

When one or more of the parathyroid glands fail to generate enough parathyroid hormone, or are not active enough, you have hypoparathyroidism. Your blood's calcium level drops as a result of this. The most frequent reason is damage to or excision of each of the four parathyroid glands.

The hallmark of hypoparathyroidism is a parathyroid hormone-resistant or deficient state that results in hyperphosphatemia, hypercalciuria, and hypocalcaemia. [47]

Inadvertent injury to one or more parathyroid glands between thyroid surgery is the most frequent cause of hypoparathyroidism. It's important to rule out magnesium and vitamin D insufficiency as additional causes of hypocalcaemia. The parathyroid glands secrete PTH when there is insufficient or excessive magnesium in the body, which can lead to hypoparathyroidism and consequent hypocalcaemia. This is believed to be caused by either too much or too little magnesium, which interferes with PTH production and secretion in parathyroid glands by impairing cyclic AMP creation. [48]

When hypocalcaemia is identified by the ca-sensing receptors (CaSR) on the main cells, the parathyroid glands respond by increasing PTH production and secretion and maintaining calcium homeostasis. Through its impact on vitamin D hydroxylation, PTH indirectly affects the gastrointestinal tract in addition to mediating its effects at the levels of the kidneys and bone. Either hyper- or hypomagnesemia can cause impaired PTH secretion. In the context of hypomagnesemia (alcohol consumption, malnourishment, malabsorption, renal wasting, etc.) or hypermagnesemia (i.e., tocolysis), hypoparathyroidism may be temporary or reversible. [47]

Magnesium has a significant impact on both PTH secretion and PTH receptor activation.

Measurements of magnesium in the blood and 25(OH) vitamin D levels are necessary to rule out deficiencies that may be a factor in low serum calcium levels. In order to detect hypercalcemia or hypocalcaemia, a 24-hour urine collection and assessment of renal function are also necessary. [47]

It is extremely uncommon for hypoparathyroidism to result from external beam radiation or infiltrative illnesses.

In all cases of hypoparathyroidism, functional hypoparathyroidism (i.e., magnesium abnormalities) must always be ruled out. In fact, it can exacerbate symptoms associated

with hypoparathyroidism in addition to serving as a potential cause of hypoparathyroidism on its own. [49]

1.4.4 MUSCLE CRAMP AND BONE PAIN

Muscle cramps are involuntary, painful, and abrupt contractions of the muscles that usually affect the lower extremities. In situations where there is no illness, like during pregnancy or vigorous physical exercise, cramps can last anywhere from a few seconds to several minutes. Moreover, metabolic problems, motor neuron diseases, and neuropathies can cause cramps.

Low serum magnesium levels are one possible reason why haemodialysis patients experience cramping in their muscles. Poor health outcomes, such as muscle cramps, are linked to low serum magnesium concentrations. Increasing the magnesium concentration in the dialysate has the potential to enhance patients' serum magnesium levels and lead to many health benefits, like less vascular calcification. [50]

Muscle cramps can be caused by hypomagnesemia through at least 4 different physiological pathways.

i. A lack of magnesium inhibits the activity of Na+/K+ ATPase in muscle cells, which stops Na+ ions from entering cells and K+ ions from leaving them. The limit for stimulation of the nerve and neurotransmitter release can be lowered by a little depolarization of the cell membrane caused by the increased proportion of sodium to potassium ions within cells. This environment increases the likelihood that different stimuli may activate muscle cells, resulting in cramping and involuntary muscular spasms. [51]

ii. A lack of magnesium lowers the level of activity of Ca2+ ATPase in muscle cells, which in turn lowers the active movement of calcium ions during muscle contraction through the cytosol to the sarcoplasmic reticulum, or S for storage. A magnesium shortage may also affect the plasma membrane's Na+/Ca2+ exchange transporter, which increases the amount of calcium ions that enter the cytosol. Greater skeletal muscle excitability is associated with a high level of ATP and use of oxygen resulting from the surplus of calcium ions in the cytosol of muscle cells. [52]

iii. Cramping in the muscles may result from hypoparathyroidism. Hypomagnesemia can cause a reversible type of hypoparathyroidism by reducing the secretion of parathyroid hormones. Raising serum magnesium can swiftly restore normal levels of serum parathyroid hormone and the related hypocalcaemia, which may also be a factor in muscle cramps. This process usually takes a few days. Since low levels of circulating active Vitamin D in chronic renal disease have been linked to secondary hyperparathyroidism, this mechanism is not likely to be a substantial issue for those on maintenance haemodialysis. [53]

iv. By controlling the renal outer medullary K+ (ROMK) channels that are situated along the distal nephron, magnesium may indirectly contribute to the development of muscle cramps. These magnesium-dependent ROMK channels become inhibited when hypomagnesemia happens. Hypokalaemia may ensue from increased potassium output by the kidneys as a result of this. Muscle cramps may arise as a result of hypokalaemia's effect on the proper depolarization of muscle cells. [54]

2. CHAPTER 2: ORTHOPEDIC APPLICATIONS

2.1. MAGNESIUM BASED IMPLANTS

Each year, many people experience bone fractures as a result of illnesses or accidents. The majority of these fractures require surgical repair with implants because they are too complicated to be treated with outside medical intervention. Conventional techniques of the process of osteosynthesis as well as osteotomy employ permanent metal implants—such as screws or plates composed of steel or titanium alloys—to fix the bone, which are subsequently removed. This is especially important for patients who are still developing. Permanent implants made of metal are often taken out a year or two following the first procedure. [55]

To promote healing or make up for lost or absent bone tissue, orthopedic biomedical materials may be implanted in or close to a bone fracture. In the event that there are permanent metal implants, they are often surgically removed when the fracture heals. When biodegradable implants are used, they disintegrate in the body, therefore removal of the implants is not required once the fractured bone has healed. In terms of expenses, this guarantees a significant benefit for patients as well as the public healthcare system. [55]

At the moment, magnesium alloys are thought to be the most exciting materials for a variety of light-weight applications. Because of its desirable qualities, which include mechanical strength, resistance to corrosion, thermal conductivity, high specific strength, and electrical conductivity, magnesium alloys have demonstrated their value in the automotive, aerospace, medical, and electronics sectors during the past few decades. As a result, in many technical and biological applications, alloys based on magnesium are replacing traditional metals like titanium, steel, and cobalt. Due to their biodegradable nature, magnesium-based alloys have gained popularity recently as a temporary orthopedic implant material. The exceptional body compatibility of Mg alloys is another crucial and significant characteristic. Magnesium is not hazardous to human health, in contrast to titanium, cobalt, and steel. [56]

Furthermore, magnesium and magnesium alloys have an elastic modulus that is same as natural cortical bone, which successfully reduces the effects of stress shielding. Magnesium-based alloys erode in bodily fluids and tissue, releasing harmless magnesium ions, alloying elements and OH ions that the body may excrete. The

distinction of stem cells into the osteoblasts and the expression of gene proteins relevant to osteoblasts by osteoblasts are both directly accelerated by magnesium ions that are released from magnesium-based alloys. Additionally, Mg ions promote vascularization in newly formed bone cells, which is essential for the exchange of waste products and nutrients across bone tissues. It's interesting to note that magnesium ions can even stop the breakdown of bone tissue by controlling osteoclasts. [57]
The use of different alloys have different effects on the human body, some of the are discussed in the table 2.

Table 2 Different magnesium alloying agents and their effects [58]

Alloys	**Effect on mechanical properties**	**Effect on biocompatibility**	**Effect on corrosion resistance**	**Disadvantages**
Al	Grain size is refined by adding 1 to 5 wt. % Al	Decreases due to release of aluminium ions	Corrosion resistance increases	Probability of developing neurological diseases
Zn	Improves resistance to traction and aging in concentrations	Reduces harmful effects of impurities by Fe and Ni on corrosion	Decreases the rate of corrosion and hydrogen evolution up to 5 wt. %	In higher concentrations, it affects mineralization and cell differentiation
Ca	Grain refining	Increases up to 1.2 wt. %	Higher concentrations deteriorate corrosion resistance	Dissolved ions may cause arthritis or kidney stones
Mn	Significant grain refining	Promotes bone growth	Increases corrosion resistance	Neurotoxic

The biggest challenge associated with using magnesium based implants for fractures is the corrosion of the material.

Magnesium in biological environment goes through the given reactions:-

$Mg \rightarrow Mg^{2+} + 2e^-$ (anodic reaction)

$2H_2O + 2e^- \rightarrow H_2 + 2OH^-$ (cathodic reaction)

$2H_2O + O_2 + 4e^- \rightarrow 4OH^-$ (cathodic reaction)

$Mg^{2+} + 2OH^- \rightarrow Mg(OH)_2$ (compound formation)

When chlorine ions from nearby tissues interact with the coating of magnesium hydroxide that forms on the outside of magnesium alloys in the human body, the layer's ability to protect is compromised. Magnesium hydroxide $Mg(OH)_2$ will combine with chlorine to generate a water-soluble magnesium chloride, which will speed up the corrosion process when the quantity of chlorides in the environment reaches 30 mmol/L. The chemical reactions shown below represent these processes:

$Mg(OH)_2 + 2Cl^- \rightarrow MgCl_2$

$Mg + 2H_2O \rightarrow Mg(OH)_2 + H_2$

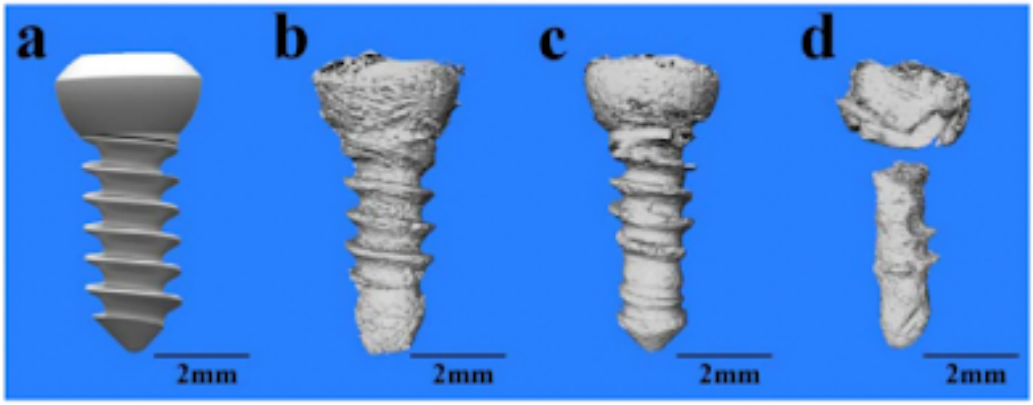
$Mg + 2Cl^- \rightarrow MgCl_2$

Given that the $MgCl_2$ salt has a modest solubility and is biocompatible with no discernible deleterious effects, the creation of a magnesium chloride layer on the outside of the implant will indicate a decrease in corrosion resistance. Conversely, the existence of hydroxyl ions raises the alkalinity, which when combined with phosphate and calcium ions causes different forms of calcium phosphates to precipitate as a surface protective layer. [55]

In engineering applications, corrosion is typically a bad thing since it causes material qualities to deteriorate. However, biodegradable implants offer great interest in the area of biomedical applications since they prevent patients from needing another surgery for removal of the permanent implant and also remove any potential long-term harm to the implant. Because of its great strength and biocompatibility, magnesium is a desirable biodegradable substance. However, as it breaks down, hydrogen is also eliminated, which can cause issues in some biological applications. The metal implants of magnesium that breaks down in aqueous solutions releases hydrogen, and the corrosion process's rise in pH could irritate the injured tissue. The hydrogen gas surrounding the implant eventually evaporates or can be extracted through a puncture,

which is sometimes "uncomfortable" but not dangerous. Magnesium has a beneficial impact in the biological process for growth of bones despite its relatively high level of corrosion; during its degradation, it releases Mg ions that are necessary to support human metabolism and have been shown to have stimulating impacts on the growth of new bone tissue. Mg-based materials are suggested for biodegradable orthopedic implants and cardiovascular stents because of these benefits. The chemical composition of the alloying metals, as well as various mechanical handling and coating techniques, can regulate the biodegradation kinetics for various magnesium alloys, or 3D structures. [55]

Figure 3 Biodegradation process of magnesium implant in its initial state (a) 3D images taken after 1 (b), 4 (c) and 7 (d) months after implantation.



Protective polymeric deposit coatings are another possible way to improve the corrosion resistance of magnesium alloy without changing the material's overall characteristics. The bulk characteristics of magnesium usually control mechanical integrity, but surface characteristics are crucial for a number of physio-chemical activities, such as bodily fluid contact and the adherence of cells and biomolecules to biomedical implants, which start the corrosion process. As a result, the coating ought to be biocompatible while also deteriorating more slowly than magnesium and its alloys. Coatings of polymeric deposits are appealing due to their range of degradation rates and strong biocompatibility with the body. [59]

Some of these coatings could be:-

1. Sol-gel coatings
2. Synthetic aliphatic polyester coatings
    a. Poly lactic acid
    b. Poly (lactic-co-glycolic) acid
    c. Poly caprolactone
    d. Polyethylenimine
3. Natural polymer coatings
    a. Collagen coatings
    b. Chitosan coatings
    c. Serum albumin coatings
4. Osteo inductive factor loaded coatings

Furthermore, deposit coatings on magnesium-based alloys may employ novel polymeric materials and multi-component systems in the future. The main benefit of solgel-based materials and synthetic polyesters (such as PLGA, PCL, and PLA) is their ease of chemical derivatization. This might make it possible to create new polymers with the intended characteristics, like improved mechanical qualities, a slow rate of hydrolysis, and less toxicity. To provide durable, non-corrosive, and biocompatible deposits coatings for orthopedic applications, coating methods can also comprise blending two or more polymers with desirable properties or layer-by-layer coating of various polymers. [59]

2.2. HARD TISSUE ENGINEERING

According to its definition, tissue engineering is a multidisciplinary discipline that uses engineering and biological science principles to create biological replacements that preserve, repair, or enhance tissue function or an organ as a whole. In order to replace or repair sections of entire tissues and organs, such as bones, blood vessels, cartilage, and skin, muscle, etc., it integrates biochemical and physio-chemical elements. The development of biomaterials intended to enhance cell growth and differentiation into a functional tissue, the facilitation of cell differentiation and proliferation techniques,

the acquisition of appropriate cell sources, differentiation, two-dimensional cell expansion, three-dimensional tissue growth, and cell and tissue storage are some of the most recent developments in tissue engineering research. One of the tissue engineering subfields that is most extensively researched is bone tissue engineering. [60]

Biomaterials are utilised in orthopedic procedures for a variety of purposes, including total joint arthroplasties, ligament and tendon repair, bone replacements, and the fixing and stabilisation of broken bones.

Bioresorbable materials have been more widely employed since the development of multifunctional tissue engineering because they may be used to transport bioactive molecules to promote the healing of a variety of hard and soft tissues, and they can be substituted with the patient's own tissue.

In orthopedics, biomaterial alternatives are now numerous and depend on tissue to be generated. Scaffolds made of synthetic polymers, silk, extracellular matrix, and fibrous collagen have all been investigated for the replacement or repair of ligaments and tendons. [61]

Therefore, a promising scaffold for bone tissue creation in load-bearing applications can be made of biodegradable magnesium scaffolds with the right mechanics coated with hydroxyapatite to improve corrosion resistance and to promote bone-forming capacity. Electrophoretic deposition, sputtering, sol-gel, and biomimetic deposits are a few of the methods available for coating metallic surfaces with hydroxyapatite.[62]

Even though biodegradable polymers are used to make scaffolds, their mechanical properties make them unsuitable for use as scaffolds in hard tissue engineering applications, where hard tissues like bone need to regenerate. For the scaffold to support the formation of bone tissue, it must be strong and have a Young's modulus that is comparable to that of bone. As a result, there seems to be a lot of interest in the use of biodegradable metallic materials as a scaffold production material in place of biodegradable polymers. Comparing metals to their conventional polymer alternative, there are several advantages. The fact that biodegradable metals are stronger and more physically and structurally stable than polymers is one of their key advantages. [60]

Metals like iron (Fe) and magnesium (Mg) foams have been investigated as possible scaffold materials. Similar to magnesium, these metals break down in the body in a safe manner. It is possible to create metal foams with the porosity and vasculature that are required for the formation of bones. A lot of research has been done on magnesium in relation to its possible application as a component of scaffold engineering for the

regeneration of bone tissue. The characteristics of magnesium that set it apart are that it resembles some of the characteristics of human bone. Researchers find magnesium's capacity to promote osteoblastic activity to be particularly intriguing. [60]

In other words, they promote osteoblast proliferation inside the scaffolds. Despite having these characteristics that make it an intriguing material, the primary issue with magnesium is that it breaks down more quickly than it heals, which lowers the implant's effectiveness. However, in the recent past, efforts have been made to decrease the pace at which pure magnesium degrades by employing magnesium alloys—which contain metals like zinc, aluminum, and zirconium—as well as surface coatings and changes. Magnesium's biocompatibility has been improved and its rate of breakdown has been regulated by surface modification approaches.

Magnesium improves the metabolism, crystallisation, and synthesis of bone minerals. Due to its resemblance and degradability in bone applications, magnesium is also being investigated for use as metallic degradable material for orthopedic implants. Because magnesium-based implants are osteoconductive, biocompatible, and biodegradable, they are utilised in load-bearing applications. Magnesium apatites have been shown to support osteoblast development and function. Additionally, by combining magnesium with bone cement, regulated degradability, biological, and mechanical properties have been attained. Magnesium has been shown to be bioresorbable, nontoxic, and to enhance bone development without inducing systemic or inflammatory reactions. By altering the porosity, the magnesium scaffold's rate of breakdown can be controlled. At this time, magnesium foams are being investigated for their potential use as scaffolds in bone tissue engineering. [60]

2.3. MAGNESIUM MATRIX NANOCOMPOSITE

Mg alloys are used for implants and are known for their better mechanical properties and biocompatibility but even those have drawbacks. [63]

It has been reported that implantation of Mg-based materials results in excessive H_2 evolution in a brief amount of time, which is dangerous for the tissues nearby, this is where nanocomposite biomaterials come into play in orthopedic applications. [64]

Metal acts as matrix and ceramic acts as the reinforcement in metal matrix nanocomposites, or MMNCs. Reinforced materials of this type are categorized as

continuous or non-continuous. Carbon nanotubes are metal matrix nanocomposites that (CNT-MMNC) are a newer kind of nanocomposites. CNT-MMNC has superior tensile strength and electrical conductivity when compared to materials made of carbon nanotubes. [65]

The ability to produce CNT-MMNCs affordably, distribute nanotubes uniformly inside the metal matrix, and create a strong bond within the metal matrix and carbon nanotubes are all important factors to take into account while developing processing processes. In addition to CNT-MMNC, carbon nitride metal matrix composites and boron nitride reinforced metal matrix composites are two other significant study areas of MMNC. [65]

The majority of metals and alloys available today can be employed as matrix materials, and for this purpose, dispersant materials that are stable throughout a variety of temperatures are needed. The only responsive metals are light metals, which is advantageous due to their low density. The three most common matrix metals that are especially helpful for aircraft applications are titanium, aluminium, and magnesium. If great strength is required from metallic matrix materials, then a high modulus reinforcements is necessary. Compared to most alloys, the resultant composites will have a greater strength-to-weight ratio. Super thermite nanocomposite refers to various types of nanocomposite, like hybrid sol-gel with a silica foundation. Super thermite nanocomposite refers to various types of nanocomposite, like hybrid sol-gel with a silica foundation.[65]

Metal matrix composites (MMCs) are a type of composite materials having two constituents out of which one is necessarily a metallic matrix and other is a reinforcing agent like carbides, borides, ceramics etc. In case the reinforcement being used was substituted with nano sized materials then the disadvantages of MMCs involving low fracture toughness and poor ductility can be avoided to some extent and the ensuing material is known as Metal matrix nanocomposites or MMNCs. [66]

Because of MMNCs' extremely desirable mechanical qualities, there is a growing amount of research interest in their potential applications as bone implants. MMNCs can withstand loads for a greater amount of time, have higher yield strengths, and can retain their mechanical and physical characteristics longer than magnesium alloys. Two or even more nanoscale reinforcements placed in metal matrices make up a nanocomposite.

MMNCs reinforced with particles like alumina, zirconia, calcium phosphate and yttria are all magnesium based bioceramics. It has been noted that adding calcium phosphate to magnesium matrices as reinforcing materials encourages osseointegration and the growth of new bone. Thanks to a variety of synergistic strengthening mechanisms, MMNCs with nanosized reinforcements have strengthening capabilities. This reduces the corrosion properties of the implants and improves grain refinement. [67]

These all positive qualities of MMNCs are what makes them perfect for biomedical and orthopedic applications.

2.4. INJECTABLE HYDROGELS

The quality of life of patients is still greatly impacted by bone-related disorders such as osteoarthritis, fractures, and bone defects that are brought through trauma, infection, or ageing. Several cells participated in well-coordinated in vivo bone repair in the bone microenvironment. Hematoma phase, hematoma organisation phase, callus phase, and remodelling phase are the four stages that fracture healing or injuries often go through. [68]

The hammered gold plate found on the skulls of prehistoric humans in Peru dates back to 2000 BC. On the Ishtkunui fossil, animal bone grafting was seen to fill in the defect in the skull. Surgeons and scientists have achieved amazing advancements in bone restoration procedures over the past few decades. During the first generation, surgeons could use variform fillers for bone lesions of any shape thanks to scaffold-based tissue engineering technologies. As the mechanism of bone regeneration deepened, scientists developed biodegradable polymers that controlled surrounding microenvironments by releasing medicinal resources. The most recent bioactive materials are made to promote the ability of host cells or organs to regenerate. Luckily, biomaterials acting as bionic extracellular matrix (e.g., mimic cement, hydrogel, polymer scaffold, etc.) have been extensively used in bone tissue creation and have demonstrated excellent therapeutic results in recent decades. [68]

The extracellular matrix, also known as the ECM, is essential for carrying out the signaling and material exchange between the developing tissue and the parent tissue throughout the regeneration process that produces natural bone. Similarly, hydrogels—which are appropriate for cell development and transfer of bioactive molecules—have

aqueous-swellable polymer with a three-dimensional network structure created by different crosslinking reactions. In tissue regeneration engineering, hydrogel materials therefore offer inherent benefits over other bioactive materials. Specifically, during bone repair, hydrogels promote the growth, adhesion, and differentiation capabilities of stem cells, particularly BMSCs. [68]

Ovijit and colleagues report that BMSCs' cell spreading, proliferation, and osteogenic differentiation were enhanced within hydrogels that allowed for adjustable stress relief. Conversely, the pharmacological components of degradable hydrogels may be able to control cell activity in real time. For example, the release of bisphosphonate via an injectable hydrogel regulated the migration of tooth relapse and the activity of osteoclasts following injection. [68]

Researchers studying the fields of tissue engineering & regenerative medicine have shown a tremendous deal of interest in hydrogels. Hydrogels are the preferred 3D cell culture and transportation systems because of their substantial water content and exceptional biomimetics capabilities, which are comparable to that of the extracellular matrix. Hydrogel-encapsulated cells are readily injected into the desired location, sparing additional open surgery and helping patients with deep, irregular, or enclosed abnormalities. [69]

Magnesium (Mg) metal's exceptional biocompatibility and in vivo degradation capabilities have led to extensive research in biomedicine. Therefore, magnesium particles (MPs) can be used in hydrogels as biodegradable templates. Particularly, hydrogen, or H2, a gas is produced during the in vivo corrosion of magnesium. It has been shown in earlier research that utilising carbon dioxide (CO2) as a gas-foaming approach is a feasible way to create pores in the hydrogel scaffolds. But in applications involving living cells, the production of CO2 depends on either acidic environments or electron beam radiation, which is far less desirable. [69]

On the other hand, when magnesium and water react, the formation of H2 gas occurs directly and doesn't require any more conditions. Furthermore, it has been shown that H2 is sufficiently moderate to react with the majority of biomolecules. MPs are therefore desirable as hydrogel foaming agents. Particularly, when MPs break down, soluble ions of magnesium (Mg2+) are continuously released. It has been demonstrated that magnesium (Mg2+) has biofunctional properties that promote cell proliferation, modify angiogenesis & inflammation, and augment osteogenesis by inducing mesenchymal stem cell (the MSC) differentiation and preventing the creation

of osteoclasts. As a result, adding MPs to hydrogel improves its structure as well as its function and makes it suitable and acceptable for use in the regeneration of bone tissue. [69]

In a study, MPs were used to create foam when injecting hydrogels, which resulted in in situ pore formation. The porous and injectable hydrogels helped with the regeneration process and matched the bone defect. First, the nutrition and oxygen diffusion was facilitated by the porous structures, which improved the viability and proliferation of the entrapped stem cells. Second, the hydrogel quickly became vascularized due to the ease with which endogenous cells and neighbouring tissue could infiltrate it. Third, the encapsulated stem cells' ability to differentiate into osteogenic tissues and support bone regeneration was impacted by the Mg2+ produced upon particle breakdown. [69]

2.5. SUPPLEMENTATION

Vitamin D and calcium are usually the first nutrients that come to mind when thinking about bone health. But magnesium is as important. The skeletal system contains over 60% of the total body's magnesium reserves, demonstrating the significance of magnesium in preserving bone integrity. [70]

Magnesium is essential for bone mineralization, which is the process of phosphate and calcium ions being integrated into bone tissue to strengthen it. According to research, having enough magnesium in the body increases bone density and lowers the risk of osteoporosis and bone fractures. [70]

According to certain research, older and postmenopausal women may see an increase in bone mineral density if they consume more magnesium through food and supplements. In a brief study, for instance, it was discovered that giving 20 postmenopausal women with osteoporosis 290 mg/day of elemental mg (as magnesium citrate) for 30 days reduced bone turnover when compared to a placebo, indicating a decrease in bone loss. [71]

Magnesium therapy is suggested for the treatment of osteoporosis. Taking magnesium as supplements can promote bone health.

Some of the magnesium rich foods that one can add in their diet in order to improve bone health are given in table 3 with their amount in milligrams per serving.

Table 3 Magnesium content in selected foods [72]

Food	**Milligrams (mg) per serving**	**Percent DV***
Banana, 1 medium	32	8
Chia seeds, 1 ounce	111	26
Cooked black beans, ½ cup	60	14
Milk, 1 cup	24-27	6
Raisins, ½ cup	23	5
Roasted pumpkin seeds, 1 ounce	156	37
Boiled spinach, ½ cup	78	19
Dry roasted cashews, 1 ounce	74	18
Smooth peanut butter, 2 tablespoons	49	12
Kidney beans, ½ cup	35	8

*DV= Daily value

CHAPTER 3: RESULTS AND DISCUSSION

This literature review revealed that magnesium plays a vital role in various biochemical process that are essential for human health.

Numerous studies indicate that magnesium deficiency is linked with an array of diseases and disorders including depletion of bone and dental health, effects on women's health and patients with diabetes, cardiovascular effects, migraines, neuromuscular effects and effects on mental health.
Bone disorders in which magnesium plays a major part includes osteoporosis, osteoarthritis, hypoparathyroidism, muscle cramp and bone pain.

In orthopedic applications, magnesium demonstrated a superior biocompatibility and biodegradability when compared to other metals generally used such as stainless steel or titanium. Magnesium is non-toxic to human body so its application for fracture repair is extremely favourable as there is no need for a second surgery because it can go through degradation within tissues without being a risk to the biological environment.

Increasing magnesium intake through foods is a good way to avoid numerous diseases. However, there is a limited research that is present at the moment on magnesium supplements and more work needs to be done.

In orthopedic applications, despite the advantages, it still warrants for further research because of the challenge of controlling the degradation of magnesium alloys inside the body. Hence, more work need to be done.

CHAPTER 3: CONCLUSION

In conclusion, magnesium is undoubtedly essential for human health as it plays critical role in various physiological processes. Its deficiency can lead to various health disorders which highlights the need of adequate intakes.

Orthopedic and biomedical applications offered by magnesium-based biomaterials are promising and offers a significant advantages over traditional materials.

The versatility of magnesium is evident due to its role in hard tissue engineering, cardiovascular health, treatment of migraine and so on. This proves that magnesium has a potential to revolutionize medical treatments but there is still need for more research to be done in completely understanding its properties and benefits.

Continued innovation and research in this field will help us overcome current challenges and fully use the potential of magnesium in improving medical technologies.

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