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The Role of Magnesium in Acute Pancreatitis and Pancreatic Injury: A Systematic Review

Ilaria Pergolini[a] Stephan Schorn[a] Helmut Friess[a, b, c]
Ihsan Ekin Demir[a, b, c, d, e]

[a]Department of Surgery, Technical University of Munich, Munich, Germany; [b]German Cancer Consortium (DKTK), Partner Site Munich, Munich, Germany; [c]CRC 1321 Modelling and Targeting Pancreatic Cancer, Munich, Germany; [d]Department of General Surgery, HPB-Unit, School of Medicine, Acibadem Mehmet Ali Aydinlar University, Istanbul, Turkey; [e]Else Kröner Clinician Scientist Professor for Translational Pancreatic Surgery, Munich, Germany

Keywords
Magnesium · Acute pancreatitis · Calcium antagonist

Abstract

Introduction: As natural calcium (Ca) antagonist, magnesium (Mg) seems to counteract Ca-signaling pathways involved in the intracellular protease activation leading to acute pancreatitis. We systematically reviewed the current literature to investigate the role of Mg in the pathogenesis of acute pancreatitis and its possible use in detecting, predicting, and preventing acute pancreatitis. ***Methods:*** A systematic search was performed in PubMed/Scopus/Web of Science to identify in vivo and in vitro studies reporting data on Mg in acute pancreatitis. ***Results:*** Twelve studies were included. Due to their heterogeneity, we conducted a review without the intent of inference. Mg deficiency in pancreatic acinar cells seems to be frequently associated with serum hypocalcemia and acute pancreatitis. Mg seems to contrast intracellular Ca accumulation which induces premature enzyme activation and acute pancreatitis. Several in vivo and in vitro experiments showed beneficial effects of Mg supplementation in counteracting Ca-signaling pathways and subsequent pathological events. Moreover, a recent randomized trial demonstrated the efficacy of Mg supplementation in reducing the incidence of post-endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis in high-risk patients. ***Conclusion:*** Mg is a natural antagonist of Ca-signaling pathways and, when deficient, predisposes to acute pancreatitis. Mg supplementation may be useful to prevent acute pancreatitis in many contexts, such as post-ERCP or after pancreatic surgery. The heterogeneity of the included studies represents an important limitation that may hinder robust conclusions.

Plain Language Summary

Magnesium seems to be involved in several important mechanisms in our body. One of these is to counteract calcium in the process that causes the activation of the acute inflammation of the pancreas, so-called acute pancreatitis. We conducted a systematic review of the current literature to better investigate the role of magnesium in acute pancreatitis and its possible use in detecting, predicting, and preventing it. We found that 11 studies were focused on this topic. These studies showed that when magnesium is deficient in the pancreas, patients more frequently have reduced serum calcium and its accumulation in the pancreatic cells. These conditions predispose to acute pancreatitis. Moreover, in vivo and in vitro experimental studies showed beneficial effects when magnesium was supplemented.

karger@karger.com
www.karger.com/vis

Correspondence to:
Ihsan Ekin Demir, ekin.demir@tum.de

Accordingly, magnesium may be useful to prevent acute pancreatitis in many clinical situations, such as after pancreatic surgery. However, the included studies were very heterogeneous, and this may hinder further solid conclusions.

Introduction

Acute pancreatitis (AP) is the development of acute inflammation in the pancreas and is one of the most common disease entities in gastroenterology that requires hospital admission. Most patients have an edematous form, which is mild, self-limited, and with an uncomplicated course, while 10–20% developed a severe necrotizing form with a fatal prognosis in 20% of cases [1, 2]. Gallstones (40–70%) and alcohol (25–35%) are the most common causes [1, 2]. AP can also occur after endoscopic retrograde cholangiopancreatography (ERCP), in 2–9% of cases [3, 4], and as a complication after elective pancreatic surgery. Several recent publications support the occurrence of AP after pancreatic resections as a trigger event of other postoperative complications such as pancreatic fistula and bleeding [5–9]. Recently, the International Study Group for Pancreatic Surgery (ISGPS) also developed a consensus definition and grading of this specific entity [10].

Magnesium (Mg) is the fourth most abundant cation in the human body and represents a critical cofactor for multiple enzymatic reactions [11]. The human body contains approximately 24 g of Mg, distributed as follows: 60% in the bones, 29% in muscles, 10% in other soft tissue, and 1% in intracellular liquids [12]. Normally, the highest concentration can be observed in tissues with intensive metabolic activity (i.e., muscle, liver, heart, and neoplastic tissue) [12].

Calcium (Ca)-signaling pathways are crucially involved in the activation of intracellular pancreatic proteases, and Mg, as a natural Ca antagonist, seems to counteract pathological Ca pathways involved in the activation process [1, 13, 14]. Experimental models showed that Mg administration can help in reducing intrapancreatic zymogen activation and prevent the associated local and systemic damage [15, 16]. Based on these studies, a randomized trial testing the efficacy of peri-interventional Mg administration to prevent post-ERCP pancreatitis was recently published with promising results, and another multicentric trial called MagPEP was initiated, but the results have not been published yet [17, 18]. This approach can also have implications for other contexts, e.g., for the management of perioperative pancreatitis-related complications (e.g., fistula, bleeding) after pancreatic surgery. In this setting, we systematically reviewed the literature to better understand the role of Mg in the pathogenesis of AP and to evaluate its possible use in detecting, predicting, and preventing AP after interventional procedures, such as ERCP and pancreatic resections.

Methods

We performed this systematic review according to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines (PRISMA checklist – online suppl. material 1; for all online suppl. material, see https://doi.org/10.1159/000540507) [19]. The study was preregistered online in the Open Science Framework (OSF) Registry. The flowchart in Figure 1 shows the search strategy. The systematic search of the literature was carried out on April 14, 2022, in PubMed, Scopus, and Web of Science using the following search terms: "magnesium" filtered by "pancreatitis," "pancreatectomy," "pancreaticoduodenectomy," "pancreatic surgery," and "pancreatic resection." Surgical terms were also included in the search strategy because, as written above, several recent publications have shown that AP may be also a relevant postoperative event following pancreatic resection and, for us as surgeons, it represents an important focus for this study. After duplicates' exclusion, two authors (IP and IED) conducted a review of titles and abstracts through all identified references. Full texts for all abstracts considered potentially eligible were retrieved and screened for relevance and assessed against the preestablished inclusion and exclusion criteria. Further publications were included through the screening of the reference list of the selected articles and the "related articles" in PubMed. When multiple articles were published from the same study group, the most recent or the most informative article was included. Any disagreement during the search and selection process was resolved by consensus between the two authors. Only original papers (e.g., no review papers, no case reports, no abstracts) written in English and providing data on Mg in AP were included. Experimental studies in vivo and in vitro were also considered. Papers focused on chronic pancreatitis were excluded. Figure 1 shows the number of excluded studies and the reasons for exclusion. The following data from the included papers were collected and described briefly in Tables 1 and 2: author details, country, year of publication, study design, and outcomes. All the information regarding the functions and effects of Mg in AP was recorded. Due to the heterogeneity of the included papers, we aimed to review the literature descriptively without the intent of inference. Only already published papers were included in this systematic review, and no patients were directly involved in the study evaluation. Therefore, an ethical approval of the study by an ethical committee was not required. Table 3 shows the actual clinical trial on Mg supplementation.

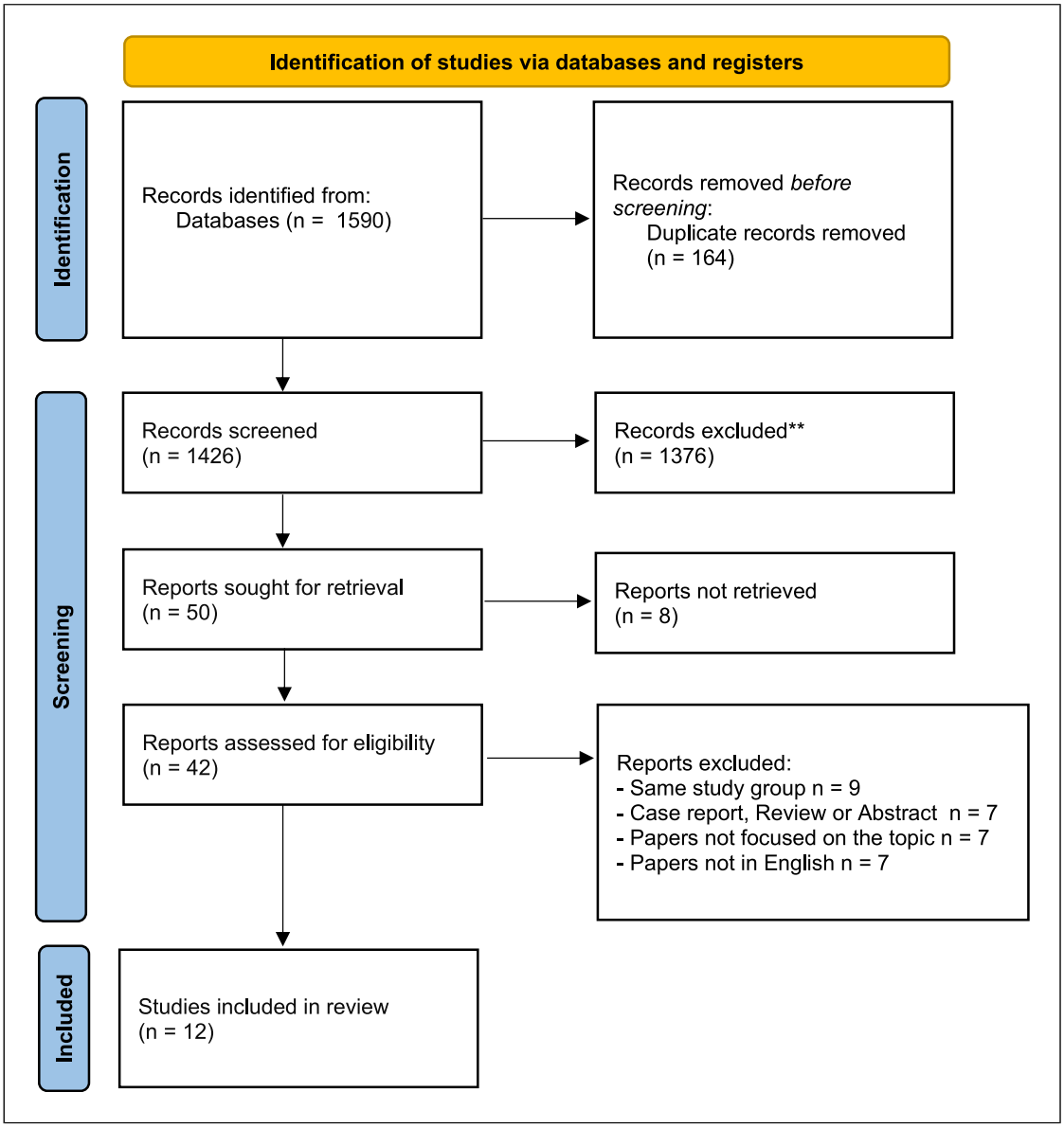

Fig. 1. Flowchart according the PRISMA Guidelines 2020 showing the study selection.

Results

After duplicates' exclusion, the original search identified 1,426 papers. Of these, 50 full texts were analyzed for eligibility. Twelve papers met the inclusion criteria for the systematic review and were included in the present study [11, 12, 14, 16, 17, 20–26]. Figure 1 shows the search strategy. The included papers were very heterogeneous in terms of publication date, objectives, methods, construction, and results (Tables 1, 2). The included papers were considered and pooled according to their main results and conclusions and the endpoints of our systematic review. Seven studies were based on in vitro or in vivo models [12, 14, 16, 20–22].

Hypomagnesemia and AP

Mg deficiency is a common event in AP, and several clinical and experimental studies analyzed its Mg distribution in the presence of this disease. In 1952, Edmondson reported for the first time the presence of decreased Mg concentration in the blood serum of patients with AP [23]. At that time, the authors described serum hypomagnesemia as a phenomenon that occurs in the first four or 5 days and is of short duration, i.e., 24–48 h [23]. Later, Ryzen et al. [22] suggested that in AP, most patients with serum hypocalcemia had a low intracellular Mg content, even in the case of normal serum Mg concentrations. In fact, patients with AP are usually dehydrated, and this can falsely result in normal or even increased serum Mg

Table 1. Basic characteristics of the experimental studies included in systematic review

Study	Country	Study design	Animals/ humans	Year of publication	Methods	Main result
Baj et al. [20]	Poland	In vivo	Wistar rats	2017	Biochemical and histological examinations at 2 h and 6 h since the induction of AP	Serum Mg increased significantly within 2 h from the induction of AP
Bhattacharya et al. [21]	USA	In vivo	Mongrel dogs/ Sprague-Dawley rats	1988	Plasma serial examinations and tissue biopsies before and after the induction of AP	Mg is reduced in serum and pancreas tissue in AP
Dabrowski et al. [12]	Poland	In vivo	Wistar rats	2003	Serial blood (at the 6th, 12th, 24th, and 48th hours) and tissue collection after the induction of AP	Concentration of Mg decreased in the serum, kidney, and pancreas because of increased excretion of Mg into the urine and shift to those tissues with higher metabolic demand
Marenberg et al. [22]	USA	In vivo	Pitman-Moore miniature pigs	1978	Serial blood collection after induction of AP by infusing a bile salt-trypsin solution into the pancreatic duct	Serum Mg was described significantly higher for 48 h after AP induction, while serum Ca dropped sharply
Mooren et al. [14]	Germany/ England	In vivo/ in vitro	Mice	2001	Isolated mouse pancreatic acinar cells under CCK stimulation incubated in buffer containing different Mg concentrations	Increased intracellular Mg concentrations directly affected the frequency and amplitude of Ca oscillations in response to secretagogue CCK stimulation by inhibiting Ca influx
Schick et al. [16]	Germany	In vivo/ in vitro	Wistar rats/ C57BL6/J mice	2013	Pancreatic enzyme activities, protease activation, morphological changes, and the immune response were investigated after Mg supplementation to pancreatic acini, rats and mice with induced AP	High extracellular Mg levels work as antagonist of Ca and reduced intracellular Ca variations, as well as intracellular trypsin and elastase activation. Mg supplementation reduced not only the intrapancreatic enzyme activation, but also edema, tissue necrosis, and inflammation in the pancreas
Singh et al. [11]	England	In vivo/ in vitro	Rats	1995	Isolated segments and acinar cells of rat pancreas incubated with CCK	In acinar cells incubated with elevated Mg concentrations, the CCK stimulation (1) failed to decrease intracellular Mg concentrations, (2) the Ca translocation from the extracellular to intracellular compartments, as well as its release from intracellular stores was significantly attenuated, (3) amylase output is significantly reduced

AP, acute pancreatitis; Mg, magnesium; Ca, calcium; CCK, cholecystokinin.

Table 2. Basic characteristics of the clinical studies included in systematic review

Study	Country	Study design	Animals/ humans	Year of publication	Methods	Main result
Edmondson et al. [23]	USA	In vivo	Humans	1952	Serial blood collection in patients with AP	Decreased Mg concentration in blood serum of patients with AP in the first four or 5 days and for short duration, i.e., 24–48 h
Krzewicki et al. [24]	Poland	In vivo	Humans	1992	Bile, plasma, and blood cell examinations in patients who underwent bile duct surgery with and without a history of AP	Reduction of bile Mg concentration and a considerable higher bile Ca/Mg ratio in patients who suffered from AP. Mg reduction is a risk factor for AP
Nimmo et al. [25]	England	In vivo	Humans	1970	Duodenal Ca and Mg concentrations after pancreatic stimulation with secretin were measured in patients with and without pancreatic disease	Increased Ca and Mg concentrations in duodenal aspirate after pancreatic stimulation with secretin in patients with previous pancreatic diseases
Ryzen et al. [26]	USA	In vivo	Humans	1990	Measurement of Mg levels in serum and in peripheral blood mononuclear cells in patients with AP, without hypocalcemia	In patients with serum hypocalcemia and AP, the intracellular Mg content was significantly reduced, even in the case of normal serum Mg concentrations. The mononuclear cell Mg content, and not the mean serum Mg concentration, correlates with serum Ca levels. Supplementation of Mg is suggested even in patients with normal serum Mg levels to treat hypocalcemia
Aletaha et al. [17]	Iran	In vivo	Humans	2022	Prospective, randomized, and double-blind controlled trial comparing the incidence of post-ERCP pancreatitis in 135 patients who received 2gMg sulfate versus 135 patients who received placebo (normal saline), administered 1 h before and 6 h after ERCP in both groups	Mg supplementation does not prevent the occurrence of post-ERCP pancreatitis in all enrolled patients (8.9% [12/135] vs. 12.6% [17/135]; $p = 0.33$), but it could significantly reduce the incidence of post-ERCP pancreatitis in high-risk patients (10.8% [8/74] vs. 26.7% [16/60]; $p = 0.017$). Median length of hospital stay was also significantly lower in the new drug group in contrast to placebo (2 vs. 3 days, $p = 0.04$)

AP, acute pancreatitis; Mg, magnesium; Ca, calcium; ERCP, endoscopic retrograde cholangiopancreatography.

concentrations, despite depleted intracellular Mg stores. Moreover, patients with AP have risk factors for Mg deficiency, such as alcohol abuse or diabetes mellitus. Of note, a study interestingly found a reduction of bile Mg concentration and a considerably higher bile Ca/Mg ratio in patients who suffered from AP [24]. The authors suggested that this reduction can be a risk factor for AP and a sign of latent total body Mg deficiency or disturbances in entero-hepatic circulation [24]. Another study found increased Ca and Mg concentrations in duodenal aspirate after pancreatic stimulation with secretin in patients with previous pancreatic diseases, including relapsing pancreatitis in comparison with those without pancreatic diseases [25].

Several studies using experimental models have also evaluated the body distribution of Mg and Ca during induced AP. In an animal model using pigs, where AP was surgically induced through the infusion of bile salt-trypsin solution in the pancreatic duct,

Table 3. Clinical trials on Mg supplementation

Name of the clinical trial	Authors	Country	Type of study	Registration number	Status of the study	Enrolled patients, *n*	Methods
Magnesium Sulfate for Prevention of Post-ERCP Pancreatitis	Aleteha et al. [17]	Iran	Single-center prospective, randomized and double-blind controlled trial	IRCT20180310039017N1	Terminated and published (2022)	270	Comparison of the incidence of post-ERCP pancreatitis in 135 patients who received 2gMg sulfate versus 135 patients who received placebo (normal saline), administered 1 h before and 6 h after ERCP in both groups
Magnesium Sulfate in the Prevention of Post-ERCP Pancreatitis (MagPEP)	Fluhr et al. [18]	Germany	Multicenter, randomized, phase III, double-blind, placebo-controlled, parallel group trial	ISRCTN46556454	Terminated, results not published (last update on May 3, 2021)	327	Comparison of the incidence and severity of post-ERCP pancreatitis in patients who receive Mg sulfate (20 mmol) versus patients who receive placebo (NaCl 0.9%), 60 min before and 6 h after ERCP

AP, acute pancreatitis; Mg, magnesium; Ca, calcium; ERCP, endoscopic retrograde cholangiopancreatography.

serum Mg was described significantly higher for 48 h after AP induction in comparison with control, while serum Ca, total, and ionized dropped sharply [22]. Similarly, in another experimental model of AP, serum Mg increased significantly within 2 h from the induction of AP, as well as amylase, transaminase, and creatinine [20]. In dogs with fulminant AP, Ca concentration was found to be increased significantly in the pancreas, liver, and muscles with concomitant serum hypocalcemia and hyperamylasemia, whereas Mg was reduced in the plasma and pancreas, but not in other tissues [21]. Another in vivo model confirmed that in the course of experimental AP in rats the concentration of Mg decreased in the serum, kidney, and pancreas [12]. According to these authors, a possible explanation for the Mg reduction in the serum can be the increased excretion of Mg into the urine induced by increased secretion of adrenocortical and thyroid hormones, as well as antidiuretic hormone as a stress reaction to AP [12]. Another reason can be the shift of Mg, induced by insulin and adrenaline, to those tissues with higher metabolic demand, like the liver and heart [12].

The Role of Mg in the Pathogenesis of AP

AP is often associated with serum hyperamylasemia, hypocalcemia, and hypomagnesemia; however, the pathogenetic mechanisms behind are still unclear. As already mentioned above, it is well known that the Ca-signaling pathways play a crucial role in the pathogenesis of AP. Here, the pathological increase of Ca concentration in acinar cells is a central event that promotes pro-inflammatory pathways such as premature trypsinogen activation, mitochondrial dysfunction, and activation of the nuclear factor-κB pathway. Overall, these events trigger a vicious cycle that further increases the intracellular Ca concentration and, ultimately, leads to acinar cell necrosis [1, 13, 27]. Figure 2 shows the most important Ca-signaling pathways.

In this context, several studies tried to investigate in detail the relationship between Ca and Mg in the pathogenesis of AP. In 1990, Ryzen and Rude [26] investigated the role of Mg deficiency in determining serum hypocalcemia in AP. As mentioned above, the authors found that in patients with serum hypocalcemia and AP, the intracellular Mg content, measured in blood mononuclear cells by atomic absorption spectrophotometry, was

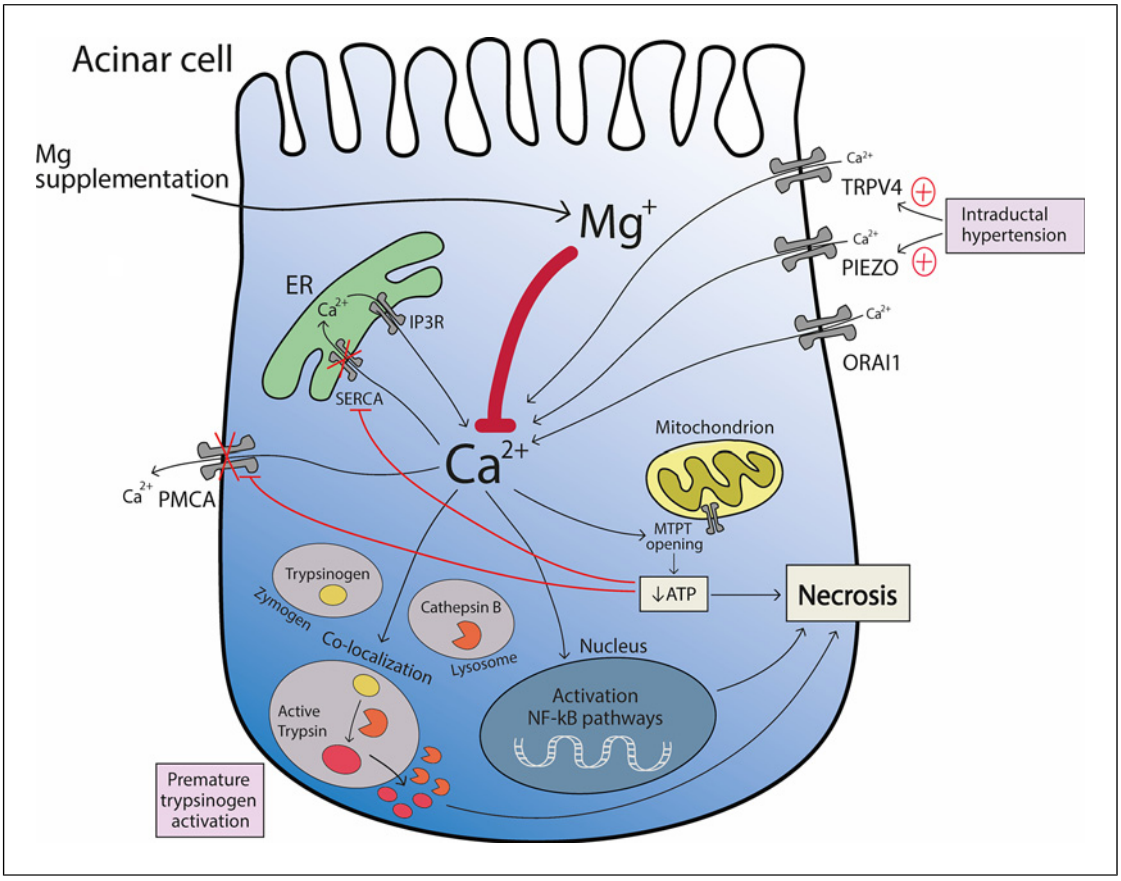

Fig. 2. Ca signaling pathways in pancreatic acinar cells involved in AP and counteracted by Mg supplementation, as natural Ca antagonist. In pancreatic acinar cells, cholecystokinin (CCK) and several pathological stimuli, i.e., alcohol and bile acid, induce inositol 1,4,5-trisphosphate receptor (IP3R)-mediated Ca release from the endoplasmic reticulum (ER). Low Ca concentration in the ER promotes the opening of Ca release-activated Ca channel protein 1 (ORAI1), through which Ca enters the cell from the extracellular space. In addition, increased intraductal pressure caused by ductal obstruction which can occur after ERCP or biliary pancreatitis can activate the PIEZO1 mechanoreceptor, as well as the transient receptor potential cation channel subfamily V member 4 (TRPV4), determining increased Ca influx from outside the pancreatic acinar cell. These events result in a pathological Ca overload in the intracellular space. Subsequently, Ca elevation promotes the opening of mitochondrial permeability transition pores (MPTPs) and loss of membrane potential across the mitochondrial membrane ensues. This process results in mitochondrial dysfunction and subsequent ATP depletion. ATP reduction impairs ATP-dependent mechanisms to reduce cytosolic Ca, such as Ca export to the extracellular space through the plasma membrane Ca^{2+} channel (PMCA) and Ca reentry into the ER through the smooth ER Ca^{2+} channel (SERCA). Overall, these events accentuate and perpetuate the pathological intracellular Ca overload, like in a vicious circle that leads to premature trypsinogen activation, activation of the nuclear factor-κB (NF-κB) pathway, and other events, and end in inflammation and cell necrosis. More in detail, the premature activation of trypsinogen to trypsin by cathepsin B occurs after the fusion of lysosomal and zymogen compartments, called co-localization. The mechanism behind remains elusive; however, once released into the cytosol, trypsin causes autodigestion inside and outside the acinar cells, and cathepsin B release causes necroptosis, a regulated form of necrosis. In detail, necroptosis is induced by the activation mediated by cathepsin B of the receptor-interacting protein kinase (RIP), including RIP1–RIP3, and of the mixed lineage kinase domain-like (MLKL) pathway, in which MLKL is phosphorylated by RIP3, leading to its oligomerization. MLKL oligomers then translocate to the plasma membrane and ultimately cause membrane rupture and necroptosis. In addition, the NF-κB pathway promotes the production and release of pro-inflammatory mediators [1, 13, 24]. Mg is a natural antagonist of Ca-signaling pathways, and Mg deficiency is frequently associated with AP. Mg supplementation can contrast or prevent these events that are crucial in the pathogenesis of AP.

significantly reduced in comparison with normocalcemic patients, even in the case of normal serum Mg concentrations. The mean serum Mg concentration did not correlate with serum Ca levels and was not significantly lower in hypocalcemic patients compared to the normocalcemic ones. By contrast, the mononuclear cell Mg content correlates with serum Ca concentration [26]. According to these data, although the study did not prove how intracellular Mg depletion contributed to hypocalcemia, Ryzen and Rude [26] suggested a probably important role of Mg deficiency in the pathogenesis of serum hypocalcemia in patients with AP and the

importance of supplementation even in patients with normal serum Mg levels to treat hypocalcemia [26].

In dogs and rats with experimentally induced AP, Bhattacharya et al. [21] also evaluated serum Mg, Ca, amylase, and parathyroid hormone levels, as well as tissue Mg and Ca concentrations. Serum hypocalcemia and hyperamylasemia occurred early and persisted throughout, while Mg was lowered and parathyroid hormone was elevated at 6 and 18 h after induction but returned to a normal level in 24 h. Concomitantly, as reported above, tissue Ca was significantly elevated in the pancreas, liver, and muscle, but depleted in the kidneys, while Mg was depleted only in the pancreas, but not in other tissues. According to the observed temporal correlation between amylase, Ca, and Mg concentrations in the serum and tissues, the authors concluded already at that time that serum hypocalcemia and excessive intracellular Ca accumulation are early cellular manifestations of AP and may play an important role in the pathogenesis of AP. Moreover, they suggested that pharmacologic antagonists able to regulate the excessive intracellular Ca accumulation may be helpful in the treatment or prevention of AP [21]. In this light, Singh and Wisdom [11] showed that in isolated acinar cells of rat pancreas, Mg may play an important role as a second messenger in the control of secretagogue-evoked amylase secretion. With normal or null extracellular Mg concentration, the digestive enzyme secretion under secretagogue stimulation was associated with marked Ca influx and elevation of intracellular Ca concentration, as well as Mg efflux and decreased intracellular Mg levels. By contrast, when acinar cells were incubated with elevated Mg concentrations, the secretagogue stimulation failed to decrease intracellular Mg concentrations and the Ca translocation from the extracellular to intracellular compartments, as well as its release from intracellular stores was significantly attenuated, resulting in a significantly reduced amylase output [11]. Later, Mooren et al. [14] investigated more in detail the intracellular distribution of Mg in response to secretagogue stimulation in isolated mouse pancreatic acinar cells and how this affects Ca signaling. This study also showed that increased intracellular Mg concentrations directly affected the frequency and amplitude of Ca oscillations in response to secretagogue cholecystokinin stimulation by inhibiting Ca influx. By contrast, the authors found that increased intracellular Ca concentration was associated with a decrease in intracellular Mg levels, but not with a Mg efflux from acinar cells. Here, the intracellular Mg movements were independent of the presence of extracellular Mg. As a possible explanation, the authors provided evidence for an intracellular store of Mg in the endoplasmic reticulum [14].

Mg Supplementation in the Treatment of AP

Because harmless and inexpensive, Mg supplementation was suggested in some of the included papers as a treatment for AP. Moreover, this should not depend on serum Mg concentrations but also be considered in patients with normal serum Mg levels [16, 24, 26]. As mentioned above, Ryzen and Rude [26] proposed Mg supplementation in all patients with AP with the intent to treat serum hypocalcemia, which is normally associated with poor prognosis in patients with AP.

In this context, in 2014 Schick et al. [16] investigated in vitro and in vivo the real effects of Mg administration on the onset and course of experimental AP. Since high intracellular Ca concentrations are a well-known risk factor for AP and Mg represents a Ca antagonist in acinar cells [14], Schick and colleagues tested whether Mg supplementation affects Ca signals and the premature protease activation, which is responsible for the development of AP. In vitro, they incubated pancreatic acinar cells with different concentrations of extracellular Mg and subsequently stimulated them with supramaximal concentrations of cholecystokinin. High extracellular Mg levels reduced intracellular Ca variations, as well as intracellular trypsin and elastase activation. These data indicated that Mg alters the availability of intracellular Ca and, therefore, can be considered a physiological Ca antagonist in acinar cells. Subsequently, the authors tested in vivo the protective effect of Mg on the severity of AP. They fed rats with different Mg concentrations, and after inducing AP, they observed that Mg supplementation affected serum Mg and, inversely, Ca concentrations and, most importantly, reduced not only the intrapancreatic enzyme activation, but also edema, tissue necrosis, and inflammation in the pancreas [16]. Besides, Mg pretreatment resulted in decreased levels of the pro-inflammatory cytokine tumor necrosis factor α and expansion of FoxP3-positive T cells, suggesting a modulating effect of Mg on the immune system, possibly reducing a pro-inflammatory immune response. The authors concluded that nutritional Mg deficiency predisposes to AP, while high nutritional or parenteral Mg can limit the severity of pancreatitis [16]. Moreover, they suggested using Mg as a natural, inexpensive, orally administrable, and well-tolerable Ca antagonist in the treatment or prevention of AP [16].

Based on these promising results, a multicentric randomized placebo-controlled phase III trial (MagPEP ISRCTN46556454) was recently designed by Fluhr et al. [18] to study the efficacy of peri-interventional intravenous Mg supplementation in preventing the onset and the severity of post-ERCP pancreatitis (Table 3). In this study, the included patients received 20 mmol of Mg sulfate or placebo 60 min before and 6 h after ERCP. Although the study has been terminated, its results have not yet been published. With the same purpose, another

randomized trial was conducted and recently published by Aletaha et al. [17] (Table 3). Here, 135 patients who received an infusion of 2 g Mg (5 cc of $MgSO_4$ 20%) as drug were compared to other 135 patients who received 5 cc saline 3% as placebo; in both groups, the infusions were administered an hour before and 6 h after ERCP. The study could show that Mg supplementation was not able to prevent the occurrence of post-ERCP pancreatitis in all enrolled patients (8.9% [12/135] vs. 12.6% [17/135]; p = 0.33), but it could significantly reduce the incidence of post-ERCP pancreatitis in high-risk patients (e.g., difficult cannulation, previous history of post-ERCP pancreatitis, etc.) of the intervention group in comparison with the placebo group (10.8% [8/74] vs. 26.7% [16/60]; p = 0.017). The median length of hospital stay was also significantly lower in the new drug group in contrast to placebo (p = 0.04). By contrast, studies that evaluated the effect of perioperative administration of Mg in patients who undergo pancreatic resection were not found in the current literature.

Discussion

Hypomagnesemia is a common event in all hospitalized patients (7–11%) and even more frequent in critically ill patients [28]. Serum Mg deficiency was also described in patients with AP, associated with serum hypocalcemia and hyperamylasemia. In our study, we sought to systematically review the literature to evaluate the current knowledge about the role of Mg in AP and, consequently, the possible applications of Mg to detect, predict, and prevent or treat this disease. As reported in the results, the heterogeneity of the included papers represents an important limitation of this study, excluding the possibility of inference and further analysis. However, the included studies have brought consistent results, showing that this topic contains important insights for improving the treatment of patients with AP and, therefore, deserves further investigation.

As the most significant result, Mg was revealed to play the role of a second messenger and Ca antagonist in pancreatic acinar cells. Mg can counteract the Ca translocation from the extracellular to intracellular compartments induced by secretagogue stimulation, as well as, the release from intracellular stores, reducing accordingly the amylase secretion [11, 14, 21]. As we mentioned above and summarized in Figure 2, the pathological elevation of Ca concentration in pancreatic acinar cells is a central event in AP that mediates several pro-cell death and pro-inflammatory pathways such as premature trypsinogen activation, mitochondrial dysfunction, activation of nuclear factor-κB, and necroptosis [1]. Different events, such as alcohol, bile acids, and increased ductal pressure caused by ductal obstruction, which can occur in post-ERCP pancreatitis and gallstone pancreatitis, can disrupt this Ca homeostasis and cause a global, sustained pathological cytosolic Ca elevation through different pathways [1]. In case of Mg deficiency, the Ca signaling responsible for the development of AP finds no obstacles in acinar cells.

In AP, the presence of intracellular Mg deficiency was described in several studies [23, 26]. Because of its intracellular distribution, Mg deficiency can also occur in case of serum Mg within the normal range [26]; dehydration or a history of alcohol abuse and diabetes mellitus, which are frequently associated with AP, may hide or disguise hypomagnesemia. Accordingly, several authors suggested the use of Mg supplementation even in patients with normal Mg blood concentrations or without clinical signs of deficiency, especially when intending to treat serum hypocalcemia, a well-known sign of poor prognosis in patients with AP [16, 26]. The study by Schick et al. [16] proved in vitro and in vivo the efficacy of Mg administration during AP in reducing the intracellular accumulation of Ca, and subsequently, the Ca-dependent intrapancreatic enzyme activation, and most importantly, the subsequent inflammation and tissue injury in the pancreas.

In favor of Mg supplementation in patients with AP, it is important to highlight that Mg is inexpensive and simple to administer, and has very limited adverse events [16]. Certainly, the current evidence that we could evaluate in this systematic review is not enough to make robust conclusions and further investigations on a larger scale are necessary to recommend the Mg supplementation in patients with pancreatic injuries. However, the results of the already published trial on post-ERCP pancreatitis were promising, and if the MagPEP trial will also prove its efficacy, Mg may become a pharmacological prophylaxis to routinely apply before ERCP [17, 18] and may also raise the possibility of using Mg supplementation in other contexts, such as the prophylactic treatment of perioperative AP after pancreatic resection.

It must be underlined that different animal models were used in the experimental models of the included studies, and AP was also induced by different techniques. Moreover, most studies on patients were conducted in Western countries and encountered significant sources of bias. The heterogeneity of the included papers represents an important limitation of this study and excludes the possibility of inference and further analysis. Overall, these issues represent important limitations and may hinder the uniformity and robustness of the reported results.

In conclusion, Mg as an antagonist of Ca signaling, which is a crucial event that triggers AP through intrapancreatic enzyme activation, seems to play an important role in the pathogenesis of this disease.

Counteracting Mg deficiency that predisposes and is frequently associated with AP with Mg supplementation may probably represent in the next future an important cornerstone in the prevention of AP in many contexts, such as post-ERCP or after pancreatic surgery. Randomized prospective trials addressing this issue warrant timely attention.

Statement of Ethics

An ethics statement is not applicable because this study is based exclusively on published literature. No patients were directly involved or included in the study evaluation.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Study concept and design, analysis and interpretation of data, and drafting of the manuscripts: I.P. and I.E.D.; acquisition of data: I.P., S.S., and I.E.D.; critical revision of the manuscript for important intellectual content and administrative, technical, or material support: S.S., H.F., and I.E.D.; statistical analysis: I.P.; study supervision: H.F. and I.E.D.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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