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Contents

Irregular Volume 9 Number 2 June 28, 2019

MINIREVIEWS

META-ANALYSIS

Contents

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Volume 9 Number 2 June 28, 2019

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MINIREVIEWS

Immunometabolism: A target for the comprehension of immune response toward transplantation

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Abstract

Organ transplantation is a life-saving procedure, however predicting graft survival is still challenging. Understanding immune-cell pathobiology is critical to the development of effective therapies to prevent rejection. Over the recent years it has become progressively evident that the complex nature of immune cell behavioral dynamics is strongly dependent on cellular metabolism, which in turn, relies on competition for nutrients, oxygen and metabolites with other immune cells and microbiota. Furthermore, the influence of the inflammatory state can lead to substantial changes in conditions within the tissue micro-environment. Considering the context of immunity, alterations in metabolic pathways (glycolysis, the tricarboxylic acid cycle, the pentose phosphate pathway, the fatty acid oxidation and synthesis, and the amino acid metabolic pathways) will influence the production of different sets of cytokines and affect transplantation outcome. It is now known that naïve, resting and effector cells acquire different metabolic profiles and studies have shown that specifically targeting some of these metabolic routes can prevent differentiation of effector T cells in favor of Tregs. Ultimately, to develop effective therapies that will prevent graft loss and understanding how cell metabolism impacts the fate and function of immune cells is now a critical point of discussion. The distinct metabolic features and requirements observed in effector and suppressive cell subsets offer promising opportunities for selective regulation of the immune responses in transplantation and will be discussed in this review.

Key words: Transplantation; Metabolic processes; Immune tolerance; Metabolic activation; Inflammatory response

Core tip: In this review we summarize the most recent findings on metabolic pathways involved in the determination of immune cell fate and highlight the relevance of

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understanding how metabolic reprogramming is involved in the activation of dendritic cells and T cells, as well as development of strategies that target metabolic reprogramming to counteract effector cell activation in order to prevent graft failure.

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INTRODUCTION

Organ transplantation is a life-saving procedure, however predicting graft survival is still challenging. Sustaining transplantation tolerance is a key to overcome inflammatory challenges which lead to episodes of rejection or fibrosis and loss of graft function. Therefore, the goal of immunotherapies is to shape immune responses towards regulation to achieve long-term graft survival and eliminate the chronic use of immunosuppressants, which inflict severe side-effects.

Understanding immune-cell pathobiology is critical to develop new effective therapies that will prevent graft rejection. In allograft transplantation, the balance of immune responses towards alloantigen will depend on the coexistence of several mechanisms such as control in the frequency and function of alloreactive T cells *via* mechanisms of suppression such as expression of inhibitory molecules [*e.g.*, programmed death (PD)-1], and induction of T regulatory cells (Tregs)[1]. Recently, it has also come to light that metabolic reprogramming impacts the fate and function of immune cells and might be a key determinant of transplantation outcome. Unlike other cells in the body, immune cells are capable of responding to their external environment and modulate their cellular behavior accordingly, for instance, availability of energetic substrates can influence cellular metabolism and in turn strongly affect immune cell fate towards acquisition of effector functions, quiescence, proliferation, *etc*[2]. This cellular metabolic reprogramming can be triggered in response to energy requirements for synthesis or decomposition of cell components, production of soluble factors such as cytokines, differentiation and cell survival, and it will condition the effector or regulatory properties of the immune cells[3].

Undoubtedly, this new field of studies in immunometabolism will enable novel therapeutic approaches which increase chances of a successful transplantation outcome. The following sections will give some insight into general metabolic pathways and more specific metabolic signatures inherent to effector and suppressive cell subsets as well as some early work regarding immunometabolism in transplantation.

MAIN METABOLIC PATHWAYS INVOLVED IN IMMUNE CELL FATE

A very fine equilibrium of internal metabolites, such as reducing/oxidizing substrates, reactive oxygen species (ROS), as well as availability of growth factors and nutrients, weigh in to determine which metabolic pathway will be followed[2,3]. The concept of energy metabolism and nutrient sensing suggests that, after food breakdown, adenosine triphosphate (ATP) can be directly metabolized from nutrients or stored as alternative energy sources, such as proteins, glycogen or lipids[4]. Specifically considering immune cell function, changes in metabolic pathways have been associated to determination in proliferation, acquisition of effector function, specific cytokine signature and return to homeostasis. To simplify, in general six metabolic pathways are generally considered (Figure 1): (1) The glycolytic metabolic pathway; (2) The pentose phosphate pathway (PPP); (3) The tricarboxylic acid cycle (TCA); (4) Fatty acid oxidation (FAO); or (5) Synthesis; and(6) The amino acid metabolic pathway summarized from O´Neill *et al*[5].

The glycolytic pathway, also named glycolysis, initiates with the transport of glucose from extracellular space by specialized transporters (such as Glut1), to ultimately generate pyruvate and other products after a series of enzymatic reactions.

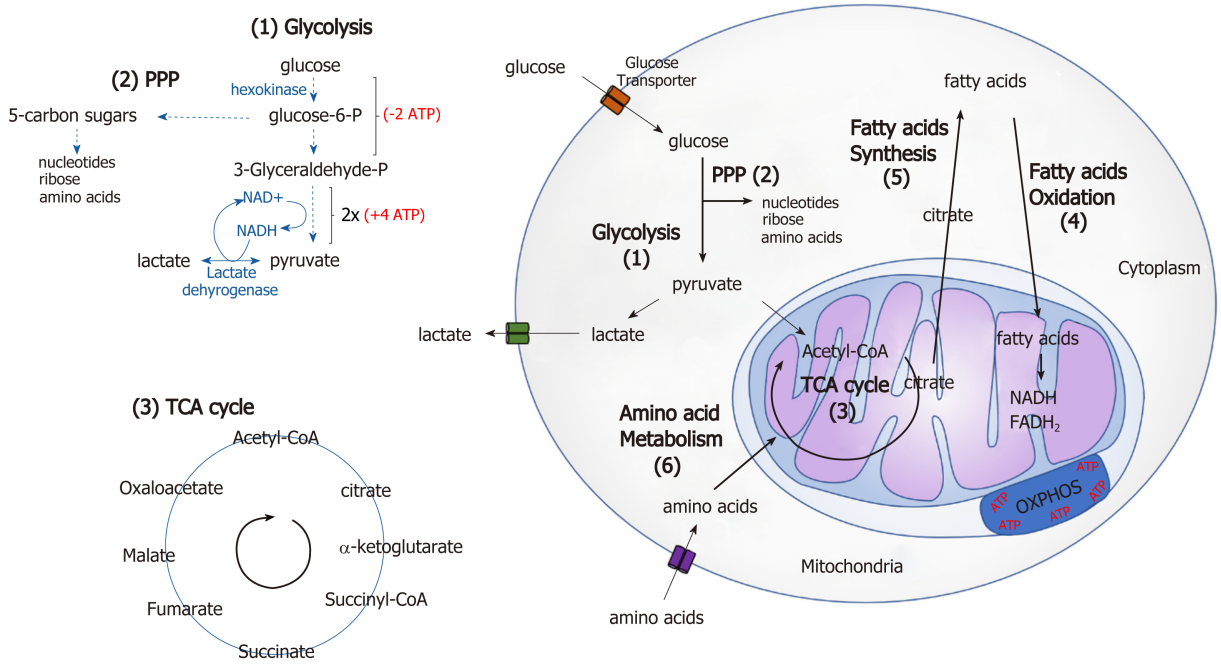

Figure 1 Six main metabolic pathways relevant for immune cell function. (1) Glycolysis is a process that occurs in the cytoplasm and involves conversion of glucose into pyruvate, (3) Which can either enter the tricarboxylic acid (TCA) cycle or be transformed into lactate and secreted. (2) The pentose phosphate pathway, is parallel to glycolysis and generates ribose for nucleotides, amino acids and nicotinamide adenine dinucleotide phosphate (NADPH), which is important for the synthesis of fatty acids and production of lipid ligands. (4) Fatty acid oxidation is a mitochondrial dependent aerobic process which consists on breaking down fatty acids into Acetyl-CoA units, generating NADH and FADH2, and driving ATP production from the E. (5) Fatty acid synthesis is a complex cytoplasmic process that is regulated by Acetyl-CoA, NADPH and fatty acid synthases to generate fatty acids. (6) Amino acid metabolism is very diverse, also important for cell growth and protein biosynthesis, as a consequence of the large number of different amino acids, which can feed different the carbon skeletons into pyruvate, acetyl CoA, and the citric acid cycle, which enter the TCA cycle. TCA: Tricarboxylic acid; PPP: Pentose phosphate pathway; OXPHOS: Oxidative phosphorylation.

After entering the cell, glucose is phosphorylated by ATP to form glucose-6-phosphate (G6P) in a reaction catalyzed by hexokinase. A series of enzymatic reactions degrade G6P to fructose-6-phosphate following by fructose-1,6-bisphosphate and finally to glyceraldehyde-3-phosphate, which, in turn, is converted to pyruvate in the cytosol[6]. In the mitochondria, pyruvate is imported and converted to Acetyl-CoA, then integrating the TCA cycle, which leads to production of NADH and FADH2, cofactors for oxidoreductase enzymes in the electron transport chain (ETC), important in the generation of ATP. Alternatively, in the cytosol, the lactate dehydrogenase enzyme can convert pyruvate into lactate, reoxidizing NADH to NAD+ which is necessary for glycolysis to continue[6]. In the absence of oxygen, glycolysis comes into action, catabolizing glucose into pyruvate, which is preferentially converted to lactate instead of Acetyl-CoA to enter the TCA cycle. Shift to glycolysis, even when oxygen is not a limitation is seen in some cases in a process known as aerobic glycolysis (fermentation) or Warburg effect, a process described by Otto Heinrich Warburg in which tumor cells tend to rely on glycolysis for ATP production rather than oxygen-dependent phosphorylation[7,8].

The PPP functions in parallel to glycolysis and is an important source for reducing molecules (*e.g.*, NADPH, required in anabolic reactions and critical to maintain redox balance under stress situations) and synthesis of pentoses (5-carbon sugars, important to maintain carbon homeostasis). The PPP reactions branches out into an oxidative and non-oxidative phase; the first oxidative phase converts G6P into NADPH, ribulose 5-phosphate and carbon dioxide, the second phase (non-oxidative) generates ribose 5-phosphate for the synthesis of nucleic acids and other sugar phosphate precursors used to build amino acids[9].

Mitochondrial FAO is a catabolic pathway that generates necessary products for the cell to produce energy, such as Acetyl-CoA, NADH+ and FADH2. The FAO is composed by two steps: the "activation" and the oxidation. The first step occurs in the cytosol and it is the formation of a fatty acid acyl-CoA with the consumption of ATP. The second step is called β-oxidation and generates quantities of Acetyl-CoA, NADH and FADH2. These products then enter the TCA cycle and the ETC, where they can be used for the generation of ATP[5]. On the other hand cells need lipids to produce cell membranes and other structures necessary for cell growth and proliferation so the

fatty acid synthesis (FAS) pathway converts intermediate products from glycolysis and TCA in acetyl-coA that is used to generate lipids[10]. In the mitochondria, citrate is synthesized from Acetyl-CoA and oxaloacetate, which is exported to the cytosol where it is cleaved to yield acetyl-CoA and oxaloacetate, then cytosolic Acetyl-CoA, is converted to Malonil-CoA and, by the effect of the fatty acid synthase, to Palmitate. Palmitate or palmitic acid is the most common saturated fatty acid in the human organism, and important for the composition of membrane phospholipids, substrate for the acylation of proteins, cholesterol synthesis and adipose triacylglycerols[6,11].

CROSSTALK BETWEEN CELL METABOLISM AND IMMUNE RESPONSES

The interplay between metabolic dysfunction and immune mechanisms involved in inflammation are being exposed by a growing number of studies and this knowledge is reshaping the understanding of what appeared to be independently functional systems of immunity and metabolism[12].

Dendritic cells (DCs) are a heterogeneous cell population key to immune homeostasis as they control activation and polarization of effector T cell responses and Treg differentiation. During DC maturation, the metabolic profile of precursors and differentiating DCs is eschewed, shifting from glycolysis to oxidative phosphorylation (OXPHOS), process that involves ROS, as well as an increase in expression of mitochondrial respiratory enzymes, ATP content and antioxidant capacity[13]. In activated DCs, glycolytic intermediates can also enter into the PPP, which support biosynthesis of nucleotides for increased protein output and the generation of NADPH, and the TCA cycle and support lipid membrane production and macromolecule biosynthesis[13,14]. Tolerogenic DCs (tolDCs), present a more active catabolic pathway, fatty acid metabolism, OXPHOS with increased respiratory capacity and highest mitochondrial oxidative activity as well as glycolytic capacity in comparison to mature DCs[14].

It is known that naive T cells have lower metabolic requirements, hence favor glycolysis and TCA cycle[15]. Once activated T cells undergo metabolic reprogramming which is believed necessary for cells to sustain the biosynthesis of lipids, proteins and nucleic acids required for cell proliferation and effector molecules, therefore, a change from OXPHOS in naïve or memory cells to increased glycolysis is observed in effector T cells[16] (Figure 2). Thus, increase in glycolysis, PPP, glutamine metabolism, combined with synthesis of cellular components characterizes early cell activation[7,15,17]. In general, *in vitro* studies have indicated that glycolysis is very important for effector cell development, evidenced also by data showing that GLUT1 deficiency impairs CD4+ effector function and proliferation while Tregs are enriched and functionally unaffected[18,19]. In a similar manner, glutamate metabolism is also involved in the differentiation of Th1 and Th17 effector T cells but does not seem to be critical for Tregs[18,20]. Effector T cells undergoing enhanced proliferation, including some subtypes of T helper cells, and CD8+ T cells, increase glycolysis and glutaminolysis as a mechanism to meet the increased metabolic demands of cell growth as well as optimize the production of proinflammatory cytokines, such as IL-2 and IFN-γ[21]. In Tregs glycolysis modulates the expression of FOXP3, as it was demonstrated that 2-DG (2-deoxy-d-glucose)-glycolysis inhibition in human T cells lead to decreased IL-2–IL-2R–STAT5 signaling, consequently limiting the generation of functionally suppressive Treg cells[22]. Furthermore, activation of the glycolytic-lipogenic metabolism seems to be involved in the Th17/Treg balance, for example, Acetyl-CoA carboxylase 1 (ACC1)-mediated de novo FAS affects Th17 cell differentiation but not Treg cells[23-25]. Potentially, drugs such as soraphen A (ACC-specific inhibitor) could be tested in preclinical animal models to verify improvement of graft survival.

In regards to lipids, they are essential components for the structure of cell membrane, which must be duplicated in preparation for each cell division, as well as important energy sources metabolized through beta-oxidation, not surprisingly, lipids are easily accessible to immune cells in adipose tissue which abundantly surrounds lymph nodes[26].

Lastly, fatty acid metabolism is involved in both CD4 and CD8 cell function. For instance, a study demonstrated that the suppression of FAS by inhibition of ACC1 restrained the generation of pro-inflammatory Th17 cells, whilst favoring the differentiation of FoxP3+ Tregs[23] while in case of memory CD8 T cells, activation favors neo-synthesis of fatty acids to support FAO[27].

In summary, differentiation, activation and effector function of immune cells seem to be directly or indirectly oriented by shifts in metabolic pathway. Thus, when

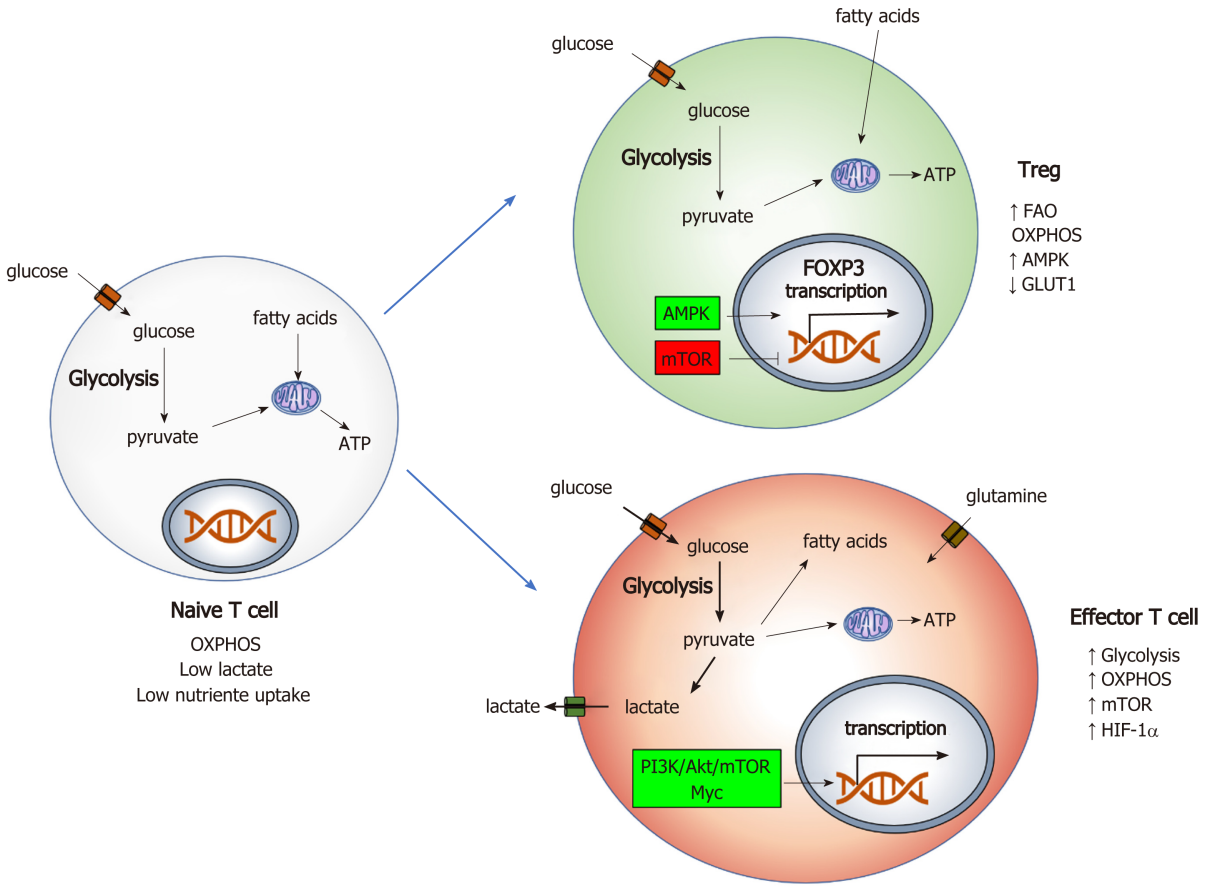

Figure 2 Main metabolic pathways in T cells – Naïve T cells are characterized by lower energy requirement, low glucose uptake and mainly use oxidative phosphorylation for energy generation. Once T cells are activated there is a switch in metabolic state which is accompanied by changes *via* the PI3K/Akt/mTOR axis and Myc. Increase in glycolysis and oxidative phosphorylation (OXPHOS) are characteristic in activated effector T cells, increase in glutamine uptake and fatty acid synthesis is also observed. In contrast, Tregs have metabolic features comparative to naïve T cells, producing energy by lipid oxidation and OXPHOS in mitochondria for the generation of adenosine triphosphate[7,42,43]. ATP: Adenosine triphosphate; AMPK: Adenosine monophosphate activated protein kinase; OXPHOS: Oxidative phosphorylation; FAO: Fatty acid oxidation.

considering metabolic parameters that affect immune cell fate, a variety factors will influence the tissue microenvironment such as: nutrient competition, oxygen consumption and metabolite production from tissue, immune cells and microbiota as well as the inflammatory state of the host[28,29].

TARGETING METABOLIC PATHWAYS IN TRANSPLANTATION

Solid organ transplantation is most-often the last resource for patients who suffer from end-stage organ disease, however, long-term acceptance and survival of transplanted tissues and organs is currently limited mainly due to immune-mediated mechanisms[30]. A great deal of effort has been dedicated to understanding the mechanisms underlying rejection by effector and emerging evidence does suggest a prominent role for nutritional and metabolic substrates on immune responses.

In transplantation, during which the tissue obligatorily goes through surgical trauma, lack of oxygenation or damage from reperfusion, the injury causes oxidative stress (OS) and release of Damage-associated molecular patterns and danger signals from necrotic cell death, which act as endogenous activators of innate immune mechanisms that promote inflammatory tissue damage and metabolic alterations in immune cells[31]. This signaling cascade will provoke the initial infiltration of cells into the allograft, followed by migration to lymph nodes, where T cells and DCs will initiate and allow propagation of allo-specific immune responses[28,29,32]. In the process of following antigenic activation, cells require a major shift in energy requirement as they change from a quiescent state to active-cytokine producing and proliferating immune cells, thus, this metabolic reprogramming includes balance between energy production and consumption based on availability of nutritional derived components,

mitochondrial or anaerobic respiration[16].

Regarding DC regulation, pharmacological intervention such as activation of AMPK signaling by peroxisome proliferator-activated receptor gamma coactivator (PGC) and Resveratrol to enhance PGC-1α activity has been demonstrated to generate tolDCs[33-35] , that have crucial role in inducing tolerance to the graft. DCs treated with Resveratrol showed reduced capacity to stimulate allogenic T cells and to induce CD4+ T cell migration[35]. Also, metabolic products like ATP may be recognized as a danger signal, whilst upon ATP degradation leads to decrease in pro-inflammatory signalling, regulating activation of antigen presenting cells or Treg cells[36,37].

Studies have shown that T cell activation and effector responses require metabolic reprogramming which relies glycolysis and glutaminolysis pathways[38-40], now researchers are investing whether intervening in this specific pathways can ameliorate graft survival. In a model of hematopoietic cell transplantation, Nguyen and colleagues demonstrated that alloantigen T cells demand on glycolysis for activation and GVHD (graft versus host disease) induction. In a pre-clinical murine GVHD model, blockage of glycolysis by use of rapamycin which inhibits mTORC1 or mTOR knockout mice, as well as use of 3-(3-pyridinyl)-1-(4-pyridinyl)-2-propen-1-one (3-PO), a specific inhibitor of pathway6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 3, which also limits glycolysis, increased survival of mice[41].

Using murine models of skin and heart allograft transplantations, another study showed the effects of glycolysis and glutamine metabolism inhibition. Using a combination of 2-DG, 6-diazo-5-oxo-L-norleucine (glutamine metabolism inhibitor) and the anti-type II diabetes drug metformin, the group demonstrated an inhibition of allo-specific CD4+ and CD8+ T cell responses, preventing or delaying rejection in fully mismatched skin and heart allograft transplantation models[40].

In summary, these very fresh data seem to indicate that it is possible to hamper alloantigen-induced activation of effector responses by targeting some metabolic pathways.

CONCLUSION

Immunometabolism is a very new field to be explored, studies which have specifically targeted metabolic pathways in transplant models are only beginning to emerge. However, based on findings that it is possible to change metabolic reprogramming of DCs and T cells it may be possible to promote transplantation tolerance and avoid rejection. Most studies so far have focused in inhibition of glycolysis and the effects in T cells; this seems to improve graft survival in murine models, however long-term effects of this type of therapies and in the full components of the immune system have yet to be understood in order to declare metabolic intervention safe. It is important to continue research and find distinct metabolic signatures in different phases of DC and alloreactive T cell activation to specifically target immune alloreactive effector responses without deleterious side-effects.

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META-ANALYSIS

Proton pump inhibitors and adverse effects in kidney transplant recipients: A meta-analysis

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Abstract

BACKGROUND

The adverse renal effects of proton pump inhibitors (PPIs) are increasingly recognized in both the general population and patients with chronic kidney disease. Several pharmacokinetic studies have also raised concerns regarding the interaction between PPIs and immunosuppressive drugs in transplant patients. Whether the adverse effects of PPIs have a clinical significance in kidney transplant recipients remains unclear. We performed this meta-analysis to assess the risk of adverse effects in kidney transplant recipients on PPI compared with those without PPI exposure.

AIM

To investigate the risk of acute rejection, graft loss, hypomagnesemia, renal dysfunction, and overall mortality in kidney transplant recipients on PPI compared with those without PPI exposure.

METHODS

A systematic review was conducted in MEDLINE, EMBASE, and Cochrane databases from inception through October 2018 to identify studies that evaluated

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the adverse effects of PPIs in kidney transplant recipients, including biopsy-proven acute rejection, graft loss, hypomagnesemia, renal function, and overall mortality. Effect estimates from the individual studies were extracted and combined using random-effect, generic inverse variance method of DerSimonian and Laird. The protocol for this meta-analysis is registered with PROSPERO, No. CRD42018115676.

RESULTS

Fourteen observational studies with 6786 kidney transplant recipients were enrolled. No significant association was found between PPI exposure and the risk of biopsy-proven acute rejection at ≥ 1 year [pooled odds ratio (OR), 1.25; 95% confidence interval (CI), 0.82-1.91, I^2 = 55%], graft loss at 1 year (pooled OR = 1.30, 95%CI: 0.75-2.24, I^2 = 0%) or 1-year mortality (pooled OR = 1.53, 95%CI: 0.90-2.58, I^2 = 34%). However, PPI exposure was significantly associated with hypomagnesemia (pooled OR = 1.56, 95%CI: 1.19-2.05, I^2 = 27%). Funnel plots and Egger regression asymmetry test were performed and showed no publication bias.

CONCLUSION

PPI use was not associated with significant risks of higher acute rejection, graft loss, or 1-year mortality. However, the risk of hypomagnesemia was significantly increased with PPI use. Thus, future studies are needed to assess the impact of PPIs on long-term outcomes.

Key words: Proton pump inhibitors; Kidney; Renal transplantation; Meta-analysis hypomagnesemia; Systematic reviews

Core tip: Several pharmacokinetic studies have raised concerns regarding the interaction between proton pump inhibitors (PPIs) and immunosuppressive drugs in transplant patients. Whether the adverse effects of PPIs have a clinical significance in kidney transplant recipients remains unclear. We performed this meta-analysis to assess the risk of adverse effects in kidney transplant recipients on PPI compared with those without PPI exposure. We demonstrate that PPI use is not associated with significant risks of higher acute rejection, graft loss, or 1-year mortality. However, PPI use is associated with 1.56-fold increased risk of hypomagnesemia. Thus, future studies are needed to assess the impact of PPIs on long-term outcomes.

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INTRODUCTION

Proton pump inhibitors (PPIs) are commonly prescribed after transplantation for prophylaxis against peptic ulcer disease and for treatment of gastro-esophageal reflux disease or dyspepsia. Prolonged exposure to this class of medication has been shown to be associated with kidney dysfunction[1,2], as well as other non-renal adverse outcomes, including hypomagnesemia[3], fracture[4], or dementia[5] in the general population. The risk of kidney dysfunction associated with PPIs is particularly concerning to kidney transplant recipients who are already at risk for acute kidney injury.

Mycophenolate mofetil (MMF) is an antimetabolite that is commonly used as part of the maintenance immunosuppression in kidney transplant recipients[6]. MMF is a prodrug that is hepatically metabolized to the active compound mycophenolic acid (MPA) after oral administration. MPA exerts its immunosuppressive effects by reversibly inhibiting the de novo synthesis of purine nucleotides, leading to reduced proliferation of B- and T-cell lymphocytes, induction of activated T lymphocyte

apoptosis, and downregulation of adhesion molecule expression, resulting in lower leukocyte trafficking and recruitment[7]. Because gastrointestinal discomfort is a common side effect of MMF, PPIs are commonly prescribed to alleviate the symptoms. However, pharmacokinetic studies[8-12] have shown that PPIs reduce the absorption of MMF and lower the exposure to MPA presumably by its potent inhibition of gastric acidification compared with another class of acid suppressant, the H2-receptor antagonists[13,14]. Randomized controlled trials[15,16] and observational studies[17-19] have also shown that reduced exposure to MPA is associated with higher risk of acute rejection and overall worse allograft outcome in kidney transplant recipients. However, the clinical significance of this drug interaction in kidney transplant recipients is unknown. Several studies[20,21] have shown a possible increased risk of acute rejection with PPI exposure whereas others have not[22-24].

Some studies[25,26] have shown that concurrent PPI can increase tacrolimus drug concentration, leading to higher risk of toxicity through cytochrome or p-glycoprotein inhibition in patients with certain Cytochrome P450 2C19 (CYP2C19) and/or CYP3A5 genotypes. However, this is not expected to increase the risk of rejection, but calcineurin inhibitor toxicity may lead to renal dysfunction. Other commonly used immunosuppressive drugs are not known to have significant interaction with PPIs.

PPI may also interfere with magnesium absorption in the gastrointestinal tract, causing hypomagnesemia[3]. The mechanism of renal dysfunction related to PPIs is not clear although acute interstitial nephritis (AIN) associated with PPIs has been purposed[1,2].

Therefore, we conducted this systematic review and meta-analysis to investigate the adverse outcomes in kidney transplant recipients on PPI compared with those without PPI exposure. The outcomes of interest include biopsy-proven acute rejection, graft loss, kidney dysfunction, hypomagnesemia, and overall mortality.

MATERIALS AND METHODS

Search strategy

The protocol for this meta-analysis is registered with PROSPERO, No. CRD420-18115676. PRISMA statement guidelines were followed for conducting and reporting meta-analysis data[27]. A systematic review was conducted in MEDLINE, EMBASE, and Cochrane databases from inception to October 2018 to identify studies that evaluated adverse effects of PPIs in kidney transplant recipients by using the search terms "kidney transplant" and "proton pump inhibitor," as described in the online supplementary data without any language restriction. References of selected articles were also manually searched for additional studies.

Inclusion criteria

Studies were eligible for this meta-analysis if the following inclusion criteria were met: (1) Randomized controlled trial, cohort (either prospective or retrospective), case–control study or cross-sectional study published as an original study to evaluate the outcomes of kidney transplantation in patients on PPIs; (2) Odds ratios (ORs), relative risk (RR), hazard ratio (HR), and standardized incidence ratio (SIR) with 95% confidence intervals (CIs) or sufficient raw data to calculate these ratios were provided; and (3) Subjects not on PPIs were used as comparators in cohort and cross-sectional studies.

Study eligibility was independently evaluated by the investigators (BB and CT). Any disagreement was resolved by mutual consensus. The quality of each study was appraised using the Newcastle–Ottawa quality scale[28]. This scale assesses each study in three domains, including the: (1) Representativeness of the subjects; (2) Comparability between the study groups; and (3) Ascertainment of the exposure of interest for the case–control study and the outcome of interest for the cohort study. The modified version of the Newcastle–Ottawa scale as described by Herzog *et al*[29] was used for cross-sectional studies.

Review process and data extraction

The two study investigators independently reviewed the titles and abstracts of all retrieved articles. Articles that apparently did not fulfill the inclusion criteria were excluded. Only potentially relevant articles underwent full-text review to determine eligibility. A standardized data collection form was used to extract the following information from the included studies: First author's name, year of publication, year of study, country where the study was conducted, study design, source of population, number of subjects, baseline characteristics of the subjects, and effect estimates. This data extraction process was performed by both investigators to ensure accuracy.

Statistical analysis

All statistical analyses were performed using Comprehensive Meta-analysis version 3 software (Eaglewood, NJ, United States). The pooled RRs of acute rejection, graft loss, hypomagnesemia, and overall mortality in kidney transplant recipients on PPIs compared with subjects not on PPIs were calculated using the generic inverse method of DerSimonian and Laird[30]. The random-effects model was used, given the high likelihood of between-study variance due to the difference in underlying population and methodology. Cochran's Q-test, which was supplemented by I^2 statistics, was used to evaluate statistical heterogeneity. I^2 statistics quantify the proportion of the total variation across studies, that is, due to true heterogeneity rather than chance. An I^2 value of 0% to 25% represents insignificant heterogeneity, > 25% to ≤ 50% represents low heterogeneity, > 50% to ≤ 75% represents moderate heterogeneity, and > 75% represents high heterogeneity[31].

RESULTS

The initial search yielded 838 articles, all of which underwent title and abstract review (Figure 1). Most of the articles were excluded at this step because they were case reports, letters to the editor, review articles, or interventional studies, which clearly did not fulfill our inclusion criteria. Eighteen studies underwent full-length article review, and four were excluded because they did not include controls or did not report the outcome of interest. Therefore, 14 studies met our inclusion criteria[20-24,32-40] and were included in the meta-analysis. The baseline characteristics of the included studies are summarized in Table 1. These 14 observational studies consisted of 6786 kidney transplant recipients (> 1907 with PPI exposure and 2528 without PPI exposure).

Acute biopsy-proven rejection and graft loss

Table 2 summarizes the findings across the studies that reported allograft outcomes. Definitions of biopsy-proven acute rejection and presumed rejection across included studies are also shown in Supplementary Table S1. Pooled data for acute rejection at ≥ 1 year were available from six studies with 2427 kidney transplant recipients (980 with PPI exposure and 1447 without PPI exposure). No significant association was found between PPI exposure and the risk of biopsy-proven acute rejection at ≥ 1 year (pooled OR = 1.25, 95%CI: 0.82-1.91, I^2 = 55%, Figure 2). At 3 mo, acute rejection risk was also not significantly different between the two groups (pooled OR = 1.54, 95%CI: 0.64-3.82). Acute cellular rejection was more common than antibody-mediated rejection (AMR) and the rejection rates were similar between the two groups, except in studies by Courson *et al*[21] and Rouse *et al*[24] which demonstrated higher rates of AMR among the PPI group. The median time to rejection was reported to be similar between the two groups across four studies (approximately 3-4 mo post-transplant). Graft loss at 1 year was also not different between those with and without PPI exposure (pooled OR = 1.30, 95%CI: 0.75-2.24, I^2 = 0%, Figure 3).

Renal function

All but one study reported no significant short term (3 mo to 1 year) difference in renal function, as summarized in Table 3. Uludag *et al*[37], which had the most extended follow-up period of all included studies (median, 109 mo; interquartile range, 82-156 mo), however demonstrated that the serum creatinine level in the PPI group was higher than that in the non-PPI group (1.44 ± 0.99 *vs* 1.24 ± 0.46 mg/dL).

Hypomagnesemia

Table 4 summarizes data across eight studies. The risk of hypomagnesemia in the PPI group was significantly higher than in the non-PPI group (pooled OR = 1.56, 95%CI: 1.19-2.05, I^2 = 27%, Figure 4) based on three studies. Sezer *et al*[35], Van Ende *et al*[33], and Uludag *et al*[37] did not report a significant difference in the magnesium level between those with and without PPI exposure, whereas Alhosaini *et al*[34] reported a significant difference between the two groups (magnesium: 1.70 ± 0.12 *vs* 1.79 ± 0.17 for those with PPI and without PPI exposure; P = 0.006). Gomes-Neto *et al*[38] and Douwes *et al*[40] (who analyzed data from an overlapping set of patients) reported a significant inverse correlation between PPI use and plasma magnesium level. The proportion of hypomagnesemia also did not differ between the two groups, but a study by Shabaka *et al*[36] noted that those with PPI exposure seemed to develop significantly more severe hypomagnesemia (defined as magnesium level < 1.3 mg/dL) compared with those without PPI exposure (21% *vs* 5%).

Overall mortality

Table 1 Characteristics of included studies

Ref.	Country	Type	Total N	Race	Immuno-suppressive regimen	CNI use (% Cyclosporine)	PPI			No PPI			Quality Scale[3]
							N	Age	M/F	*N*	Age	M/F	
Patel *et al*[32] 2012	United States	Retrospective	561	NR	Tacrolimus, MMF, Prednisone	0%	155	52±13[1]	NR	406	48±14	NR	3-2-2
Knorr *et al*[20] 2014	United States	Retrospective	597	52% Black	rATG, MMF, Tacrolimus, Prednisone	<3%	213	55±12	122/91	384	55±13	210/174	4-2-3
van Boekel *et al*[22] 2014	The Netherlands	Retrospective	202	98.5% Caucasian	Tacrolimus, MMF. Prednisone	0%	125	47.7±12.8	61.6%/38.4%	77	46.7±13.3	66.2%/43.8%	4-2-3
Van Ende *et al*[33] 2014	Belgium	Cross-sectional	512	98% Caucasian	Varies	47% (tacrolimus 35%)	101	53 ± 13	59%/41%	411	53 ± 13	59%/41%	4-2-3
Alhosaini *et al*[34] 2015	United States	Retrospective	83	59% Caucasian, 19% Black	CNI (Tacrolimus, Cyclosporine), MPA, Prednisone	5/83 (6%)	43	54 ± 15.1	25/18	40	49.7 ± 16.4	24/16	4-2-3
Sezer *et al*[35] 2015	Turkey	Retrospective	354	NR	NR	NR	164	38.6 ±10.7	NR	96	NR	38.6 ±10.7	3-2-2
Courson *et al*[21] 2016	United States	Retrospective	286	51% Caucasian, 17% Black, 10% Asian	Tacrolimus, MMF or MPS, early steroid withdrawal	0%	171	56±13	118/53	115	54±13	88/27	4-2-3
Patel *et al*[23] 2017	United States	Retrospective	522	24% Black	Tacrolimus, reduced-dose MMF, prednisone	11/522 (2%) converted to cyclosporine	183	54 (44-63)[2]	102/81	339	53 (43-60)	219/120	4-2-3
Shabaka *et al*[36] 2017	Spain	Cross-sectional	938	NR	CNI-based regimen	NR	NR	NR	NR	NR	NR	NR	3-2-2
Rouse *et al*[24] 2017	United States	Retrospective	211	55% Caucasian, 30% Black	Tacrolimus, MMF or MPS, Prednisone	0%	35	55±10.7	25/10	176	63±14	124/52	4-2-3
Uludag *et al*[37] 2017	Turkey	Retrospective	292	NR	NR	NR	223	36±10	129/104	69	33±11	42/27	3-2-2
Kipp *et al*[39] 2018	United States	Retrospective	819	NR	NR	NR	404	NR	NR	415	NR	NR	3-1-2
Douwes *et al*[40] 2018	The Netherlands	Cross-sectional	706	NR	NR	NR	NR	53 ± 13	57%/43%	NR	53 ± 13	57%/43%	3-1-2

Gomes-Neto *et al*[38] 2018	The Nether-lands	Cross-sectional	703	NR	NR	NR	NR	53 ± 13	57%/43%	NR	53 ± 13	57%/43%	3-1-2

[1]Data expressed as mean ± SD;
[2]Data expressed as Median (Range);
[3]According to the NOS (Newcastle-Ottawa Scale) classification. NR: Not reported; CNI: Calcineurin inhibitor; MMF: Mycophenolate mofetil; MPS: Mycophenolate sodium; MPA: Mycophenolate; rATG: Rabbit antithymocyte globulin; PPI: Proton pump inhibitors.

All-cause mortality data were available from five studies (Table 5), with three studies reporting 1-year survival and two reporting longer-term all-cause mortality. One-year mortality did not significantly differ between PPI and non-PPI use (pooled OR = 1.30, 95%CI: 0.51-3.29, I^2 = 41.4%; Figure 5). The two studies that reported long-term mortality outcomes (Douwes *et al*[40] and Gomes-Neto *et al*[38]) seemed to analyze data from a highly overlapping set of patients (n = 706 *vs* 703); hence, pooled HR was not calculated. With a median follow-up duration of 5.4 years (range, 4.8-6.1 years) in both studies, the adjusted HRs for all-cause mortality was significantly associated with PPI use (HR = 1.94, 95%CI: 1.32-2.88, and HR = 2.01, 95%CI: 1.43-2.83, respectively).

Evaluation for publication bias

The funnel plots (Supplementary Figure S1 to Figure S4) and Egger's regression asymmetry test were performed and showed no significant publication bias (P > 0.05 for all outcomes).

Sensitivity analysis

Sensitivity analysis was performed by excluding one study at a time to investigate the effect of each study on the pooled OR for each outcome assessed. The pooled effect estimate from this sensitivity analysis remained essentially unchanged.

DISCUSSION

This meta-analysis showed no significant association between exposure to PPIs and higher risk of acute biopsy-proven rejection, graft loss, or overall mortality, but a significantly higher risk of hypomagnesemia among those with PPI exposure was noted. No short-term difference in renal function was found between the two groups.

Despite several pharmacokinetic studies that have clearly showed significantly reduced MPA exposure following concomitant administration of PPIs and MMF in both healthy volunteers[12,41] and in immediate post-transplant kidney transplant recipients[10,11], there was no significant association between PPI use and increased risk of acute rejection in our study, suggesting that the effect may not be large enough to be clinically significant. Because none of the included studies reported MPA drug level or direct gastric pH measurement, it is difficult to ascertain whether a significant interaction between PPIs and MMF exists in the real-world setting. Three studies (van Boekel *et al*[22], Courson *et al*[21], and Patel *et al*[23]) reported the total cumulative MMF exposure or mean daily dose between the two groups. In all three studies, despite the PPI group receiving a slightly lower cumulative MMF dose compared to the non-PPI group (non-significant in the study by van Boekel *et al*[22] and Patel *et al*[23]; significant in the study by Courson *et al*[21]), no significant difference in acute rejection was found. Interestingly, in black patients, PPI was found to be significantly associated with a higher risk of acute rejection in one study[20].

Another potential reason for the lack of a significant association between PPI use and acute biopsy-proven rejection is that the majority of the kidney transplant recipients enrolled in the included studies were on tacrolimus, with none or only a small percentage of recipients on cyclosporine. The use of tacrolimus as the calcineurin inhibitor instead of cyclosporine may help lower the risk of reduced MPA exposure with PPI use. Cyclosporine, unlike tacrolimus, can reduce the enterohepatic recirculation of MPA in the gastrointestinal tract[42,43], thus further lowering total MPA exposure. The enteric-coated mycophenolate sodium does not appear to have a significant interaction with PPI[8,41,44], unlike MMF.

We did not demonstrate a significant difference in renal function as measured by estimated glomerular filtration rate or serum creatinine between the PPI and the non-PPI group in the short term (3 mo to 1 year). Extrapolating from observational studies in the general population, this is not unexpected as the risk of kidney dysfunction seems to be associated with more prolonged PPI use and may have a long latent

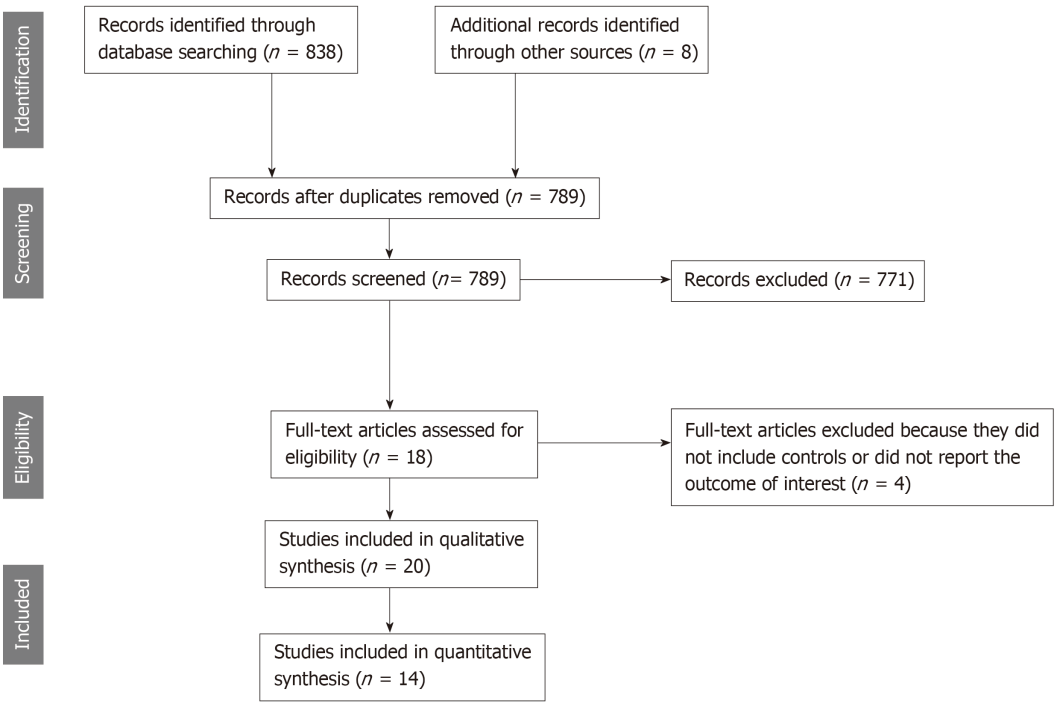

Figure 1 Study selection.

period[1,45]. Uludag *et al*[37] also confirmed this observation by noting a significantly higher serum creatinine level in PPI users compared with non-users at a longer median follow-up of 109 mo.

The risk of hypomagnesemia in the PPI group was significantly higher than that in the non-PPI group in our study. This is consistent with studies in the general population that report hypomagnesemia with prolonged PPI use[3]. The exact mechanism of PPI-induced hypomagnesemia is unknown. Urinary magnesium excretion has been shown to be low in patients with hypomagnesemia related to PPI use[46], suggesting that reduced absorption from the gastrointestinal tract is the main cause. It is hypothesized that the TRMP6 (transient receptor potential melastatin) pathway in gut epithelial cells, which mediates magnesium absorption, is inhibited by the high pH milieu caused by PPI use[47]. This inhibition is more pronounced in certain individuals with additional polymorphisms of the related cellular pathway proteins or other risk factors, which explains why the incidence and degree of hypomagnesemia vary among PPI users[47]. Some studies have also reported that high-dose oral magnesium supplementation can correct hypomagnesemia associated with PPI[48], suggesting that the paracellular passive absorption in the bowel remains intact.

In kidney transplant recipients, hypomagnesemia has been shown to be associated with various adverse consequences[49]. Low magnesium level has been associated with accelerated decline of allograft function and a higher rate of graft loss in patients with cyclosporine-induced nephropathy[50], consistent with animal studies showing a higher degree of renal tissue fibrosis associated with low magnesium[51] that appears to be partially correctable with magnesium supplementation[51,52]. Hypomagnesemia may also lead to a higher incidence of new-onset diabetes after transplant[53], which is a separate risk factor for allograft loss and overall mortality.

Our study did not show a significant difference in the 1-year overall mortality, as expected, because the risks of acute rejection, graft loss, and kidney dysfunction did not significantly differ between the PPI and non-PPI groups. Only hypomagnesemia was found to be significantly associated with PPI use; hence, this may not be clinically significant to drive a mortality difference at least in the short term. However, Douwes *et al*[40] and Gomes-Neto *et al*[38] reported a significant association between PPI use and long-term all-cause mortality despite adjustment for confounders. Furthermore, both studies also showed a significant interaction between PPI use and hypomagnesemia. As noted previously, Uludag *et al*[37] has also reported significantly worse kidney function in the PPI group with longer follow-up (median, 109 mo). Hypomagnesemia or renal dysfunction may be a late manifestation associated with prolonged exposure to PPIs, which may eventually be clinically significant enough to cause higher mortality. Further studies are needed to clarify this question.

Although we believe the literature review process was rigorous and the included

Table 2 Acute rejection and graft loss

Ref.	Biopsy-proven acute rejection at 1 yr (%)	Biopsy-proven or presumed rejection at 3 mo (%)	Median time to rejection	Antibody mediated rejection (%)	Graft loss (%)
Patel *et al*[32] 2012					
PPI	25 (16%)	NR	4.1 mo	3.3%	NR
No PPI	60 (15%)	NR	3.3 mo	3.1%	NR
P	0.69	-	NS	NS	-
Knorr *et al*[20] 2014					
PPI	32/213 (15%)	NR	110 ± 91 d	1/32 (3.1%)	9/213 (4.2%)
H2A	46/384 (12%)	NR	110 ± 112 d	2/46 (4.3%)	19/384 (4.9%)
P	0.15	-	1.0	NR	0.84
van Boekel *et al*[22] 2014					
PPI	NR	25/125 (20%) BPAR: 13/125 (10.4%)	NR	NR	NR
H2RA	NR	15/77 (19.5%) BPAR: 7/77 (9.1%)	NR	NR	NR
P	-	NS	-	-	-
Courson *et al*[21] 2014					
PPI	16/171 (9.4%)	NR	116±92 d[1]	5/16 (31%)	4/171 (2.3%)
H2RA	3/115 (2.6%)	NR	both	0	2/115 (1.7%)
P	0.029	-	NS	0.53	1
Patel *et al*[23] 2017					
PPI	11/183 (19%)	12/183 (4.9%)	106 (57-286) days[2]	1/11 (9.1%)	9/183 (4.9%)
H2RA	28/339 (14%)	9/339 (3.5%)	139 (96-339) days	2/28 (7.1%)	8/339 (2.4%)
P	0.35	0.44	0.28	NR	0.12
Rouse *et al*[24] 2017					
PPI	5/35 NR		NR	2/5 (40%)	NR
H2RA	26/176	NR	NR	3/26 (12%)	NR
P	1.0	-	-	0.03	-
Uludag *et al*[37] 2017					
PPI	36/233 (15.5%)	NR	NR	NR	11/233 (4.7%)
No PPI	5/69 (7.2%)	NR	NR	NR	2/69 (2.9%)
P	0.08	-	-	-	0.51

[1]Data expressed as mean ± SD;
[2]Data expressed as Median (Range). NR: Not reported; NS: Not significant; H2RA: H2-receptor antagonists; PPI: Proton pump inhibitors.

studies were of high quality, this meta-analysis has some limitations. Therefore, the interpretation of the results needs to be performed with caution. First, this meta-analysis is based solely on observational studies. Although this is appropriate for our clinical question, it may be inherently subject to selection bias and unadjusted confounders. Second, certain important baseline characteristics could not be obtained or compared across all studies. Of interest to transplant recipients, comparison of different immunosuppressive regimens, drug level, dosage, and adherence to both immunosuppressive drugs or acid suppressive therapy between the two groups was not possible in most included studies due to either their observational or retrospective design. Third, the definitions of various outcomes of interest varied across studies, such as the cut-off value for hypomagnesemia, definition of severe rejection, or the use of different criteria for the classification of AMR and cell-mediated rejection. Finally, most of the included studies only reported follow-up data for a relatively short-term period (approximately 1 year). Therefore, we cannot rule out the possibility that prolonged exposure of PPIs (longer than a year) may lead to adverse outcomes. Further study is needed to address whether long-term PPI exposure in kidney transplant recipients is associated with worse outcomes.

In conclusion, PPI use was not associated with significant risks of higher acute rejection, graft loss, or 1-year mortality. However, the risk of hypomagnesemia was significantly increased with PPI use.

Table 3 Renal function

Ref.	eGFR			Cr		
	PPI	No PPI	*P*	PPI	No PPI	*P*
Knorr *et al*[20]	53.1 ± 20.2[1]	55.1 ± 20.6	0.29	NR	NR	-
van Boekel *et al*[22]	49.5 ± 12.3	50.7 ± 12.5	NS	1.5 ± 0.4 at 3 mo	1.5 ± 0.4	NS
Patel *et al*[23]	49.0 (39.4–63.2)[2]	49.9 (39.3–60.8)	0.78	NR	NR	-
Uludag *et al*[37]	-	-	-	1.49 ± 0.99 mg/dL	1.24 ± 0.46 mg/dL	0.017
Alhosaini *et al*[34]	49.4 ± 14.9	52.8 ± 14.3	0.29	-	-	-
Kipp *et al*[39]	NR	NR	-	1.896 ± 1.53	1.812 ± 1.25	*P* = 0.4098

[1]Data expressed as mean ± SD;
[2]Data expressed as Median (Range). NR: Not reported; NS: Not significant; eGFR: Estimated glomerular filtration rate; PPI: Proton pump inhibitors.

Table 4 Hypomagnesemia

Ref.	Serum / Plasma magnesium level			Hypomagnesemia				
	PPI	No PPI	*P*	Definition of hypomagnesemia	PPI	No PPI	*P*	Correlation between PPI and hypomagnesemia	Magnesium supplementation
Sezer *et al*[35]	1.5 ± 0.04 mg/dl	1.7 ± 0.02 mg/dl	*P* < 0.05	NR	NR	NR		NR	NR
Shabaka *et al*[36]	NR	NR		NR	OR 1.55, (95%CI 1.09-2.20)	1		NR	NR
Kipp *et al*[39]	NR	NR		NR	215 (53.1%)	185 (44.6%)	*P* < 0.013	NR	NR
Alhosaini *et al*[34]	1.70 ± 0.12	1.79 ± 0.17	0.006	Serum Mg < 1.8 mg/dL	33/43	24/40	*P* > 0.05	NR	Use of Mg supplement: PPI 47% *vs* Non-PPI 21% (*P* = 0.02)
				Serum Mg < 1.3 mg/dL	9/43 (21%)	2/40 (5%)	*P* = 0.03		
Uludag *et al*[37]	0.728 mmol/L	*vs* 0.755 mmol/L,	*P* = 0.061	NR	NR	NR		NR	NR
Van Ende *et al*[33]	NR	NR		Serum Mg < 1.7 mg/dL	β: −0.84 (0.26; 2.71), *P* = 0.78			β: −0.84 (0.26; 2.71), *P* = 0.78	NR
Douwes *et al*[40]	NR	NR		Serum Mg < 1.8 mg/dL (0.75 mmol/L)	HR 3.25 (1.26-8.39)	1		β: -0.08, *P* = 0.046	Mean Mg intake: 330 ± 85 mg/d, (*P* = 0.204)
Gomes-Neto *et al*[38]	NR	NR		NR	β: -0.05, *P* = 0.04	NR		β: -0.05, *P* = 0.04	NR

[1]Data expressed as mean ± SD; [2]Data expressed as Median (Range); NR: Not reported; NS: Not significant; PPI: Proton pump inhibitors; Mg: Magnesium.

Table 5 Mortality

Ref.	1-yr mortality			Mortality beyond 1 yr (PPI *vs* no PPI)
	PPI	No PPI	*P*	
Knorr *et al*[20]	9/213 (4.2%)	17/384 (4.4%)	1	
Courson *et al*[21]	3/171 (1.8%)	3/115 (2.6%)	0.687	
Patel *et al*[23]	6/183 (3.3%)	3/339 (0.9%)	0.007	
Douwes *et al*[40]	NR	NR		HR 1.94 (95%CI: 1.32-2.88)
Gomes-Neto *et al*[38]	NR	NR		HR 2.01 (95%CI: 1.43-2.83)

NR: Not reported; NS: Not significant; eGFR: Estimated glomerular filtration rate; PPI: Proton pump inhibitors.

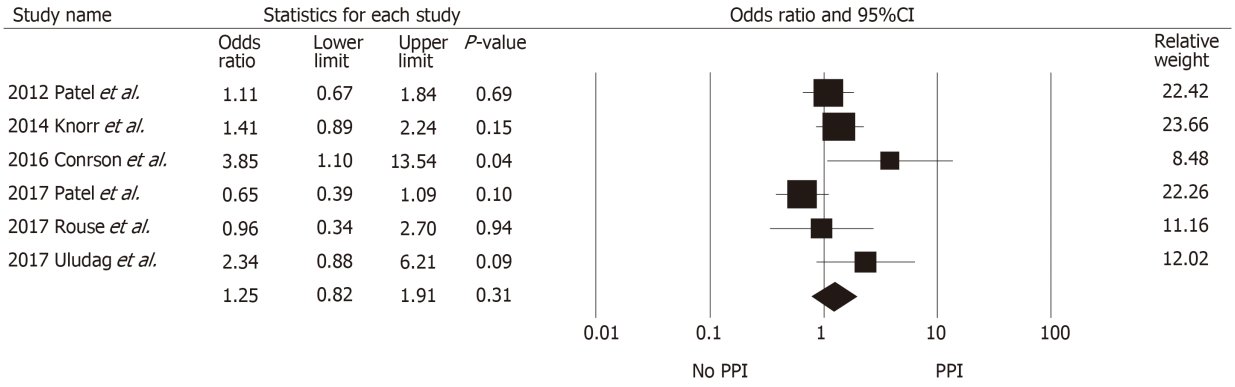

Figure 2 Forest plot of all included studies evaluating the risk of biopsy-proven rejection at one year or more in proton pump inhibitors users compared with non-users.

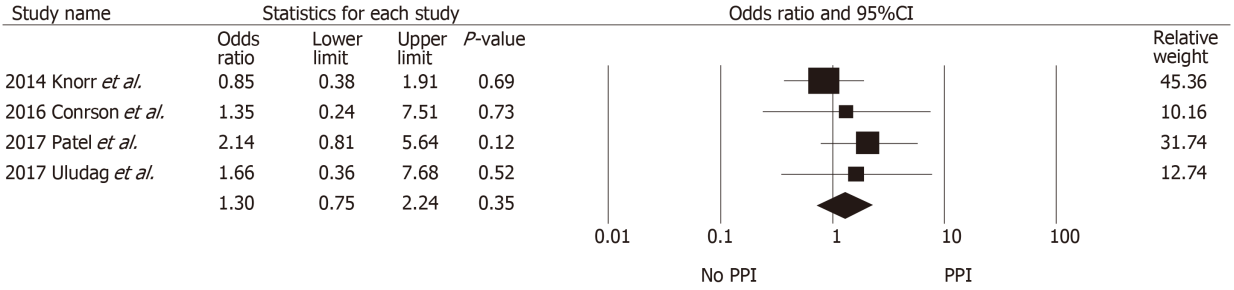

Figure 3 Forest plot of all included studies evaluating the risk of graft loss in proton pump inhibitors users compared with non-users.

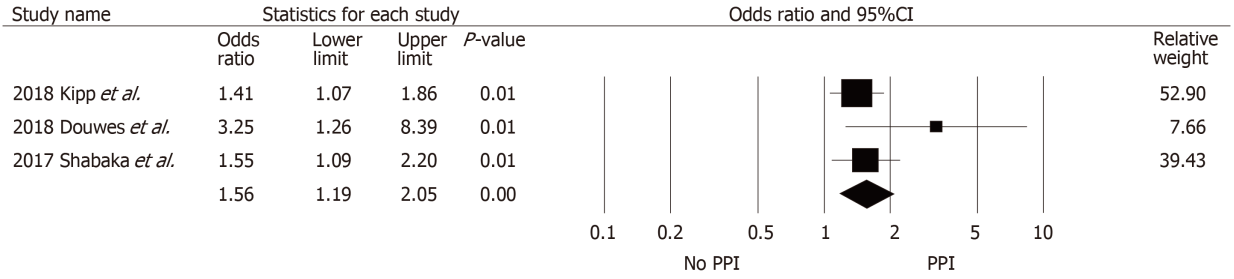

Figure 4 Forest plot of all included studies evaluating the risk of hypomagnesemia in PPI users compared with non-users.

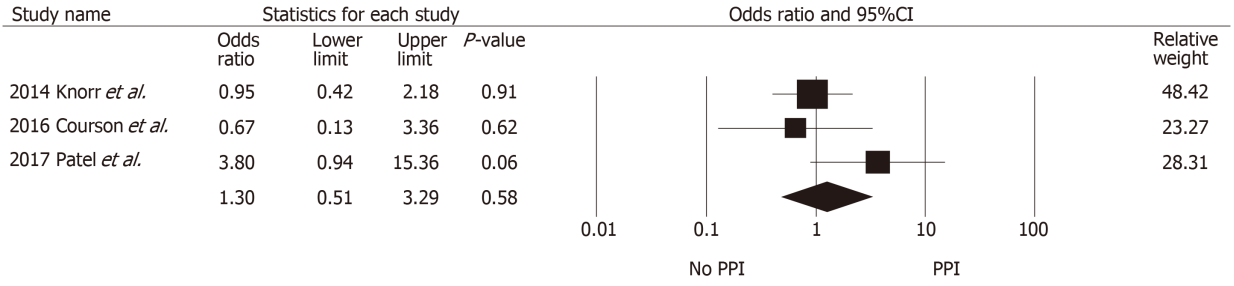

Figure 5 Forest plot of all included studies evaluating the risk of one-year mortality in PPI users compared with non-users.

ARTICLE HIGHLIGHTS

Research background

Adverse renal effects of PPIs are increasingly recognized in clinical practice. Pharmacokinetic studies have also raised concerns regarding the interaction between PPIs and immuno-

suppressive drugs in transplant patients. Whether the adverse effects of PPIs have a clinical significance in kidney transplant recipients remains unclear.

Research motivation
Proton pump inhibitors are commonly used after transplantation for prophylaxis against peptic ulcer disease and for treatment of gastro-esophageal reflux disease or dyspepsia. Prolonged exposure to this class of medication has been shown to be associated with kidney dysfunction, as well as other non-renal adverse outcomes, including hypomagnesemia, fracture, or dementia in the general population. The clinical significance of this drug interaction in kidney transplant recipients is unknown. Several studies have shown a possible increased risk of acute rejection with PPI exposure whereas others have not.

Research objectives
We performed this systematic review and meta-analysis to investigate the adverse outcomes in kidney transplant recipients on PPI compared with those without PPI exposure.

Research methods
A systematic review was conducted in MEDLINE, EMBASE, and Cochrane databases from inception to October 2018 to identify studies that evaluated adverse effects of PPIs in kidney transplant recipients. The outcomes of interest include biopsy-proven acute rejection, graft loss, kidney dysfunction, hypomagnesemia, and overall mortality. The protocol for this meta-analysis is registered with PROSPERO, No. CRD42018115676.

Research results
The authors found no significant association between exposure to PPIs and higher risk of acute biopsy-proven rejection, graft loss, or overall mortality, but a significantly 1.56-fold higher risk of hypomagnesemia among those with PPI exposure was noted. No short-term difference in renal function was found between the two groups.

Research conclusions
PPI use was not associated with significant risks of higher acute rejection, graft loss, or 1-year mortality. However, the risk of hypomagnesemia was significantly increased with PPI use. In the long-term, PPI use may also be associated with kidney dysfunction and increased overall mortality.

Research perspectives
This study demonstrated significant hypomagnesemia in kidney transplant recipients who received PPIs. Since hypomagnesemia is associated with new onset diabetes new-onset diabetes after transplantation, future large-scale clinical studies are needed to assess the impact of PPIs on long-term outcomes.

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