

Research Article

The Association between Vitamin D and Rejection in Adult Renal Transplant Recipients: A Meta-Analysis

Chanjuan S^{1*}, Junrui L^{1*}, Shuman L¹, Zixue S¹, Zengjie D¹, Jiusheng W¹, Changlin M² and Linping X¹

¹Department of Health Services Management, Second Military Medical University, China

²Department of Nephrology, Changzheng Hospital, China

*Corresponding author: Changlin Mei and Linping Xiong, Department of Health Services Management, Second Military Medical University, China

Received: December 21, 2017; Accepted: February 19, 2018; Published: February 26, 2018

Abstract

The problem has been discussed a lot, but the results remain controversial. Since no consensus had been reached yet for whether vitamin D insufficient is a major contributor for rejection in renal transplant patients, we performed a meta-analysis of the association between them. Pub Med, Medline, web of science, Ovid and Springer databases were searched for observational studies linked with vitamin D and rejection in adult renal transplant recipients. A meta-analysis was conducted by pooling data from relevant cohort and case control studies. The Q statistic and I² were used to measure heterogeneity. Subgroup analysis and meta-regression were conducted to detect the source of heterogeneity. When significant heterogeneity was observed statistically, a random-effect model can be used to estimate the odds ratio. And sensitivity analysis was conducted to make sure whether the results were stable. The analysis consisted of seven studies including five cohort studies and two case control studies, with a total of 2731 participants. These studies contained different vitamin D doses with a varying degree of intervention duration. Pooled odds ratio was 1.07, 95% confidence interval: [0.50-2.28], with significant heterogeneity among these studies (I²=82%, P<0.01). Vitamin D has no association with rejection in adult renal transplant recipients. There is a necessity that future investigations are encouraged to reveal the underlying mechanisms and the risk factors for rejection.

Keywords: Vitamin D; Rejection; Renal transplant recipients

Abbreviations

ACR: Acute Cellular Rejection; CI: Confidence Interval; CKD: Chronic Kidney Diseases; ESRD: End-Stage Renal Disease; PTDM: Post Transplant Diabetes Mellifluous; NOS: Newcastle-Ottawa Scale; OR: Odds Ratio; RR: Risk Ratio; VDR: Vitamin D Receptor

Introduction

Chronic Kidney Diseases (CKD) is highly prevalent in the general population, which have become a worldwide epidemic with an occurrence rate of approximately 5%-15% [1]. When the CKD is developing to End-Stage Renal Disease (ESRD), kidney transplantation is a preferred treatment for the increasing number of patients [2]. Renal transplant recipients usually have low vitamin D levels, especially in the early post-transplantation period [3]. Vitamin D is an important hormone which closely correlated with many immune disorders. It not only maintains the basic metabolism of calcium and phosphorus, but also affects immune functions of the body [4]. More and more people have realized that vitamin D is one of the largest modifiable risk factors for health [5].

Since the kidney is an active organ of vitamin D, it is also increasingly appreciated that there may be an association between vitamin D and allograft outcomes in renal transplant recipients [6]. Some retrospective cohort studies stated that vitamin D can improve the prognosis of graft, reduce graft loss and prevent rejection by inhibiting allograft rejection [7]. Various case control studies have been also projected to the conclusion that higher 25(OH) D level

was independently associated with lower incidence of rejection. In contrast, the others hold the reverse opinion that the incidence of rejection in renal transplantation was not associated with a low 25 (OH) D level [8]. A cross-sectional study was carried out by Maggie K.M. Ma, which showed there was no significant difference in the 25 (OH) D levels between renal transplant patients [9].

Although vitamin D supplement could provide immunomodulatory effects, the effects of vitamin D deficiency on allograft may not be entirely attributable to immune factors [10]. So the association between vitamin D with renal outcomes is not well described in these recipients. The problem has been discussed a lot, but the results remain controversial. Since no consensus had been reached yet for whether vitamin D insufficient is a major contributor for rejection in renal transplant patients, we performed a meta-analysis of the association between them.

Methods

Literature search

Pub Med, Medline, Ovid, web of science, and Springer databases were searched for relevant publications concerning the association between vitamin D and risk of rejection. The search was further updated to 2 April, 2017 in order to cover newer studies published without any language limitations. The following terms “vitamin D”, “rejection” and “renal or kidney transplant” were searched. More substitutions about Vitamin D were presented in (Table 1). Reference lists of relevant studies or reviews were also screened. The search strategy is presented in (Figure 1).

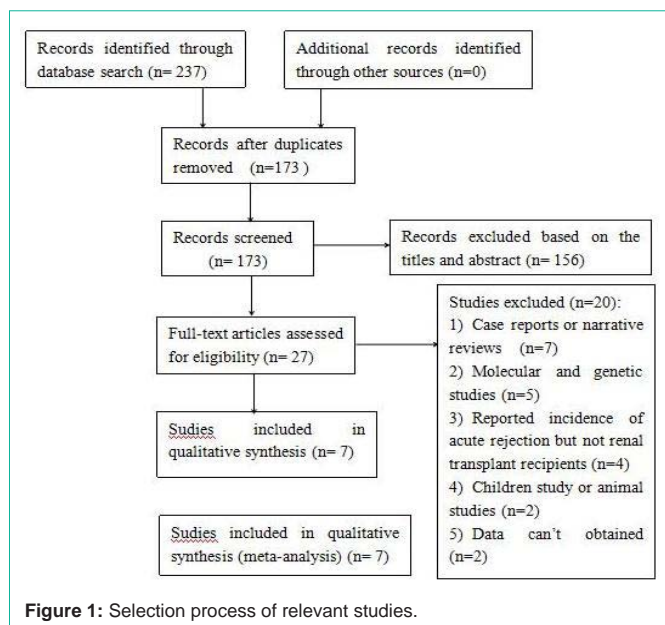


Figure 1: Selection process of relevant studies.

Study selection

All the studies need adhere to the following inclusion and exclusion criteria.

The inclusion criteria were as follows:

1. Participants were made up of renal transplant recipients aged 18 years or older without a history of any transplantation.
2. Studies design was case-control or cohort providing the adjusted Odds Ratio (OR), Risk Ratio (RR) and 95% Confidence Interval (CI).
3. The exposure was vitamin D (including other forms, such as 25(OH) D3, 1,25(OH) 2D3 and so on). Meanwhile, the end point was rejection, in other words, the primary or secondary outcomes must list rejection.
4. The comparison groups were divided based on the amount of vitamin D.
5. The exclusion criteria were as follows:
6. We excluded case reports, narrative reviews, animal studies and those with a sample size <50.
7. The latest article was chosen if a cohort study had been reported in more than one publication.
8. Studies involving multi-organ transplantation (e.g. liver transplantation) were also excluded.
9. Studies whose languages were not Chinese or English were excluded, so were the literature which failed to provide exact data.

Data extraction and quality assessment

All the studies were searched and selected for full-text review if they met the selection criteria. When necessary, we contacted the original authors for elaboration. The following data was collected: first author’s name, year of publication, type of study, country, sample size, mean age, length of follow-up, and dose regulation of vitamin D

Table 1: Substitutions of Vitamin D.

Number	Substitutions
1	Vitamin D
2	1,25-dihydroxyvitamin D
3	25 dihydroxycholecalciferol
4	25-hydroxyvitamin
5	Cholecalciferol
6	Ergocalciferol
7	Calcitriol

sufficient, conclusion.

Then, these articles were identified independently by two authors (Shan and Long) using a standardized data extraction format, with disagreements resolved by discussion or consulting another author. We used the Newcastle–Ottawa Scale (NOS) [11] to assess cohort or case-control studies. Articles scoring 0–3, 4–6, and 7–9 were defined as poor, fair and good quality, respectively [12].

Statistical analysis

Review Manager (Rev Man) version 5.3 was used to analyze the collected data after entering them into that program. On the first step, what we need to do is to confirm either Risk Ratio (RR) or Odds Ratio (OR) value is the eligible choice. The OR was taken to measure the association between vitamin D and rejection since both cohort and case-control studies were comprised of the meta analysis. And OR was regarded as approximately equal to RR, according to a previous publication [13-15]. It can transform into RR by the formula $RR = OR / [(1 - P_0) + (P_0 \times OR)]$, where P_0 represents for the incidence of rejection of the non-exposed group [13]. Secondly, heterogeneity across studies was assessed using the I2 statistic [14]. If the significant level was at $P > 0.10$ and $I^2 < 50\%$, slight heterogeneity existed. When no statistically significant heterogeneity was observed, a fixed-effect model was used to estimate the odds ratio; otherwise, a random-effect model was selected [16]. In addition, sensitivity analysis was conducted to make sure whether the results were stable. If $OR < 1$, the incidence of the experimental group was less than that of the control group.

Results

Study selection

As is shown in the (Figure 1), we searched out 237 relevant studies in total initially from the databases mentioned above. Except for 64 duplicates, there were 173 records left to be assessed. Alternatively, 156 articles were excluded and 27 were remained after scanning of the titles and abstracts. 20 of 27 articles were rejected for a variety of reasons, in that they did not meet the requirements of study designs (n=7), objects (n= 4) and exposure (n=5), sample size (n=2) and some of those cannot get available data (n=2). After reading the full text, seven studies which met inclusion and exclusion criteria were included in the present meta-analysis finally.

Characteristics and quality

The main characteristics of the seven studies including five cohort and two case-control studies are presented in (Table 2). Among them, three were from America, two were Korea, and the rest were from

Table 2: Characteristics of Included Studies.

Study	Year	Study types	Country	Sample size	Mean age	Dosage of sufficient vitamin D	Time of follow-up (year)	Effect measures (95% CI)
Tae Hyun Ban et al [18]	2016	case-control	Korea	174	43	12.1ng/mL	1	HR=0.10 (0.03–0.4)
Luciano Moscarelli et al [19]	2016	cohort	Italy	360	51	20ng/mL	1	HR=3.67 (1.4–9.6)
Marie Courbebaisse et al [20]	2011	cohort	France	64	48	30ng/mL	1	OR=1.87 (0.6,5.7)
John R.Lee et al [21]	2014	cohort	America	216	52.5	20ng/mL	1	HR=2.84 (1.1–7.5)
T Horwedel et al [22]	2015	cohort	America	1418	51.4	20ng/mL	2	OR=0.45 (0.3–0.8)
Megan A. Rech et al [23]	2014	cohort	America	89	51	16ng/mL	1	OR=4.3 (1.1–18.0)
Young Eun Kwon et al [24]	2015	case-control	Korea	450	41.1	15ng/mL	0.5	HR=1.99 (1.3–3.0)

Table 3: Results of quality assessment of selected studies according to NOS.

Author	Selection				Comparability		Outcome assessment			score
	1	2	3	4	5	6	7	8		
Tae Hyun Ban et al [15]	*	*	*	*	*			*	*	7
Luciano Moscarelli et al [16]	*	*	*		**		*	*	*	8
Marie Courbebaisse et al [17]	*	*	*	*	**			*	*	8
John R.Lee et al [18]	*	*	*		*		*	*	*	7
T Horwedel et al [19]	*	*	*	*	**			*	*	8
Rech et al [20]	*	*	*	*	*		*	*	*	9
Young Eun Kwon et al [21]	*	*	*		**			*	*	7

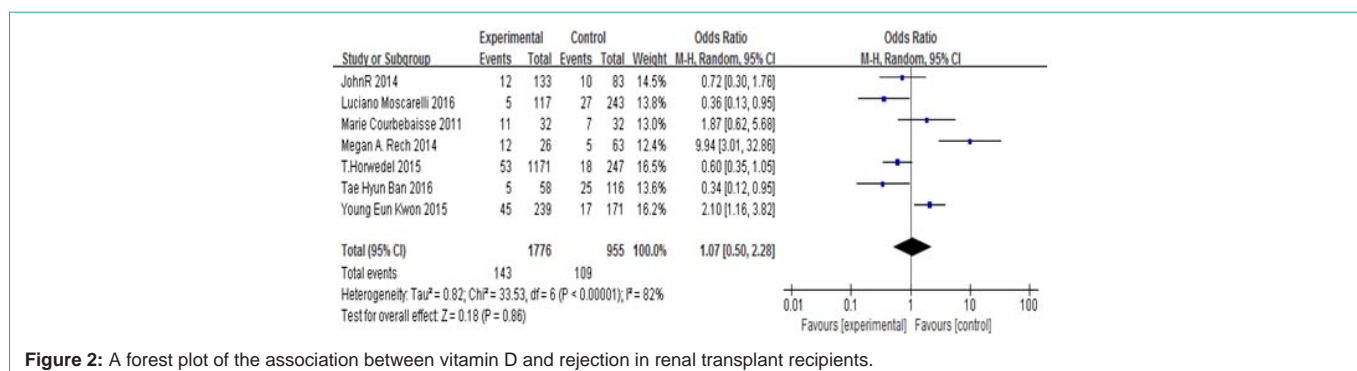


Figure 2: A forest plot of the association between vitamin D and rejection in renal transplant recipients.

Italy and French respectively. From the perspective of sample size, the participants of study ranged 64 to 1418, with 2731 participants in all. The second study’s was less than one hundred while the fifth study’s was more than one thousand, and the rest studies’ were distributed from 100 to 300. Besides, the standard dose of sufficient vitamin D used in the studies was different at the level of 12.1, 15, 16, 20 and 30ng/mL. According to the Newcastle–Ottawa Scale (NOS) [11], seven studies were of good quality and have a mean score of 7.7. (Table 2) and (Table 3) gives a detail about quality assessment.

* The study met the criteria of the NOS, and got one point in the item.

Vitamin D and rejection

As was shown in (Figure 2), 252 of 2731 patients occurred rejection in total. Pooled data from the seven studies in exposed group, the incidence of rejection in adult renal transplant recipients was 8.1% (143/1776) while the other group was 11.4% (109/955).

Figure 2 has shown a forest plot which presented the association between vitamin D and rejection in adult renal transplant recipients. Heterogeneity across the seven studies was found to be statistically significant (I²=82%, P<0.05). By the random effect model, the pooled OR was 1.07(95% CI [0.50-2.28]), which suggested no significant increased risk of adult renal transplant recipients for rejection in those who were exposed to sufficient vitamin D compared with those who were not.

For smaller heterogeneity, we conducted subgroup analysis to make out the source of high heterogeneity in terms of year, study type, country, sample size, mean age, sex, follow up time and dosage of sufficient vitamin D. The result viewed that the major factors influencing the association between vitamin D and rejection in adult renal transplant recipients were sex and year. When we divided the seven studies into different groups (Figure 3) and (Figure 4) according to sex and year respectively, the heterogeneity dropped to 0.

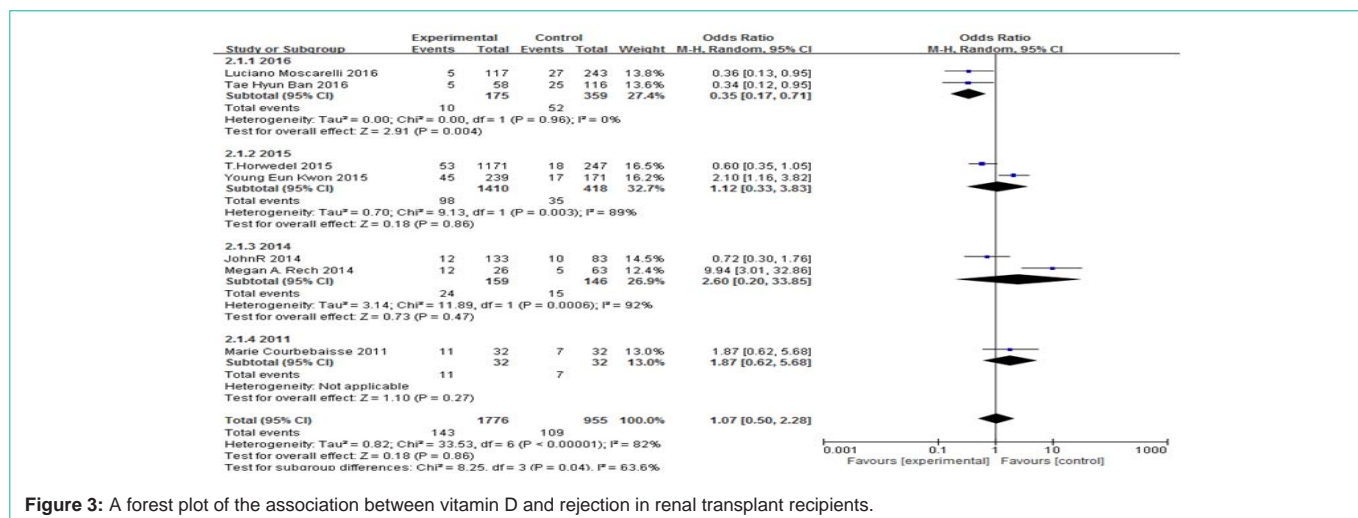


Figure 3: A forest plot of the association between vitamin D and rejection in renal transplant recipients.

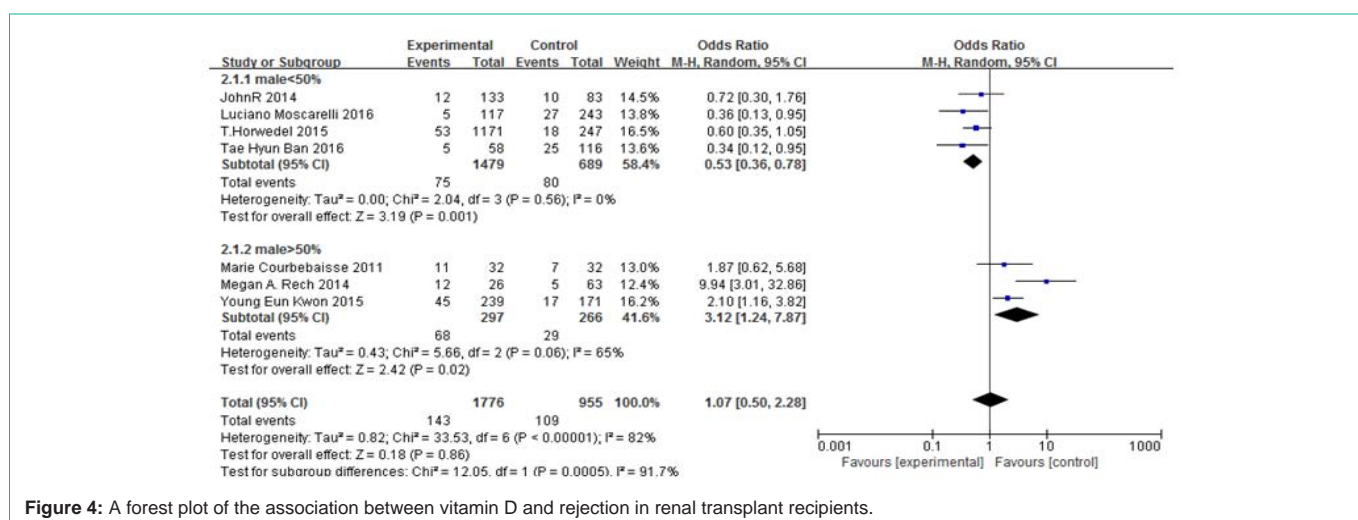


Figure 4: A forest plot of the association between vitamin D and rejection in renal transplant recipients.

Sensitivity analysis and publication bias

While excluding one study at a time, sensitivity analysis saw the fact that no obvious changes was found of vitamin D and rejection, which indicated that the results were stable (OR=0.51,95% CI:[0.35,0.75]). Publication bias testing also indicated no obvious asymmetry in the funnel plot (P=0.37).

Discussion

Rejection is a form of graft damage in combination with immune and non immune factors [25]. A large amount of literature only have reported that Vitamin D Receptor(VDR) agonists have pleiotropic activities on the immune response, as well as on cell growth and differentiation [26], that can control allograft rejection and promote the induction of transplantation tolerance [27].

However, researchers just know that vitamin D plays a leading role in our diary resulting in many diseases such as cancer [28], Post Transplant Diabetes Mellifluous (PTDM) [29], bacterial infections and soon [30]. No study noticed the association between vitamin D and rejection was influenced by non-immune factors. So we can't confer that vitamin D may be an effective treatment for renal transplant recipients [26]. There is a necessity for us to reveal the

real association between vitamin D and rejection, even underlying mechanisms and the risk factors for rejection.

It is the first meta-analysis to identify the association between vitamin D and rejection in adult renal transplant recipients. A total of 7 studies were included in the meta-analysis. Remarkably, we didn't include randomized controlled trials or prospective cohort studies according to inclusion and exclusion criteria.

In other organ transplantation studies, pre-transplant circulating levels less than 5ng/mL of 25(OH) D levels were independently associated with moderate to severe ACR episodes within 2 months post transplantation in a study of 133 liver transplant recipients [31]. Also, in another study of 102 lung transplant recipients, those with 25(OH) D levels less than 30ng/mL had more episodes of Acute Cellular Rejection (ACR) and more aggressive ACR during the first year of post transplantation than those with levels greater than 30ng/ML [32].

In our meta analysis, these data involving 2731 patients. After pooling these seven studies, the results revealed that the risk of rejection was lower in sufficient vitamin D group than the other group (8.1% vs 11.4%) but there was no statistical difference between

the two groups. So we can't support that vitamin D is a protective factor for rejection in adult renal transplant recipients. There was no evidence to demonstrate that sufficient vitamin D can reduce the incidence of rejection in adult renal transplant recipients. More concretely, the precise prevalence of vitamin D deficiency in renal transplant recipients is unclear. Maybe the quality and heterogeneity of included studies attenuate the strength of the result in a way [17].

Subgroup analysis was used to explain the big heterogeneity. The most vital factor affecting the relationship of vitamin D and rejection in adult renal transplant recipients were noticed to be sex and year of publication. But it is a pity that there has been no study published yet about sex or year of publication influencing the association between vitamin D and rejection in KTRs. But it could be explained as follows with the biggest possibility. From the perspective of year of publication, we think it was normal the results varied at the beginning of the study. As research goes deeper, the results of different studies are more likely to come to an agreement. So the heterogeneity dropped to 0% in two studies of 2016. From the perspective of sex, we speculated that the male usually have a habit of smoking and drinking which is a unhealthy lifestyle leading to high rate of rejection. Of course, any other potential factors might exist. We could not determine temporarily.

However, there were certain limitations in the study.

First, our study objects are not for all ages and the selected studies are limited, which are prone to give rise to bias [33]. Although we attempted to adhere to the guidelines for reporting meta-analyses of observational studies, inherent limitations generated inevitably in terms of different study designs, countries, follow-up time, dose criteria of sufficient vitamin D and so on [34,35].

Second, findings are only confined to renal transplant recipients but not all organ transplant recipients in the high prevalence of rejection and vitamin D deficiency. Further investigations need to be implemented to confirm some clinical consequence.

Third, our meta-analysis only considered the problem whether vitamin D is link with the incidence of rejection but don't check whether rejection is related to vitamin D in return.

Conclusion

In conclusion, the meta-analysis provides powerful evidence that vitamin D has no association with rejection in adult renal transplant recipients. And sufficient vitamin D isn't certified to be a protective factor for rejection. The observed correlation between vitamin D and rejection in two groups isn't significant and doesn't make sense on clinical and public health.

More and more studies are needed to explore the underlying mechanisms and elucidate the causal pathways [36] that associate vitamin D and rejection. Also, randomized controlled trials or prospective cohort studies are expected to improve the level of prevention and the treatment of rejection in adult kidney transplant recipients in the future [37].

Next, we will bring much more new studies and children patients into our research to explore the specific mechanism and general rules about the associations between vitamin D and rejection as well as

seeing risk factors.

Acknowledgment

The authors would like to thank Prof. Linping Xiong for his insightful comments, constructive suggestions and guidance. The authors also thank coauthor, Junrui Long for providing some amendments. The project was supported by Shanghai Three-year Planning on Public Health System Construction (Grant No.: SCREENING Study GWIV-18).

References

- De Nicola L, Zoccali C. Chronic kidney disease prevalence in the general population: Heterogeneity and concerns. *Nephrol Dial Transplant*. 2016; 31: 331-335.
- Bienaimé F, Girard D, Anglicheau D, Canaud G, Souberbielle JC, Kreis H, et al. Vitamin D Status and Outcomes After Renal Transplantation. *J Am Soc Nephrol*. 2013; 24: 831-841.
- Marie Courbebaisse, Corinne Alberti, Sandra Colas, et al. Vitamin D supplementation in renal transplant. *Biomed Central*. 2014; 15: 430-441.
- Hou Qingtao, Lv Xiafei. A Meta analysis of Vitamin D receptor gene polymorphism and susceptibility to type 2 diabetes mellitus. *Chinese Journal of general medicine*. 2014; 27: 344-352.
- Snelson M, Clarke RE, Coughlan MT. Stirring the Pot: Can Dietary Modification Alleviate the Burden of CKD?. *Nutrients*. 2017; 9: E265.
- Lavin PJ, Laing ME, O'Kelly P, Moloney FJ, Gopinathan D, Aradi AA, et al. Improved renal allograft survival with vitamin D receptor polymorphism. *Renal Failure*. 2007; 29: 785-789.
- Courbebaisse M1, Alberti C, Colas S, Prié D, Souberbielle JC, Treluyer JM, et al. Vitamin D supplementation in renal transplant recipients(VITALE): a prospective, multicentre, double-blind, randomized trial of vitamin D estimating the benefit and safety of vitamin D3 treatment at a dose of 100,000 UI compared with a dose of 12,000 UI in renal transplant recipients: study protocol for a double-blind, randomized, controlled trial. *Trials*. 2014; 15: 430.
- Saravanan P, Davidson NC. Risk Assessment for Sudden Cardiac Death in Dialysis Patients. *Circ. Arrhythm. Electrophysiol*. 2010; 3: 553-559.
- Ma MK, Mok MM, Yung S, Tang CS, Chan TM. High prevalence of vitamin D insufficiency in southern Chinese renal transplant recipients. *Renal Failure*. 2012; 34: 980-984.
- Xie KeNan, Chen Huiping. Vitamin D, chronic kidney disease and renal transplantation. *Journal of Nephrology and dialysis kidney transplantation*. 2013; 22: 385-390.
- Wells GA, Shea B, O'Connell D, Peterson J, Welch V, Losos M, et al. The Newcastle Ottawa Scale (NOS) for assessing the quality of non-randomized studies in meta-analyses. 2014.
- Weifeng S, Lixi L, Yali R, Qiangqiang G, Ming K, Shuwang G. History of kidney stones and risk of chronic kidney disease: a meta-analysis. *PeerJ*. 2017; 5: e2907.
- Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med*. 2002; 21: 1539-1558.
- Aune D, Lau R, Chan DS, Vieira R, Greenwood DC, Kampman E, et al. Nonlinear reduction in risk for colorectal cancer by fruit and vegetable intake based on meta-analysis of prospective studies. *Gastroenterology*. 2011; 141: 106-118.
- Adorini L, Amuchastegui S, Daniel KC. Prevention of chronic allograft rejection by Vitamin D receptor agonists. *Immunology Letters*. 2005; 100: 34-41.
- Higgins J, Green SE. *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0. The Cochrane Collaboration (Eds): [J]. Naunyn-Schmiedeberg's Archiv für experimentelle Pathologie und Pharmakologie. 2011; 14: 38.

17. Long J, Duan G, Tian W, Wang L, Su P, Zhang W, et al. Hypertension and risk of depression in the elderly: a meta-analysis of prospective cohort studies. *Journal of Human Hypertension*. 2015; 29: 478-482.
18. Ban TH, Kim JH, Jang HB, Lee YS, Choi BS, Park CW, et al. Clinical effects of pre-transplant serum 25-hydroxyvitamin D level on post-transplant immunologic and non-immunologic outcomes in kidney transplant recipients. *Transplant Immunology*. 2017; 40: 51-56.
19. Luciano Moscarelli, Giulia Antognoli, Elisa But, et al. 1,25 Dihydroxy vitamin D circulating levels, calcitriol administration, and incidence of rejection, CMV infection, and polymath virus infection in renal transplant recipients. *Clinical Transplantation*. 2016; 8:1347-1352.
20. Courbebaisse M, Alberti C, Colas S, Prié D, Souberbielle JC, Treluyer JM, et al. Vitamin D supplementation in renal transplant. *Biomed Central*. 2014; 15: 430.
21. Lee JR, Dadhania D, August P, Lee JB, Suthanthiran M, Muthukumar T. Circulating Levels of 25-Hydroxyvitamin D and Acute Cellular Rejection in Kidney Allograft Recipients. *Transplantation*. 2014; 98: 292-299.
22. Horwedel T, Botkin K, Hagopian J, Bowman L, Brennan D. Vitamin D Supplementation and rejection Following Kidney Transplantation. *Am J Transplant*. 2015.
23. Rech MA, Fleming JN, Moore CL. 25-Hydroxyvitamin D Deficiency and Opportunistic Viral Infections After Kidney Transplant. *Experimental and Clinical Transplantation*. 2014; 12: 95-100.
24. Kwon YE, Kim H, Oh HJ, Park JT, Han SH, Ryu DR, et al. Vitamin D Deficiency is an independent risk factor for urinary tract infections after renal transplants. *Medicine*. 2015; 94: e594.
25. Chen Weiguo, Luo Hong, Chen Zhaojie. Research progress of non immunological factors in chronic rejection (CR). *Southwest national defense medicine*. 2002; 12: 465-467.
26. Cross NB, Webster AC, Connell PJO, Craig JC. Antihypertensives for Kidney Transplant Recipients: Systematic Review and Meta-Analysis of Randomized Controlled Trials. *Tnsplantation*. 2009; 8: 7-18.
27. Tanaci N, Karakose H, Guvener N, Tutuncu NB, Colak T, Haberal M. Influence of 1,25-Dihydroxyvitamin D3 as an Immunomodulator in Renal Transplant Recipients: A Retrospective Cohort Study. *Transplantation Proceedings*. 2003; 35: 2885-2887.
28. Park YJ, Kim SU, Lee KH, Lee JH, Kwon E, Jung HY, et al. Vitamin D deficiency is associated with increased risk of bacterial infections after kidney transplantation. *The Korean Journal of Internal Medicine*. 2017; 32: 505-513.
29. Le Fur A, Fournier MC, Gillaizeau F, Masson D, Giral M, Cariou B, et al. Vitamin D deficiency is an independent risk factor for PTDM after kidney transplantation. *Transplant International*. 2016; 29: 207-215.
30. Sezer S, Uyar M, Arat Z, Özdemir FN, Haberal M. Potential Effects of 1, 25-Dihydroxyvitamin D(3) in Renal Transplant Recipients. 2005; 37: 3109-3111.
31. Bitetto D, Fabris C, Falletti E, Fornasiere E, Fumolo E, Fontanini E, et al. Vitamin D and the risk of acute allograft rejection following human liver transplantation. *Liver Int*. 2010; 30: 417-444.
32. Lowery EM, Bemiss B, Cascino T, Durazo-Arvizu RA, Forsythe SM, Alex C, et al. Low vitamin D levels are associated with increased rejection and infections after lung transplantation. *J Heart Lung Transplant*. 2012; 31: 700-707.
33. Ahmadpoor P, Ilkhanizadeh B, Ghasemahdi L, Makhdoomi K, Ghafari A. Effect of Active Vitamin D on Expression of Co-Stimulatory Molecules and HLA-DR in Renal Transplant Recipients. *Experimental and Clinical Transplantation*. 2009; 7: 99-103.
34. Sawinski D, Uribarri J, Peace D, Yao T, Wauhopp P, Trzcinka P, et al. 25-OH-Vitamin D deficiency and cellular alloimmunity as measured by panel of reactive T cell testing in dialysis patients. *Am J Transplant*. 2010; 10: 2287-2295.
35. Özdemir BH, Özdemir AA, Sezer S, Çolak T, Haberal M. Influence of 1, 25-Dihydroxyvitamin D3 on Human Leukocyte Antigen-DR Expression, Macrophage Infiltration, and Graft Survival in Renal Allografts. *Transplantation Proceedings*. 2011; 43: 500-503.
36. Pan A, Sun Q, Okereke OI, Rexrode KM, Hu FB. Depression and Risk of Stroke Morbidity and Mortality: A Meta-analysis and Systematic Review. *JAMA*. 2011; 306: 1241-1249.
37. Zheng Z, Wenhua L, Milgrom DP, Zheng Z, Paul M, Schroder, et al. Liver Transplantation Versus Liver Resection in the Treatment of Hepatocellular Carcinoma: A Meta-analysis of Observational Studies. *Transplantation*. 2014; 97: 227-234.