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Review Article

Evaluation of Serum Interleukin-6 Levels in the Renal Transplant Recipients: A Systematic Review and Meta-Analysis of Case-Control Studies

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Abstract

AIM: The purpose of this meta-analysis was the assessment of the serum IL-6 levels in the renal transplant recipients compared to the healthy controls.

MATERIAL AND METHODS: Four databases including PubMed, Web of Science, Scopus, and Cochrane Library were searched up to July 2018 without language restriction. The quality of studies was evaluated using the Newcastle-Ottawa scale (NOS). A continuous random-effects meta-analysis was used by RevMan 5.3 using the mean difference (MD) and 95% confidence intervals (CIs). Also, a regression model was done by Comprehensive Meta-Analysis version 2 (CMA v2).

RESULTS: Out of 615 studies identified in the databases, 15 studies included and analysed in the meta-analysis. The studies were reported from 1994 to 2018. The meta-analysis included 1035 renal transplant recipients and 682 healthy controls. The pooled MD of the serum IL-6 levels in the transplant recipients compared to the healthy controls was 3.25 pg/mL [95%CI: 2.17, 4.32; P < 0.00001; I2 = 98% (P < 0.00001)]. Meta-regression analysis showed that one of the reasons of heterogeneity is the year of publication (Correlation coefficient (r) = 0.208, p-value = 0.00002).

CONCLUSION: An elevated serum IL-6 level in the renal transplant recipients compared to the healthy controls showed that the serum level of this marker could be used for the evaluation of inflammation in ESRD patients undergoing renal transplantation.

Introduction

Chronic kidney disease (CKD) is the usual name for various disorders impacting renal structure and functions [1]. The incidence of cardiovascular disease in patients of end-stage renal disease (ESRD) is 10–20-fold that in the general population [2]. Renal transplantation (RT) is the treatment of choice for ESRD patients [3], [4]. Acute rejection is a common complication after RT and is associated with reduced graft survival [5]. Cardiovascular and cerebrovascular diseases are the leading causes of death following renal transplantation [6], [7] that the main underlying reason is inflammation [7]. Inflammation is generally controlled by following changes in concentrations of C-reactive protein (CRP), cytokines, and chemokines [8]. Interleukin-6 (IL-6) is reportedly responsible for acute complications in patients with ESRD such as fever, headache, and hypotension [9]. This cytokine is also a reliable marker of disease severity and inflammatory organ injury in rheumatoid arthritis [10] and oral lichen planus [11]. Therefore, it has been found to act as both a pro-inflammatory and anti-

inflammatory cytokine [12]. Also, the serum IL-6 levels increase depending on the reduction of renal function [13].

The meta-analysis aimed to assess the serum IL-6 levels in the renal transplant recipients compared to the healthy controls.

Material and Methods

The meta-analysis created according to a guideline for the preferred reporting items for systematic review and meta-analysis (PRISMA) literature search [14].

The research protocol was supported by the Ethics Committee of Kermanshah University of Medical Sciences, Kermanshah, Iran (Ethical code: IR.KUMS.REC.1396.597). A comprehensive search was used with the databases of PubMed, Web of Science, Scopus, and Cochrane Library up to July 2018. A combination of terms “kidney transplantation" or "renal transplantation" or "kidney transplant" or "renal transplant" and “serum” and "interleukin-6" or “IL-6” was used in the search without language restriction. The studies were selected for evaluation of the serum IL-6 levels in the renal transplant recipients compared with the healthy controls. The studies included in this meta-analysis had to: (I) use a case-control design; (II) report the serum IL-6 levels in the renal transplant recipients (III) report the controls without renal transplantation and any systematic disease (the healthy controls). Before transplantation, the more renal transplant recipients were on renal replacement therapy (pretransplant dialysis) and had immunosuppressive treatment.

One reviewer (M.S) searched the articles and then selected the relevant publications and other authors reviewed them independently. We applied a regular protocol and recording information for data extraction from each publication including the first author’s name, the year of publication, the country which the study was reported, number/the mean age/male (%) of the cases and healthy controls, immunosuppressive regimen, measured method of IL-6 level, and transplantation evolution.

The quality of studies was evaluated using the Newcastle-Ottawa scale (NOS) [15], in which the maximum total score is 9 for the case-control study. The quality evaluation was done by one author (M.S) for each study.

To compare serum IL-6 levels in the renal transplant recipients compared with the healthy controls, a continuous random-effects meta-analysis was done by Review Manager 5.3 (RevMan 5.3, The Cochrane Collaboration, Oxford, United Kingdom) using the mean difference (MD) and 95% confidence intervals (CIs). Heterogeneity among studies was evaluated with the Q, and the I^2 statistic and results were defined as heterogeneous for $P < 0.10$ or $I^2 > 50\%$ [16] and *P*-value (2-sided) < 0.05 was estimated statistically significant in the meta-analysis study. Also, the publication bias was estimated by funnel plot using Begg’s and Egger’s tests. The unit of measurement of IL-6 levels was pg/mL. The meta-regression analysis is a technique used to evaluate heterogeneity between the studies. This statistical approach determines whether there is a significant association between the study period and the pooled MD of the serum IL-6 levels. A regression model by Comprehensive Meta-Analysis version 2 (CMA v2) was done with the p-value and regression coefficient (r) to evaluate the strength of this association.

Results

Out of 615 studies identified in the databases, after excluding duplicate studies, 344 studies were screened that 312 studies were excluded. Out of 32 studies that their full-texts were assessed for eligibility, 17 studies were removed with the reasons (Figure 1). At last, 15 studies included and analysed in the meta-analysis.

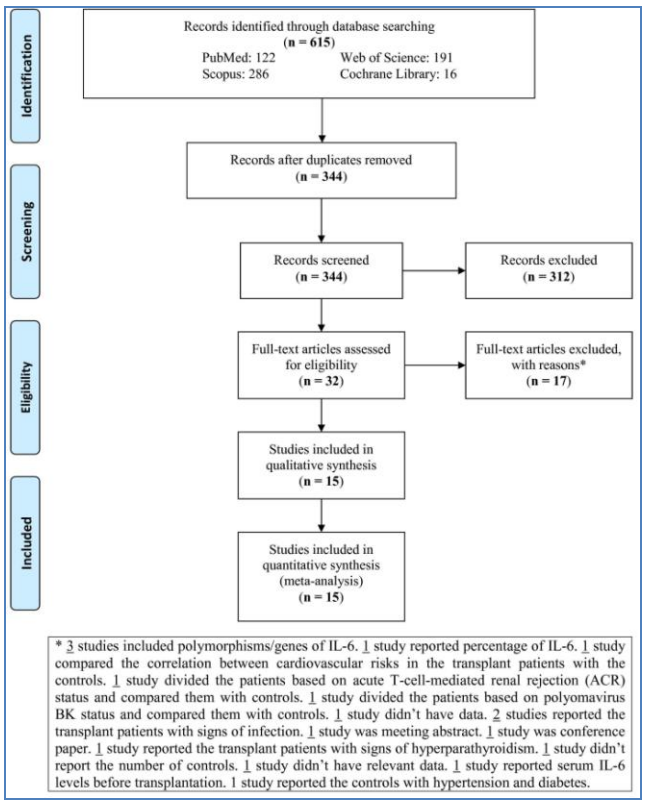

Figure 1: Flowchart of the study

The features of 17 studies that have been included in the meta-analysis are shown in Table 1.

The studies were reported from 1994 to 2018. Three studies [17], [18], [19] were reported from Poland, two [7], [20] from Turkey, two [15], [16] from Iran, and also Canada, Germany, the USA, Argentina, Spain, Connecticut, India, and China (one study each) [6], [8], [21], [22], [23], [24], [25], [26]. The meta-analysis included 1035 renal transplant recipients and 682 healthy controls. Six studies [3], [8], [20], [24], [25], [27] reported pretransplant dialysis in all or more recipients. Eight studies [6], [8], [17], [18], [19], [22], [25], [27] reported stable transplantation as inclusion criteria in the recipients and two other studies [23], [26] showed acute rejection and stable evolutions. The mean age, male percentage, immunosuppressive regimens, and measured method of IL-6 level are shown in Table 1.

Table 1: Characteristics of the studies included in the meta-analysis (n = 15)

	Country	No. of Transplant recipients/ mean age, year/No. of males	No. of healthy controls/ mean age, year/ No. of males	Pretransplant dialysis in all or more recipients	Immunosuppressive regimen	Measured Method of interleukin-6 level	Transplantation evolution
Nickerson, 1994 [21]	Canada	38/46.1/24	31/matched/matched	-	Azathioprine, Prednisone, and cyclosporine	ELISA kits (R & D systems, Quantikine human IL-6 immunoassay, Minneapolis, MN)	-
Waiser, 1997 [22]	Germany	145/-/-	20/-/-	-	Cyclosporine and methylprednisolone	ELISA kits (R&D Systems, Quantikine human IL-6 immunoassay)	Stable
Preston, 2002 [8]	USA	10/-/-	10/-/-	Yes	-	ELISA kits (MMP-2 and MMP-3, Amersham Life Science, Buckinghamshire, England; IL-6, Biosource International, Inc., Camarillo, Calif., USA)	Stable
Malan Borel, 2003 [23]	Argentina	13 rejection:11 stable/-/-	20/-/-	-	Prednisone, cyclosporine or FK506	ELISA kits (the Quantikine immunoassay (R & D Systems Inc., Minneapolis, USA)	Acute rejection vs. stable
Lauzurica, 2005 [24]	Spain	178/53/117	40/-/-	Yes	Corticosteroids or azathioprine and Cyclosporine or tacrolimus	An immunofluorimetric automatized method in Immulite-1 (DPC-Dipesa)	-
Malyszko, 2006 [17]	Poland	96/52.7/48	33/50.6/-	-	Cyclosporine, prednisone, and azathioprine	(high-sensitivity assays) from Bender MedSystem (Vienna, Austria)	Stable
Malyszko, 2008 [18]	Poland	90/46.2/43	30/44.8/14	-	Cyclosporine/tacrolimus, azathioprine/mycophenolate mofetil plus prednisone.	kits from Bender MedSystems (Vienna, Austria)	Stable
Shaqman, 2010 [25]	Connecticut	90/53/48	72/51/12	Yes	Prednisone, and cyclosporine	ELISA kits (Diagnostic Products, Los Angeles, CA)	Stable
Malyszko, 2013 [19]	Poland	62/44.3/35	24/51.6/-	-	Calcineurin inhibitor in combination with mycophenolate mofetil and prednisone.	Enzyme immunoassay (EIA) using a commercially available kits from Bachem (St. Helens, UK).	Stable
Sonkar, 2013 [26]	India	40 rejection:50 stable/32.3/-	90/30.4/-	-	Cyclosporine, azathioprine, and prednisone.	ELISA kits (Beckman Coulter Inc, Marseille, France)	Acute rejection vs. stable
Xue, 2014 [6]	China	25/44.3/12	25/45.9/15	-	Cyclosporine, mycophenolate mofetil, and prednisone.	ELISA kits (Boster Biological Engineering (Huhan, China).	Stable
Colak, 2015 [20]	Turkey	45/40.7/24	36/42.1/19	Yes	Calcineurin inhibitors, steroids and mycophenolate mofetil	ELISA kits (Camarillo, CA, USA)	-
Avci Çiçek, 2016 [7]	Turkey	82/41.8/43	81/46.7/-	-	-	commercial kit (eBioscience, Austria)	-
Eskandari Naji, 2017 [3]	Iran	30/48.5/18	30/50.4/15	Yes	Cyclosporine, CellCept, and prednisolone	ELISA (DIA source, Belgium, catalog number: KAP1261)	-
Argani, 2018 [27]	Iran	30/49/18	30/50/15	Yes	Prednisolone, calcineurin inhibitor, and CellCept	ELISA kits (IBL International GmbH, Germany).	Stable

Figure 2 is shown the forest plot of random-effects analysis that the pooled MD of the serum IL-6 levels in the transplant recipients compared to the healthy controls was 3.25 pg/mL [95%CI: 2.17, 4.32; $P < 0.00001$; $I^2 = 98\%$ ($P < 0.00001$)]. Therefore, the serum IL-6 level in the transplant recipients was significantly higher than the healthy controls.

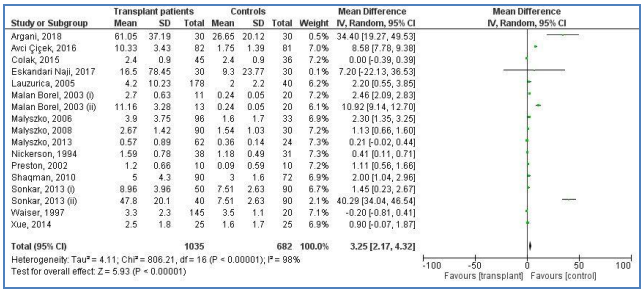

Figure 2: Forest plot of random-effects of serum interleukin-6 levels in the renal transplant recipients compared to the healthy controls. i: the renal transplant recipients with stable evolution, and ii: the renal transplant recipients with acute rejection evolution

Table 2 shows the quality score for each study included in the meta-analysis. The mean score was 5.8 for all case-control studies.

Table 2: Quality ratings for the studies included by Newcastle-Ottawa quality assessment scale (n = 15)

The first author, year	Selection	Comparability*	Outcome	Total score
Nickerson, 1994 [21]	2	0	2	4
Waiser, 1997 [22]	2	0	2	4
Preston, 2002 [8]	2	0	2	4
Malan Borel, 2003 [23]	4	1	2	7
Lauzurica, 2005 [24]	3	0	2	5
Malyszko, 2006 [17]	3	1	2	6
Malyszko, 2008 [18]	3	2	2	7
Shaqman, 2010 [25]	3	1	2	6
Malyszko, 2013 [19]	2	0	2	4
Sonkar, 2013 [26]	3	2	2	7
Xue, 2014 [6]	3	2	2	7
Colak, 2015 [20]	4	2	2	8
Avci Çiçek, 2016 [7]	3	0	2	5
Eskandari Naji, 2017 [3]	2	2	2	6
Argani, 2018 [27]	3	2	2	7

*One star if two groups matched via age and another star if two groups matched via sex or body mass index (BMI).

Figure 3 shows the funnel plot of studies entered to the analysis. Egger's test (p-value (2-tailed) = 0.042) reveal, but and Begg's test (p-value (2-tailed) = 0.067) didn't reveal a significant sign of publication bias between the involved studies.

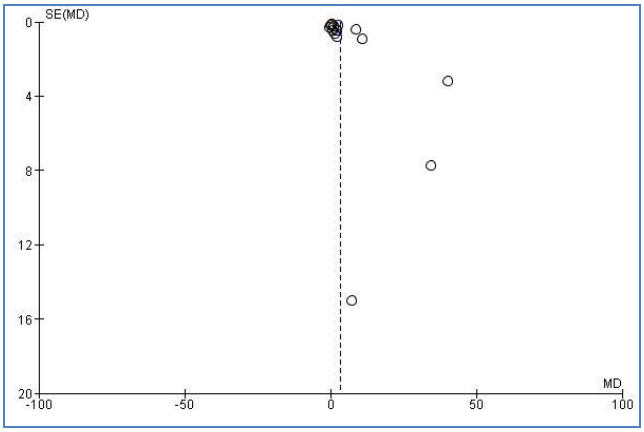

Figure 3: Funnel plot of random-effects of serum interleukin-6 levels in the transplant recipients compared to the healthy controls

Meta-regression analysis identified a significant statistical relationship between the pooled MD of serum IL-6 levels in the renal transplant recipients compared with the healthy controls and the year of publication. This means that one of the reasons for heterogeneity is the year of publication (Correlation coefficient (r) = 0.208, p-value = 0.00002). Significant positive correlation showed that there was an increase in the MD of the serum IL-6 with time (Figure 4).

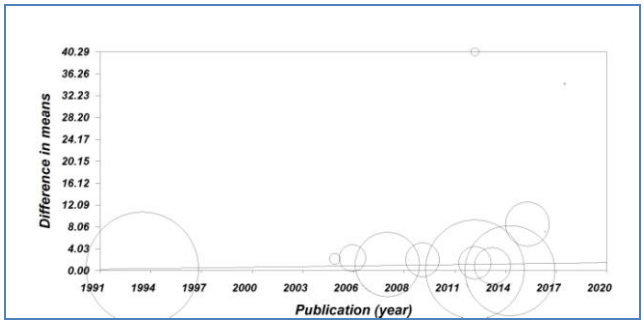

Figure 4: Meta-regression analysis the study period versus the mean difference of the serum IL-6 levels

Discussion

The elevated serum IL-6 levels in the renal transplant recipients compared to the healthy controls have been shown in this meta-analysis study. The Th1 cytokine pattern is generally related to the rejection of the transplantation; a Th2 cytokine pattern may lead to transplant tolerance and stable graft survival. [13]. Inflammation is the most important underlying mechanism in cardiovascular disease and other systemic diseases [1]. Increased IL-6 leads to chronic inflammatory conditions such as the synthesis of acute phase proteins like CRP, hypercoagulability and accelerated atherosclerosis. [7], [28], [29], [30], [31] that can cause to the loss of renal function [7]. Also, some mechanisms including volume overload and oxidative stress can cause the usual increase in inflammatory symptoms (including IL-6) [32].

Serum levels of IL-6 increased significantly after renal transplantation [33]. The results received show an obvious relationship within the serum levels of IL-6 and graft rejection [23]. Levels of IL-6 have been greatly reduced in desirable evolution and raised with increasing renal failure. Therefore, the level of IL-6 can be used as an indicator of graft evolution and as a prerequisite for proper evaluation of renal biopsy [23]. The changes in the serum levels of IL-6 in transplanted patients can lead to several factors that affect the production of cytokines. Also, IL-6 may act a function in the close correlation between the high incidence of inflammation, cardiovascular disease, and malnutrition in HD patients [34]. CRP elevation may only represent the end stage of substantial inflammation, and other inflammatory markers may be more sensitive indicators of early inflammation injury, almost in HD patients [8]. Therefore, levels of CRP can correlate with IL-6 levels [9]. Serum levels of IL-6 in HD patients are significantly higher than in renal transplant recipients [20], [35]. The injury to the endothelium might trigger the release of IL-6 in renal transplant recipients [26]. This increase in IL-6 could be the result of increased activation of nuclear factor-kappa B, which is an inducible transplantation factor necessary for the activation of multiple important inflammatory cytokine genes like to the IL-6 gene [36]. 1) Pretransplant dialysis in the recipients. 2) Different immunosuppressive treatment in the recipients. 3) Differences in the measured method of IL-6 levels. 4) The sample size was small in some studies. 5) There was high heterogeneity in the analysis. 6) Low quality of more studies. Therefore, these limitations cause a bias between the studies.

In conclusion, about the limitations, there was an elevated serum IL-6 level in the renal transplant recipients compared to the healthy controls. The results may indicate potential usefulness of the serum level of this marker as an indicator of immunologic risk and can be used for the evaluation of inflammation in ESRD patients undergoing renal transplantation. *HRO* and *SG* conceptualised this study, designed the methodology for data collection, collected and analysed the data, and wrote the manuscript. *SVJ* and *MS* extensively supported the development of the study concept, data analysis, and the writing, editing and finalising of the manuscript. *All authors* read and approved the final manuscript.

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