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Review Article

Association between adiponectin levels and cardiovascular disease risk in dialysis patients: a meta-analysis

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Abstract: Objective: The aim of this study was to evaluate the association between adiponectin levels and risk of cardiovascular disease (CVD) in dialysis patients. Methods: A systematic search of PubMed, Web of Science and the Cochrane Library was performed for studies dated up to December 2015 on the association between adiponectin concentrations and CVD risk. Random-effect model was selected to pool the hazard ratios (HR) with their 95% confidence interval (CI). The quality of the included papers was evaluated according to the Newcastle-Ottawa Scale (NOS) score. Meta-analysis was performed using RevMan 5.3 software. Results: A total of 9 studies comprising 2296 dialysis patients were included in this meta-analysis. Combined analysis revealed that adiponectin levels were inversely associated with CVD risk (HR: 0.93, 95% confidence interval: 0.89-0.98, P=0.003), with heterogeneity among the studies (P=0.02, I^2=58%). No evidence of publication bias was found in our meta-analysis. Conclusions: This meta-analysis on available clinical evidence demonstrated that lower adiponectin levels were significantly associated with higher risks of CVD in dialysis patients.

Keywords: Adiponectin, cardiovascular disease, dialysis, meta-analysis

Introduction

End-stage renal disease (ESRD) is a major public health problem worldwide. The global average prevalence of ESRD patients on dialysis is 215 per million population [1]; more than 1.5 million people undergoing dialysis treatment experience a mortality rate that is substantially higher than the general population [2]. An increasing number of studies report that cardiovascular disease (CVD) mortality among ESRD patients is 10 to 20 times higher than that of the general population [3]; CVD is also a leading cause of death among dialysis patients [4, 5]. Therefore, the identification of potential diagnostic markers to better explore survival prediction and treatment strategies is important.

Adiponectin is a 244 amino acid protein that is abundantly derived from adipocytes. Unlike other adipokines, adiponectin levels are paradoxically reduced in obesity [6]. The adiponectin also appears to have inverse regulatory effects on inflammation, oxidative stress, insulin resistance and atherosclerosis [7-10], and it has shown a significant association with the risk of breast cancer, stroke and type 2 diabetes [11-13].

Relevant studies have revealed that serum adiponectin levels were increased in chronic kidney disease (CKD) and dialysis patients [14-16], and both several CVD risk factors and inflammatory markers were reportedly related to adiponectin levels [17, 18]. However, the association between serum adiponectin and CVD risk in dialysis patients remains unclear. Previous studies have shown that elevated adiponectin levels predicted higher CVD risk in dialysis patients [19, 20]. However, some studies found that lower adiponectin levels were associated with future CVD events in the dialysis population [21, 22].

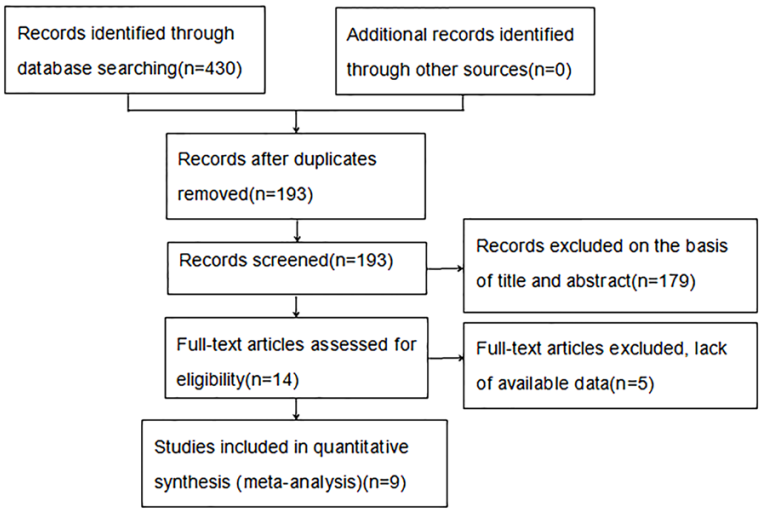

Figure 1. Flow chart of study selection.

To address the controversial question of whether adiponectin expression is associated with CVD risk in dialysis patients, we systematically searched for research literature and meta-analyzed the available evidence. As far as we know, this is the first meta-analysis on the predictive value of adiponectin for the clinical outcome in dialysis patients.

Materials and methods

Search strategy

A systematic search of PubMed, Web of Science, and the Cochrane Library was performed for studies on the association of adiponectin levels and risk of CVD in dialysis patients up to December 2015. Searches were carried out without restrictions on publication language using the MeSH terms and keywords 'adiponectin', 'cardiovascular disease' and 'dialysis'. To avoid missing any relevant studies, reference lists in included articles were searched manually to identify highly related studies.

Inclusion and exclusion criteria for literature

Inclusion and exclusion criteria were established before searching the literature. We included studies that have the following characteristics: (1) have a cohort, case-control, or cross-sectional design; (2) report the association between adiponectin levels and CVD risk; and (3) record sufficient information to analyze risk ratio (RR) estimates (or odds ratio (OR) estimates in cross-sectional studies) or hazard ratio (HR) estimates with their 95% confidence interval (CI). We excluded the following: (1) animal and autopsy studies; (2) literature review; and (3) studies with overlapping or duplicate data.

Data extraction and quality assessment

Two authors independently extracted the inclusive records by screening the titles and abstracts of publications, based on study design, participants, exposure, and endpoints. After excluding duplicates and irrelevant records, the following data were collected: the first author's name, year of publication, location in which the study was performed, number of participants, disease type, dialysis mode, age range of participants, study design, duration of follow-up (months), study quality score, and HR estimates and their 95% confidence interval (CI). If one study provided several risk estimates, the most completely adjusted estimate was identified.

The quality of all eligible studies was evaluated according to the Newcastle-Ottawa quality assessment scale, which comprised the following three items: patient selection, comparability of groups, and ascertainment of outcome [23].

Statistical analyses

HRs with corresponding 95% CIs were analyzed using RevMan 5.3 to assess the association between adiponectin levels and CVD risk in dialysis patients. The DerSimonian-Laird random effects meta-analysis [24] was applied to obtain pooled HR estimates in individual studies. Heterogeneity among studies was quantified using X^2 test and I^2 statistic [25]. Subgroup and sensitivity analyses were performed to explore the source of heterogeneity. Publication bias was investigated using Begg's and Egger's tests [26]. A p value of less than 0.05 was considered statistically significant.

Table 1. Characteristics of the included studies

First author	Year	Location	No. of participants	Disease type	Dialysis mode	Age (years)	Study design	Follow-up (months)	HR (95% CI)	Study quality
Diez (21)	2009	Spain	184	NA	HD/PD	19-86	P	31.2	0.75 (0.55-1.02)	6
Drechsler (19)	2009	Germany	1255	Diabetes	HD	18-80	P	48	1.03 (0.85-1.25)	7
Eid (27)	2014	Egypt	Cases: 110	NA	HD	Cases: 55.53	P	24	0.96 (0.93-0.99)	7
			Controls: 34			Controls: 50.71				
Rao (22)	2008	USA	182	NA	HD	62.2	P	12-78	0.50 (0.29-0.88)	7
Tung (28)	2015	Taiwan	78	NA	PD	52.14	P	42	0.93 (0.88-0.98)	7
Zoccali (29)	2002	Italy	227	NA	HD	59.9	P	31	0.97 (0.93-0.99)	8
Yu (18)	2008	China	Cases: 59	Non-diabetes	PD	Cases: 49.6	P	39	0.847 (0.75-0.957)	7
			Controls: 10			Controls: 45.1				
Kim (30)	2010	Korea	80	Non-diabetes	HD/PD	67.1	P	29.3	0.899 (0.818-0.987)	6
Kacso (20)	2015	Romania	77	Diabetes	HD	61.08	P	36	5.02 (0.98-25.66)	7

Abbreviations: HD, hemodialysis; PD, peritoneal dialysis; NA, not available; P, prospective; HR, hazard ratio; CI, confidence intervals.

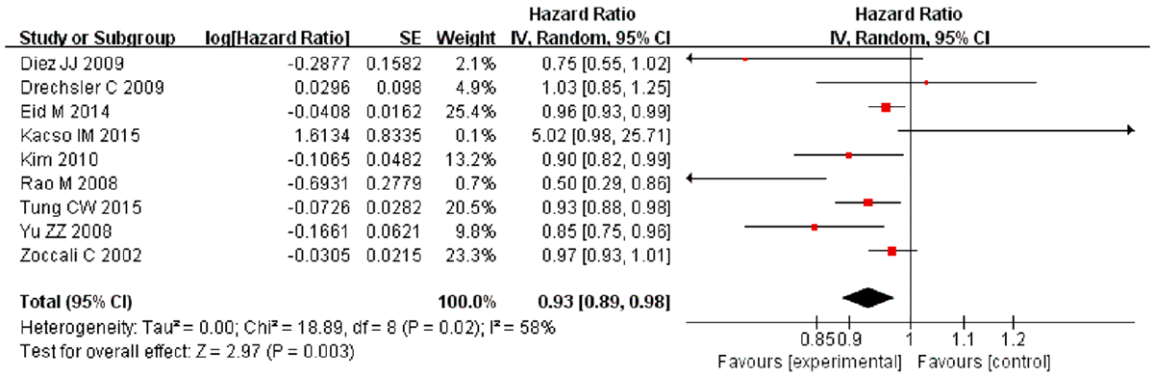

Figure 2. Forest plot showing the association between adiponectin levels and cardiovascular disease risk in dialysis patients.

Results

Studies and data included in meta-analysis

Literature search yielded 430 potentially relevant citations. Of these, 237 duplicates were excluded. After screening abstracts and full reviews of original articles, 179 publications were excluded because of irrelevance to the current study, and 5 reports were removed because of insufficient data. The remaining 9 studies [18-22, 27-30] that have data on the association between adiponectin levels and CVD risk in dialysis patients were included in the meta-analyses, which comprised 2296 subjects (**Figure 1**). The main characteristics of included studies are summarized in **Table 1**. These 9 studies were published from 2002 to 2015. Four studies were performed in Europe, 3 in Asia, 1 in North America, and 1 in Africa. Sample size ranged from 69 participants to 1255 participants and the mean/median follow-up durations varied from 12 months to 78 months. All the included publications were prospective studies. The study quality scores ranged from 6 to 8.

Association between adiponectin levels and CVD risk

Nine studies were used to estimate the summary effects of adiponectin on CVD risk (**Figure 2**). Results of the correlation between adiponectin and CVD risk were inconsistent. A negative association between adiponectin and CVD risk was established in five studies [18, 22, 27, 28, 30], whereas no statistically significant association was observed in the other four studies [19-21, 29]. Overall, the association between adiponectin level and CVD risk was statistically significant, and the pooled HR from the nine studies was 0.93 (95% CI: 0.89-0.98), with heterogeneity among the studies (P=0.02, I^2=58%).

Table 2. Differences between studies by subgroup analyses

Subgroup	No. of Studies	Samples	HR (95%) CI	Heterogeneity within subgroups		Heterogeneity among subgroups		References
				P-value	I^2 (%)	*P*-value	I^2 (%)	
Geographic region								
Europe group	4	1743	0.96 (0.81-1.13)	0.07	57	0.61	0	19, 20, 21, 29
Non-Europe group	5	553	0.92 (0.86-0.97)	0.03	62			18, 22, 27, 28, 30
Follow up (months)								
<36	4	635	0.95 (0.92-0.99)	0.21	33	0.48	0	21, 27, 29, 30
≥36	5	1661	0.90 (0.78-1.04)	0.02	67			18, 19, 20, 22, 28
Sample size								
<100	4	304	0.90 (0.83-0.98)	0.10	51	0.27	18.4	18, 20, 28, 30
≥100	5	1992	0.96 (0.90-1.01)	0.07	54			19, 21, 22, 27, 29
Disease type								
Diabetes	2	1332	1.83 (0.41-8.15)	0.06	72	0.34	0	19, 20
Non-diabetes	2	149	0.88 (0.82-0.95)	0.45	0			18, 30
Dialysis mode								
HD group	5	1885	0.96 (0.90-1.03)	0.04	60	0.22	32.6	19, 20, 22, 27, 29
PD group	2	147	0.90 (0.83-0.98)	0.17	47			18, 28

Abbreviations: HR, hazard ratio; CI, confidence intervals; HD, hemodialysis; PD, peritoneal dialysis.

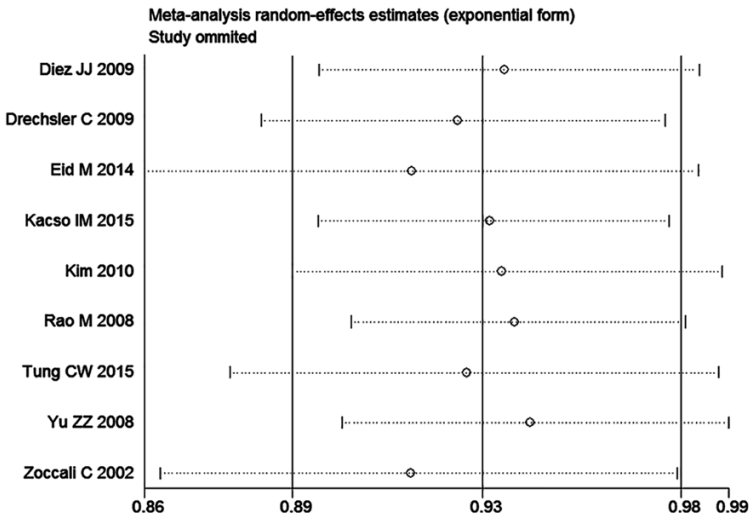

Figure 3. The stability of the study was detected through sensitivity analysis.

We performed subgroup and sensitivity analyses to evaluate the influence of a single study or factors that might modify this association, such as geographic region, time of follow-up, sample size, disease type, and dialysis mode. Our meta-analysis reported that geographic region (P=0.61), time of follow-up (P=0.48), sample size (P=0.27), disease type (P=0.34), and dialysis mode (P=0.22) were not the source of heterogeneity. The detailed results of the subgroup analysis are summarized in **Table 2**. We determined that most of the heterogeneity can be accounted for the studies by Yu ZZ et al. [18] and Rao M et al. [22]. After excluding the two studies, heterogeneity was no longer observed (P=0.13, I^2=40%).

Sensitivity analysis

We conducted sensitivity analysis by omitting one study during each round of analysis to check if any single study affects the results. No individual study was found to change the final pooled results (**Figure 3**), thereby validating the rationality and reliability of our meta-analysis.

Publication bias

Finally, Begg's and Egger's tests were performed to assess publication bias. No evidence of publication bias was found in our meta-analysis (P=0.35) (**Figure 4**).

Discussion

Adiponectin is a 244 amino acid long polypeptide that has played an intriguing role as a potential modifier of CVD and death since 1995 when it was reported for the first time [31]. This

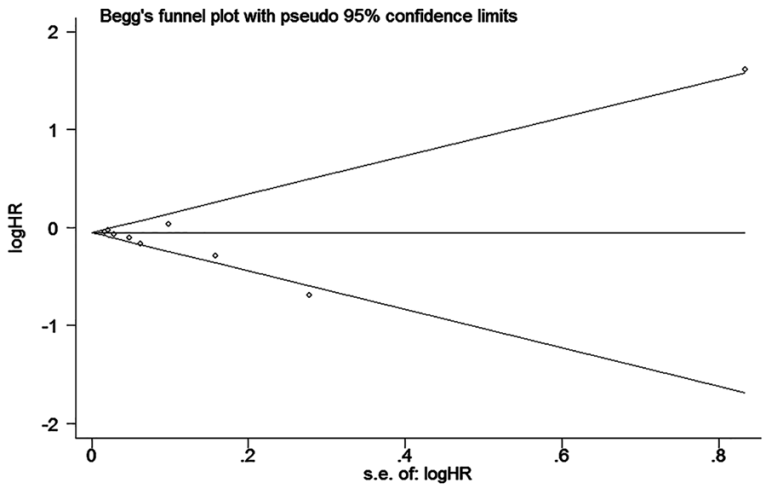

Figure 4. Funnel plot of publication bias for the association of adiponectin levels with cardiovascular disease risk in dialysis patients.

hormone is traditionally thought to have anti-inflammatory, anti-atherogenic, and anti-diabetic properties [32]. Thus, it was widely hypothesized that adiponectin could be a valuable predictor of the development of CVD in CKD and dialysis patients. A meta-analysis performed by Wu ZJ et al. [33] demonstrated that adiponectin levels were significantly associated with higher risks of all-cause and cardiovascular mortality in subjects with CVD. Zoccali C et al. [29] revealed that adiponectin was an inverse predictor of cardiovascular outcomes among patients with end-stage renal disease.

The strong association between adiponectin levels and CVD risk may be explained by several underlying mechanisms. First, adiponectin is strongly anti-inflammatory and anti-oxidative, acting through the nuclear factor-*k*B pathway [34, 35]. Second, it reduces protein synthesis and apoptosis through the AMP activated kinase pathway, decreasing infarct size and cardiac hypertrophy [36]. Third, adiponectin may also have a direct anti-apoptotic, anti-oxidative, and anti-inflammatory effect on cardiomyocytes [37].

In recent years, prospective cohort studies have shown that adiponectin was increased in CKD and dialysis patients [14-16]. Several previous studies have reported that elevated adiponectin levels predicted higher CVD risk in dialysis patients [19, 20], whereas some studies mentioned that low adiponectin levels were a risk factor for future CVD events in the dialysis population [21, 22]. Researchers have not reached an agreement on the issue of whether adiponectin is associated with CVD risk in dialysis patients.

In the present study, meta-analysis of nine prospective studies indicated that adiponectin was inversely associated with CVD risk in dialysis patients. This is the first meta-analysis on the association between adiponectin and CVD risk in dialysis patients. All studies included in our meta-analysis reported a multivariate-adjusted estimate, thereby mitigating the possibility of known confounders influencing our results.

In the meta-analysis, we found heterogeneity in our pooled results, which may have arisen from differences in geographic region, time of follow-up, sample size, disease type, and dialysis mode. Thus, we used subgroup analysis to explore the causes of heterogeneity for these covariates. However, the factors mentioned above were not the source of heterogeneity, thereby suggesting the possible existence of other unknown confounding factors. Then, we conducted sensitivity analysis by omitting one study at a time. We determined that most of the heterogeneity was accounted for the studies of Yu ZZ et al. [18] and Rao M et al. [22]. After excluding the two studies, heterogeneity was no longer detected ($P=0.13$, $I^2=40\%$). In Yu ZZ et al. [18], participants from the comparison group were not dialysis patients but healthy volunteers. The Rao M et al. [22] study did not exclude patients who exhibited clinical evidence of acute cardiovascular events. These factors may contribute to the source of heterogeneity.

The present study has several strengths. First, the studies included in this meta-analysis strictly met the inclusion criteria. Second, all extracted HRs were directly obtained from published statistics, and the result was more reliable than the calculated values from the data in the article or extrapolated from the survival curves. Third, we conducted Begg's and Egger's

tests to assess publication bias, and the results showed no obvious publication bias on the association between adiponectin levels and CVD risk in dialysis patients. Nevertheless, our meta-analysis has several limitations. First, the sample sizes of several included studies were relatively small. Second, there was heterogeneity among the studies, which may affect the outcome, although a random effects model is used. Third, we did not include unpublished studies and some eligible data could be missed.

In conclusion, our meta-analysis of prospective studies indicates an inverse association between adiponectin levels and CVD risk in dialysis patients. Dialysis patients with lower adiponectin levels may be at higher CVD risk, in which case appropriate treatment strategies can be instituted to prevent cardiovascular events. Future studies with long-term follow up, large sample size, and representative participants are needed to further explore the association in dialysis patients.

Disclosure of conflict of interest

None.

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