

## Vitamin B12 supplementation in end stage renal diseases: a systematic review

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### Abstract

**Background:** Hyperhomocysteinemia is a risk factor for cardiovascular disease particularly in patients with end stage renal disease (ESRD). Vitamin B12 supplementation on its own still remains as a controversial issue for clinicians in decreasing the level of homocysteine in this group of patients.

**Methods:** Using all randomized controlled trials (RCTs), clinical trials and pre-post-trial studies found during January 1999 to March 2014, we conducted a systematic review which assessed the effects of vitamin B12 in decreasing homocysteine levels in patients with ESRD.

**Results:** The findings of this study revealed that, overall, the greatest effect of B12 supplementation on decreasing homocysteine levels in patients with ESRDs occurred when it was combined with folate supplementation. It was also demonstrated that injection treatments might be more beneficial than oral intake treatments.

**Conclusion:** More rigorous studies are needed to draw a firm conclusion about B12 therapy and the level of homocysteine in patients with ESRD.

**Keywords:** Homocysteine, Kidney Failure, Vitamin B12, Hemodialysis, Kidney, Amino Acids, Renal Failure, Review.

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### Introduction

Hyperhomocysteinemia is an important risk factor for cardiovascular disease (1). Homocysteine is a nonessential amino acid, and a metabolite for methionine metabolism. It has two fates: remethylation to methionine which is catalyzed by the vitamin B12 dependent enzyme, methionine synthase, and transsulphuration to cystathionine, and then into cysteine. The two essential substances in the remethylation pathway are vitamin B12, as a cofactor, and folate as a substrate. Vitamin B6 is another crucial cofactor for transsulphuration of homocysteine to cystathionine (2). Many of hemodialysis patients are B12 depleted (3). Dialy-

sis patients usually have poor nutritional intake, predisposing them to B12 deficiency (4). Moreover, food sources of vitamin B12 contain high concentrations of electrolytes which are dangerous for dialysis patients, and limit them to foods with low vitamin B12 content. In addition, B12 is a typical middle-sized chemical molecule to be cleared with new high-flux dialyzers (3). Therefore, plasma total homocysteine (tHcy) concentration is noticeably increased in end-stage renal disease (ESRD) (5). Furthermore, comparing to patients with normal renal function, the prevalence of hyperhomocysteinemia and the resulting death caused by atherosclerotic vascular

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disease are substantially greater in ESRD patients (6). Hcy-lowering therapy is an effective approach for hyperhomocysteinemia therapy of ESRD patients (7-9). However, it is controversial whether cobalamin supplementation alone could be useful in lowering the tHcy concentration in these patients (10). Focusing on this controversy, we conducted a systematic review to assess the effects of vitamin B12 supplementation alone on tHcy concentration in ESRD patients.

## Methods

### Search Strategy

We found no systematic review or meta-analysis on this subject; therefore, we searched all English and Persian medical literature published from January 1999 to March 2014 in PubMed, Google Scholar, Ovid, Cochrane Library, EMBASE, CINAHL, Springer, Proquest, Scopus, Web of Science, Science Direct, SID, Iranmedex and Magiran databases.

The main search key words were as follows: “vitamin B12” AND “homocyste-

ine” AND “End Stage Renal Disease” with their synonyms, related words and Medical Subject Headings (MeSH) terms. The search strategy used in the PubMed database can be found in Appendix 1.

A total of 1964 articles were collected, of which 18 were duplicates. Titles of the remaining articles were reviewed for their relevance to the homocysteine lowering effect of vitamin B12 in end-stage renal disease. If the articles were potentially relevant, then their full texts were retrieved. A further 1928 articles were excluded due to failing to meet the eligibility criteria. After reading the full text of the articles, 12 were excluded because in those studies vitamin B12 was not administered alone. All the titles and abstracts which were derived from the searches were extracted by a reviewer. In the event that the reviewer determined that an article did not meet the eligibility criteria, then the article would have been rejected on initial screening. An evaluation of the full texts was conducted by a review team. Two reviewers evaluated the full articles separately.

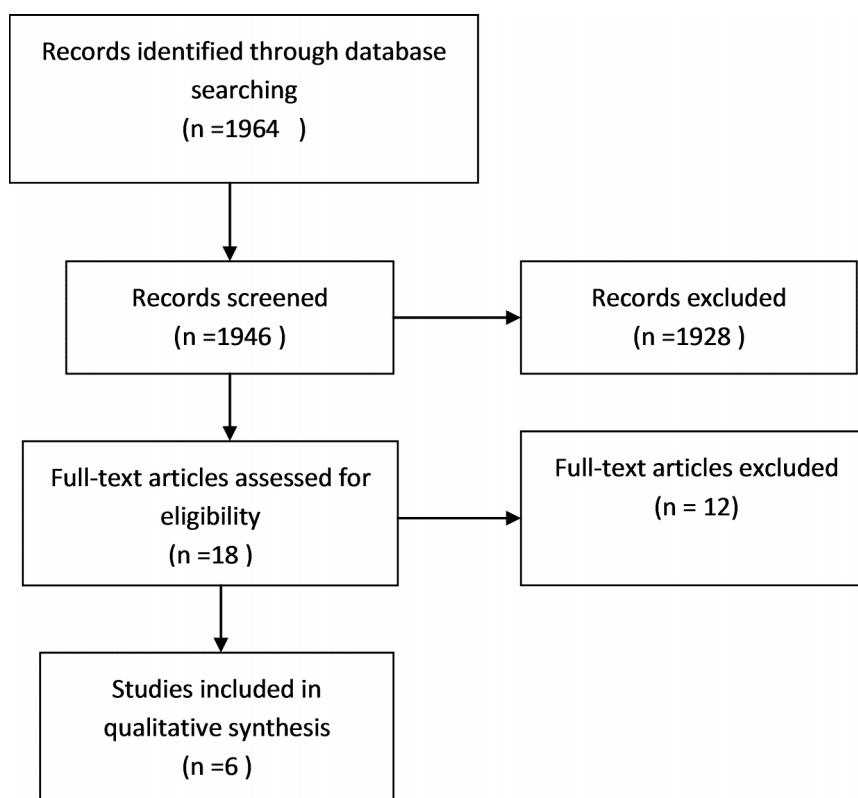


Fig. 1. Flowchart of the Procedure used to Select the Relevant Articles

Any disagreements between the reviewers were resolved by discussion until consensus was reached.

### Inclusion Criteria

Randomized controlled trials (RCTs), clinical trials and pre-post-trials were selected for this systematic review. The focus was on dialysis patients with end-stage renal disease. Figure 1 demonstrates the procedure applied to select the relevant articles.

### Results

Only 6 out of the total of 1964 articles were eligible for the systematic review. Most of these studies were trials (RCTs, cross over and prospective), and only one study was quasi-experimental (pre-post-treatment) (Table 1). These studies were heterogeneous with respect to the following factors: type of administration (oral or intravenous), chemical construction of B12 (hydroxycobalamin, methylcobalamin, cyanocobalamin or not defined), duration of intervention, period of outcome assessment, study design and quality (Table 1). There-

Table 1. Methodological Description of the Included Studies

Author/Year/Location	Sample size	Type of Study	Intervention/Comparison (Study Arms)	Study Exclusion/Inclusion Criteria	Comments
Chiu, Y. W. 2009, Taiwan <sup>[11]</sup>	75	RCT	I: Received vitamin B12 1mg/week intravenously for 3 months C: Received folic acid 3mg/week intravenously for 3 months Combination group: Received intravenous supplementation with both agents weekly for 3 months	Inclusion criteria: -Hemodialysis patients without any acute illness	Masking was NOT reported. Method of random allocation was not mentioned Hemodialysis period was not similar in different arms of the study.
Pastore, A. 2006, Italy <sup>[10]</sup>	200	RCT(cross over)	Group 1: Based on 3 genotypes CC, CT and TT, Initially received cobalamin 1250 µg per week for 2 months, orally, then received 15 mg folic acid daily for 8 weeks, orally. Group 2: Initially received folic acid 2 months, then B12 for next 2 months.	Exclusion criteria: -Receiving folic acid and/or vitamin B12 before the study Inclusion criteria: -All patients had baseline tHcy concentrations >20 µmol/L -All had been undergoing HD for at least 3 months and duration of 4 h each time.	Loss to follow-up was as high as 52% but not considered in the analysis (Intention to treat analysis). Study was single-blinded.
Polkinghorne, 2003, Australia <sup>[2]</sup>	28	RCT	I: Received hydroxycobalamin 1 mg per month for 3 months, administered by intramuscular injection. C: Received placebo (saline) for 3 months	Exclusion criteria: -Current high dose folic acid supplementation(>5mg/w) -Vitamin B12 deficiency -Past medical history of cancer or inflammatory bowel disease -Recent return to dialysis after transplantation, imminent live donor transplant -Current use of antifolate or anti convulsant medication Inclusion criteria: -Age>18y - Hemodialysis at least 1 month prior to recruitment	The participants and the investigator were blind; however, nurses who injected placebo or B12 were not blind. Power is not large enough to show small changes (less than 30%).

Table 1. Continued

Arnadottir, M., 2003, Sweden <sup>[13]</sup>	28	RCT	I: Received 2mg B12 tablets 3 times a week for 6 weeks orally C: Received no such treatment	Nothing mentioned	Participants or the researchers were not blind; control group did not take placebo.
Trimarchi H. 2002 Argentina <sup>[12]</sup>	62	Prospective Randomized trial	I: Group A received methylcobalamin 500 micro gram twice/week plus folic acid 10 mg/day; group B received folic acid 10 mg/day alone; group C received no vitamin supplementation, and group D was on Methylcobalamin 500 micro gram twice/week alone. C: folic acid 10 mg/day alone; no vitamin supplementation for 4 months postdialysis	Exclusion criteria: -Previous vitamin supplementation Inclusion criteria: -Patients between 19 and 86 y -Requiring HD for at least 5 months	Randomization and blindness was not described in the study. The study was single-blinded.
Dierks, J. 1999 Norway <sup>[5]</sup>	14	Quasi-experimental	Before: Cyanocobalamin, 1mg per week for 4 weeks was administered in B12 deficient participants Intravenously. After: Changes of tHcy after the injection of vitamin B12 was measured.	Inclusion criteria: -low serum cobalamin concentrations	The sample size was too small. Inclusion or exclusion criteria was not defined exactly.

I: Intervention, C: Comparison

fore, it was not appropriate to synthesize the results for a meta-analysis.

The findings of the trials and quasi-experimental studies are summarized in Tables 2 and 3, respectively.

Six interventions administered B12 alone. All 5 selected trials applied B12 in at least one study arm (2, 10-13).

There were four groups in Chiu's study (Table 1) (11). In one group, B12 was injected alone while all other three groups had taken folate in advance. In the final assessment, the blood levels of tHcy were decreased significantly in all groups, including the group which received B12 alone. However, the combination group showed an added effect, indicating the synergistic role of folate and B12 in tHcy lowering.

In Polkinghorne's trial (2), one mg vitamin B12 was administered intramuscularly in one group to determine whether B12, without the effect of folic acid, could lower the homocysteine (Table 1). However, in their study, the tHcy concentration was not different in the two groups at the end of the

intervention. Therefore, they concluded that there was no decrease in tHcy levels within the three months of intramuscular administration of B12 alone.

Arnadottir (13) held a trial on folate-replete hemodialysis patients. The treatment group received vitamin B12 tablets (orally) at a dose of 2 mg 3 times a week for 6 weeks while the control group received no treatment. At the end of the study period, plasma tHcy concentration decreased significantly in both groups with no difference between them.

There were four study arms in Trimarchi's study (12). One group received only 500 µg Me-Cobalamin twice a week, but at the end of the study, no significant changes of tHcy level was observed in this group, indicating the minor role of B12 in tHcy level correction.

The role of genotype in the reduction of tHcy was discussed in two different studies. In a cross-over design, Pastore et al. (10) compared the effect of folate and B12 supplementation on Hcy (homocysteine) reduction. Consecutive vitamin therapy de-

Table 2. Findings of the Included Studies (Randomized Controlled Trials)

Author	Control mean difference	% of change for control group	P value for control group	Intervention mean difference	% of change for intervention group	P value for intervention group	Difference between control and other groups		
Chiu 2009	3.3	↓16.4	<0.05	5.9	↓29.3 $\alpha$	<0.05	<0.005		
Pastore 2006	Group 1 $\gamma$	CC	25.2	↓35.39	0.021	7.8	↓38.9 $\beta$	<0.05	NS
		CT	81.4	↓60.97	<0.05	5.3	↓8.5	0.2	Not applicable
		TT	221.7	↓74.49	<0.01	16.7	↓19.4	0.41	Not applicable
	Group 2 $\delta$	CC	26	↓45.61	0.2	17	↓36.95	<0.05	Not applicable
		CT	44.3	↓63.92	<0.05	12.1	↓23.22	0.169	Not applicable
		TT	88.5	↓42.24	0.237	-8.8	↑11.62	0.497	Not applicable
Polkinghorne 2003	-2	↑8.22	-	2.01	↓7.89 $\epsilon$	-	0.4		
Arnadottir 2003	5	↓23.15	<0.05	3.6	↓17.3 $\kappa$	<0.01	NS		
Trimarchi 2002		-1.4	↑5.4	NS	12.3	↓54.6 $\lambda$	0.003	<0.001	
					8.7	↓43.7 $\mu$	0.012	<0.001	
					2.3	↓8.6 $\nu$	NS	NS	

$\alpha$ : Vitamin B12 administered 1mg/week intravenously for 3 months

$\beta$ : IV supplementation with folic acid 3mg plus B12 1mg intravenously for 3 months/week

$\gamma$ : Initially received cobalamin 1250  $\mu$ g per week for 2 months, orally, then received 15 mg folic acid daily for 8 weeks, orally.

$\delta$ : Initially received folic acid 2 months, then B12 for next 2 months

$\epsilon$ : Hydroxycobalamin 1 mg/month for 3 months administered by intramuscular injection

$\kappa$ : B12 tablets 2mg, administered 3 times a week for 6 weeks orally

$\lambda$ : Received methylcobalamin 500 micro gram twice/week plus folic acid 10 mg/day

$\mu$ : Received folic acid 10 mg/day alone

$\nu$ : Received methylcobalamin 500 micro gram twice/week alone

NS: Not significant

NA: Not Applicable

Table 3. Findings of the Included Quasi-Experimental Study

Author	Difference between baseline and final assessment (median)	% of change	Difference between before and after (P value)	
Dierkes 1999	CC	13.2	↓38.15	NS
	CT,TT	12.2	↓26.69	NS
	All	11.4	↓27.94	0.01

NS: Not significant

creased tHcy in both groups and the decrease was genotype-dependant.

Only one study was conducted based on a before/after design (5). In this study, the effect of intravenous injection of cyanocobalamin was investigated in ESRD patients with low serum cobalamin concentration.

Because tHcy concentration was unequal among these studies at baseline, plasma tHcy decreased significantly either with normal or deficient levels of tHcy. In a semi-experimental study, Dierkes et al. (5) concluded that the tHcy lowering effect of B12 may be due to the reduction of cellular

tHcy rather than renal clearance, and it is influenced by genotype.

## Discussion

To our knowledge, this was the first review to focus on the role of B12 alone in lowering tHcy in patients with end-stage renal disease. A significant proportion of ESRD patients have physiological vitamin B12 deficiency. These patients may have a defect in their ability to convert vitamin B12 into its active form, hydroxycobalamin, which is needed for homocysteine metabolism (14-15). In addition, transcobala-

min II, which is necessary for the entry of vitamin B12 into tissues, may be impaired in ESRD (6, 14-15). Therefore, tHcy concentration increases in patients with ESRD. It is debatable whether vitamin B12 supplementation alone could reduce tHcy concentration in these patients. Moreover, it is reported that folate supplementation can lower the high levels of homocysteine in ESRD patients (16-18). However, it is not clear whether vitamin B12 could reduce homocysteine without the high-dose of folic acid. In the current review, all the included studies administered B12 alone, but with different approaches.

In Chiu's study, the reduction of tHcy in B12 group was significantly more than the Folinic acid group (Table 2). It is also noted that the combined supplementation was the most effective method (11). In this study, there was no significant difference between the patients with respect to age, sex, MTHFR C667T genotype, plasma levels of folic acid, VitB12, or tHcy level at baseline. However, the only difference among the patients was the period of hemodialysis at that time. Therefore, the tHcy level of the vitamin B12 group might have been affected by the difference in hemodialysis duration (11).

In Polkinghorne's trial (2), patients with current high dose supplementation with folate were not included in the study. The levels of B12 and folate in serum were normal in these patients, but the haemodialysis period was in a very wide range; and this may cause mixed results and could be adjusted initially. Compared with another study (20), the supplemental dose of B12 in Polkinghorne's study (2) appears to be too low (1 mg/month vs. 2-3 mg/week) which may have led to such a result.

Arnadottir et al. held a trial on folate-replete hemodialysis patients (13). The study samples were on hemodialysis for at least 3 months and had all been receiving folic acid in advance. However, the simultaneous decrease of serum homocysteine concentration was not consistent in the control and intervention groups; this point was

not well described by the article (13). This result may be due to the confounders which were not considered by the researcher in advance, which makes the result rather unreliable.

In Trimarchi's study, the random allocation, blindness of patients and having a control group were almost impeccable (12).

In Pastore's study, the consecutive vitamin therapy lowered tHcy in both groups, and the decrease was genotype-dependant (10). In Fodinger's study, despite the role of genotype and folate in the tHcy concentration, B12 administration made no changes in ESRD patients (20). The results of the last two studies indicated that the effect of B12 on tHcy should be measured in patients with normal serum folate. This finding is inconsistent with that of the Dierk's study, in which the level of serum folate was normal, but B12 level was low and B12 supplementation lowered tHcy by 35% (5). In a study by Trimarchi, the patients received no supplementation in advance, and B12 supplementation resulted in no changes in the tHcys level (12).

Only one study was performed based on a quasi-experimental design (5). In this study, the intravenous injection of cyanocobalamin lowered the tHcy level in ESRD patients with low serum cobalamin concentrations. The author suggested that the reduction of cellular tHcy was the cause, rather than the renal clearance, which is influenced by genotype. With respect to the result of the study, some points should be considered. First, the result was probably due to the low baseline serum cobalamin in patients. In other words, the correction of B12 deficiency, rather than B12 supplementation, was effective. Furthermore, according to the article, sample size was too small to represent a significant difference. And finally, the study design could have been more improved by having a control group. One strong point of the study was the inclusion of genotype. They indicated that the reduction of homocysteine levels in patients with CC genotype is much more than in those with T allele (CT, TT). It

seems that the essential role of cobalamin in remethylation of tHcy was the reason behind the simultaneous reduction of homocysteine and folate levels. They concluded that folate is used as substrate and this cycle is influenced by genotype (5).

### Conclusion

In all the included studies, the design, dosage of supplements, method of application, status of other supplements and treatments were different, and this makes the final conclusion relatively difficult. It seems that the maximum effect of B12 supplementation in ESRD patients is yielded by injection, rather than oral intake. Furthermore, the administration of pharmacologic dosage of B12 in combination with folate makes it more efficient. Conducting future studies with randomized controlled design, sufficient sample size and on patients with normal level of folate and B12 is highly recommended to clarify the effect of B12 supplementation on tHcy concentrations in ESRD.

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### Appendix-1

Search Strategy in PubMed:

("Vitamin B 12"[Mesh] OR "Vitamin B 12 Deficiency"[Mesh] OR "factor III, vitamin B 12" [Supplementary Concept] OR "Vitamin B Complex"[Mesh] OR "Vitamin B Complex" [Pharmacological Action] OR "Vitamin B Deficiency"[Mesh] OR (vitamin AND ("b12" OR "b 12")) OR Cyanocobalamin OR Cobalamins OR Cobalamin OR "HMQC" OR ("factor III" AND corrinoid) OR "5-hydroxybenzimidazolylcobamide" OR "5-hydroxybenzimidazolylcobamid" OR "5-hydroxybenzimidazolylcobamide" OR "5-hydroxybenzimidazolylcobamid")

AND

("Hyperhomocysteinemia" [Mesh] OR

"Homocysteine"[Mesh] OR "Homocystine"[Mesh] OR "Homocystinuria"[Mesh] OR Hyperhomocysteinemias OR homocystinuria OR homocysteine OR homocystine OR "thcy" OR "hcy" OR "2-amino-4-mercaptoputyric acid" OR "2 amino 4 mercaptoputyric acid")

AND

("Kidney Failure, Chronic"[Mesh] OR "Renal Dialysis"[Mesh] OR "Uremia"[Mesh] OR "Renal Insufficiency"[Mesh] OR "Renal Replacement Therapy"[Mesh] OR "Hemofiltration"[Mesh] OR "Hemodiafiltration"[Mesh] OR "Ultrafiltration"[Mesh] OR "Kidneys, Artificial"[Mesh] OR ((Kidney OR RENAL) AND (End-Stage OR End Stage OR failure OR Insufficiencies OR Insufficiency OR replacement OR artificial)) OR (Chronic AND (Kidney OR RENAL) AND (Failure OR Insufficiencies OR Insufficiency )) OR ESRD OR ((Dialyses OR Dialysis) AND (Renal OR Extracorporeal)) OR Hemodialysis OR Hemodialyses OR Uremias OR Uremia OR Hemofiltration OR Ultrafiltration OR Hemodiafiltration)

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