Available online **www.ijpras.com**

International Journal of Pharmaceutical Research & Allied Sciences, 2016, 5(2):128-134

Research Article

ISSN : 2277-3657
CODEN(USA) : IJPRPM

A Comparative study on the effects of vitamin C and Pramipexole on restless legs syndrome treatment in hemodialysis patients: A randomized, double-blind, placebo-controlled trial

Shahram Rafie[1] and Majid Jafari[*2]

[1]*Assistant Professor of Neurology, Department of Neurology, Golestan Hospital, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran*
[2]*Resident of Neurology, Department of Neurology, Golestan Hospital, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran*
*****E-mail: jafarimd90@gmail.com*

ABSTRACT

Restless leg syndrome (RLS) is a neurological movement disorder defined by an unpleasant sensation in the legs, especially during sitting and lying down. The aim of this study was to evaluate the effect of vitamin C and comparing it with that of pramipexole in the treatment of RLS in patients undergoing hemodialysis. This double-blind clinical trial was performed on 45 patients undergoing hemodialysis and met the diagnostic criteria proposed by the International Restless Leg Syndrome Study Group (IRLSSG) for RLS diagnosis. Patients were divided in three groups: pramipexole, vitamin C, and placebo, and received drugs daily for 8 weeks. Prior to the initiation and after the completion of the experiment, the scoring questionnaire of the IRLSSG was completed for all the patients.Before and after the intervention, the IRLS score in the three groups of vitamin C, pramipexole and placebo were 24.73±7.06 and 12.20±5.95(p <0.001), 26.83±7.51 a nd 13.71±4.32(p <0.001), and 23.20±6.73 and 21.27± 7.13. (p= 0.002).The three groups were not significantly different with regard to the IRLS scores prior to the intervention (p=0.005). However, the Tukey's test demonstrated that the vitamin C and placebo groups and the pramipexole and placebo groups were significantly different regarding the IRLS scores obtained after the intervention (p<0.001), (p=0.004), and the pramipexole group was not statistically significantly different from the vitamin C group (p=0.77).Vitamin C was shown to be an inexpensive, safe and without serious adverse effects in short-term follow-up supplementation for treatment of RLS in hemodialysis patients.

Key words: restless legs syndrome, hemodialysis patients, vitamin C, pramipexole

---

INTRODUCTION

Restless leg syndrome (RLS) is a neurological movement disorder, commonly accompanied by sleep disorders. The syndrome is defined as an unpleasant sensation in the legs, especially during sitting and lying down. The sensation mostly occurs deep in the medial surface between the knees and ankles (1).Prevalence of the syndrome has been reported to be 5-10%. The syndrome may occur at any age(2). During recent years non-medication based techniques including physical and herbal agents have been dramatically developed for the treatment of different disorders.

The International Restless Legs Syndrome Study Group (IRLSSG) has suggested the following clinical criteria for diagnosis of RLS:
1. The uncomfortable and irritating sensation in the legs that urges the individual to walk or move the legs.

2. The symptoms emerge or aggravate at rest during sitting or lying down in the bed and are relieved by moving the legs.
3. The symptoms are aggravated in the evening or night, especially at rest.
4. The movement restlessness is observed as small minimal movements in the toes and calves and/ or sudden twisting movements of the leg in the bed (3).

The etiology of the disorder is unknown. However, some pathophysiological mechanisms have been suggested for the syndrome including the central nervous system disorder(4), genetic factors , uremia , iron deficiency , folate deficiency, pregnancy , medications such as tricyclic antidepressants and selective serotonin re-uptake inhibitors (5),(6), as well as some chronic conditions including diabetes, Parkinson's disease, peripheral neuropathy, renal failure, and hemodialysis (7). The prevalence of the syndrome in patients with chronic renal failure is higher than that in the general population, ranging from 20% to 80% (8), and the prevalence in patients undergoing hemodialysis has been reported in the range of 8.8-83%(9), (10).

For the treatment of RLS, different medications such as dopamine agonists including cabergoline, pergolide, ropinirole, pramipexole, carbidopa, levodopa, and gabapentin as well as opioids and benzodiazepines have been used. Each of these medications is accompanied by a specific success rate and, of course, some adverse effects(11). For instance, levodopa may aggravate the symptoms in some patients. Dopamine agonists may be associated with some adverse effects such as nausea, fatigue, drowsiness, headache, diarrhea, nasopharyngitis, orthostatic hypotension, and weight gain (12). In a study, 74% of the patients experienced the adverse effects of the medications; thus, prescription of the medications has some limitations in patients with underlying medical conditions (13). Moreover, considering the complaint of nausea in hemodialysis patients, there are limitations in using these medications for such patients. Therefore, the search for novel drugs with fewer adverse effects has been carried out. One of these candidate drugs is vitamin C. In hemodialysis patients, it has been demonstrated that vitamin C has therapeutic effects in sleep disorders and sensorimotor disorders such as leg cramps(14).

This is while vitamin C deficiency is observed in hemodialysis patients, which is associated with the high oxidative stress in these patients. Vitamin C has antioxidant property that is frequently used for preventive and therapeutic purposes(15).

In this regard, and considering the limitations in prescribing the available drugs, the present study was performed to evaluate the effect of vitamin C and compare its effect with pramipexole in the treatment of RLS in patients undergoing hemodialysis.

MATERIALS AND METHODS

The current study is a double-blind clinical trial performed in Ahvaz, Southwest Iran from May 2014 to July 2014. Forty-five patients in the age range of 18-80 years old, who regularly underwent hemodialysis, were included the study based on diagnostic criteria proposed by the International Restless Leg Syndrome Study Group (IRLSSG) for RLS diagnosis(16). The study protocol was approved by Ethics Committee of Ahvaz Jundishapur University of Medical Sciences. (Code: ajums.REC.1392.236) All the patients signed an informed written consent prior to participation in the study.

The exclusion criteria were having unstable vital signs, being affected by an acute disease; taking one of the tricyclic antidepressants, selective serotonin re-uptake inhibitors, dopamine antagonists, dopamine blocking antiemetic, lithium, and hypnotic antihistamines(11); and having the history of renal stone(17).

Totally, 134 hemodialysis patients were screened and 47 patients met the inclusion criteria, among whom two were unwilling to participate in the study. Forty five patients were randomly assigned to three groups. Patients in Group A received pramipexole tablet (0.18 mg, daily), Group B received vitamin C tablet (250 mg daily), and Group C received the placebo. The three groups were treated for 8 weeks and the medications were administered once daily two hours before going to bed.

All the medications were prepared by the Faculty of Pharmacy of Ahvaz, Jundishapur University of Medical Sciences, and provided in labeled bottles. Prior to initiation and after the completion of the study, the scoring questionnaire from IRLSSG was completed for all of the patients. At the two stages, the items were asked by one physician. The questionnaire included 10 items, each being scored in the range of 0-4. In general, each participant could be scored in the range of 0-40; the higher scores indicated more severe states of the disorder(18). The data were gathered analyzed using SPSS 13.

In case of normality, the data were analyzed using t-test, paired t-test, and analysis of variance (ANOVA); otherwise the non-parametric test of Mann-Whitney and the chi square test were used.
The study was registered in IRCT. (Code: Irct2014071218451N1)

RESULTS AND DISCUSSION

Forty four individuals participated in the study, among whom 15 (34%), 14 (32%), and 15 (34%) received vitamin C, pramipexole, and placebo, respectively. The three groups were evaluated with regard to the contextual variables such as age, sex, and history of undergoing hemodialysis (Tables 1 and 2).

Duration of hemodialysis in the vitamin C, pramipexole, and placebo groups were 2.30±1.78, 3.44±3.02, and 2.14±1.76 years, respectively. The three groups were not significantly different in this respect (p=0.275).

The IRLS score in the group that received vitamin C was 24.73±7.06 and 12.20±5.95 before and after the intervention (p<0.001). The IRLS score in the pramipexole group was 26.83±7.51 and 13.71±4.32 before and after the treatment, respectively (p<0.001). The score was 23.20±6.73 and 21.27±7.13 before and after the treatment in the placebo group, respectively (p=0.002).

According to the results obtained from the analysis of variance (ANOVA), the three groups were not significantly different with regard to the IRLS scores prior to the intervention (p=0.005). However, the Tukey's test demonstrated that the vitamin C and placebo groups and the pramipexole and placebo groups were significantly different regarding the IRLS scores obtained after the intervention (p<0.001), (p=0.004). This is while the pramipexole group was not statistically significantly different from the vitamin C group considering the mean IRLS scores obtained after the intervention (p=0.77).

During the treatment in the pramipexole group, one patient was excluded because of severe nausea and vomiting and in one patient the drug dose was decreased by half. There was no side effect in other groups.

The current study was performed to evaluate the effect of vitamin C and pramipexole in the treatment of RLS in hemodialysis patients.

Zhang et al. performed a study on 167 patients undergoing hemodialysis and 215 patients undergoing continuous ambulatory peritoneal dialysis (CAPD). They reported that plasma vitamin C level decreased as a result of an increase in the age and dialysis vintage in dialysis patients. Moreover, the plasma vitamin C level was found to be higher in female, as compared with male, patients (18). These findings collectively suggest that vitamin C deficiency may be associated with age and gender in patients. Thus, any difference in terms of age and sex could lead to a bias in the results.

The underlying pathophysiology of RLS is not fully understood. However, different mechanisms have been suggested for the condition. An effective factor in pathophysiology of the disease is dopaminergic dysfunction(19).In this regard, administration of dopamine agonist agents and the medications increasing the production of dopamine can be helpful in RLS treatment. Vitamin C is one of the drugs which can be effective because it enhances the production of tyrosine hydroxylase in the brain(19), stimulating dopamine production(11), (14).

Another probable reason for the effectiveness of vitamin C can be its antioxidant effect. Accordingly, in the Zhang et al. study carried out on 128 hemodialysis patients treated with vitamin C (200 mg per day), it was demonstrated that vitamin C, at this dosage, can reduce the biomarkers of inflammation in these patients(18).

Wang and Miyata et al. study observed that the concentration of in vitro plasma ascorbic acid in uremic patients decreased more rapidly (0.16% per min) than that in normal subjects (0.09% per min)(20), (21). This finding suggested that the uremic plasma consumes more vitamin C than the healthy plasma, which may be related to excessive toxin retention and metabolic acidosis(22) In vivo, the volume overload and bio-incompatibility of dialysis materials and non-sterile dialysate may also contribute to the inflammatory condition (22), (23).

Zhang hypothesized that vitamin C, as an electron donor, had anti-oxidative effects, and its oral supplementation could improve the inflammatory status in hemodialysis patients. Tarng et al(24) reported that the 8-OHdG level of cellular DNA, as an evaluative indicator of oxidative DNA damage in reactive oxygen species mediated diseases, is reduced after vitamin C supplementation for 8 weeks in chronic hemodialysis patients.

Iron deficiency is one of the mechanisms suggested for the underlying pathophysiology of RLS (5). Recent evidence has shown that the plasma vitamin C level is positively associated with levels of hemoglobin(25). Previous studies show that the vitamin C supplementation improves the responsiveness to EPO in hemodialysis patients with refractory anemia and hyperferritinemia(26). Vitamin C mobilizes storage iron by reducing ferric iron (Fe+3) to ferrous iron (Fe+2), including the portion of tissue iron as hemosiderin(27), leading to an increased bioavailability of iron and improved red blood cell production, thus indirectly leading to improved RLS symptoms.

Iron deficiency has, however, been implicated in RLS through CSF, MRI, autopsy and genetic studies(28).Iron can affect the dopaminergic system in several ways. It has been known as a cofactor for the tyrosine hydroxylase which affects dopamine synthesis. Iron deficiency reduces dopaminergic D1 and D2 receptors in the caudate nucleus and putamen(29). Iron deficiency also causes a decrease in the density of the dopamine transporter and reduces the binding of dopamine to its receptors in the caudate, putamen and nucleus accumbens in rats(30).It is not surprising that the supplementation of iron to RLS patients with low ferritin levels relieves the symptoms in a relatively short period of time. Therefore, vitamin C can enhance the number of dopaminergic D1 and D2 receptors via increasing the bioavailability of iron, and consequently improve the symptoms of restless leg syndrome.

Novel mechanistic insights into vitamin C in patients on dialysis are being elucidated. For example, high-dose vitamin C has been shown to ameliorate dialysis-associated blood reactive oxygen species and total antioxidant score, decrease peroxidation of plasma lipid and red cell membranes, and reduce hemolysis and levels of proinflammatory cytokines(31). Vitamin C administration also leads to shifts in several polypeptides identified in proteomic analysis from abnormal expression levels observed in patients on dialysis toward the expression levels seen in normal controls(32).

Moreover, the level of vitamin C is usually low in the hemodialysis patients, attributed to its loss during hemodialysis(33)and limited use of some food such as fresh fruits and vegetables rich in vitamin C to avoid hypokalemia in the patients(34).In this regard, these patients require receiving vitamin C supplementation.

In the present study, the IRLS score confirmed severity of RLS. In the group that received vitamin C, the difference between the pre- and post-intervention scores was considerable. This indicates the positive effect of vitamin C in reducing the symptoms of RLS.

Table 1: Demographic characteristics of patients

Variable		Groups			P
		Vitamin C	Pramipexole	Placebo	
Sex	Male	5(33.3%)	5(35.7%)	10(66.7%)	0.12
	Female	10(66.7%)	9(64.3%)	5(33.3%)	
Age		53.13± 9.52	56.58± 13.19	58.53± 7.76	0.34

Table 2: Mean and standard deviation of the participants with regard to the contextual variables in the three groups

Variable	Groups			P
	Vitamin C	Pramipexole	Placebo	
	Mean ± SD	Mean ± SD	Mean ± SD	
BUN	49.00±14.10	49.17±16.04	48.33±10.89	P=0.98
Hb	9.21±1.21	9.07± 1.72	10.07±1.11	P=0.11

Sagheb et al evaluated the effect of supplementation with vitamin C (200 mg/d), vitamin E, and a combination of the vitamins in RLS treatment in 60 hemodialysis patients. They reported that vitamin C reduced the IRLS score in the patients (34). Our results are in agreement with what they have reported.

Moreover, in the present study, the different the IRLS scores before and after the treatment was considerable in the pramipexole group.

Miranda et al administered pramipexole initial dose of 0.125 mg/d 2 hours prior to bedtime to relieve the RLS symptoms in uremic patients who underwent hemodialysis. They followed the patients for 8 months on average and reported positive results of the treatment, which are consistent with our findings (35).

Pellecchia et al compared the effectiveness of ropinirole, a dopamine agonist, with levodopa in treatment of the RLS in hemodialysis patients. They reported that ropinirole improved the IRLS score and was more effective than levodopa (36).

In this study, we observed the effectiveness of vitamin C and that of pramipexole were the same in relieving the symptoms of IRLS.

administration of pramipexole is accompanied with various adverse effects including nausea, vomiting, fatigue, drowsiness, orthostatic hypotension, insomnia, constipation, asthenia, hallucinations, extrapyramidal syndrome, accidental injury, dream abnormalities, confusion, dystonia, gait abnormality, hypertonia, dry mouth, amnesia, urinary frequency, peripheral leg edema, somnolence, headache, diarrhea, nasopharyngitis, and weight gain (37). These adverse effects are observed in many patients.

This is while hemodialysis patients experience many of these complications in their course of disease. This indicates that the administration of vitamin C, which lacks these adverse effects, is preferred in these patients and the short-term vitamin supplementation in the present trial was well tolerated in our patients. Moreover, no vitamin-related side effect, including urinary stone formation, was seen during the trials.

The compassion of vitamin C and pramipexole in treatment of RLS has not been carried out so far. A limitation of the present study was the small sample size that could influence the results. Another limitation to consider was the short-time follows up period because some studies have shown that long-term use of vitamin C can produce hyperoxaluria, oxalate containing urinary stones, and renal damage (21).

Thus, considering the positive effect of vitamin C in the relief of the RLS symptoms, carrying out a similar study with larger sample size and longer follow up is suggested.

CONCLUSION

Vitamin C was shown to be an effective and safe supplementation for the treatment of RLS in hemodialytic patients. The treatment was not accompanied with serious adverse effects in short-term follow up. Therefore, the supplementation could be considered as an alternative or additive treatment to the conventional treatments available. To evaluate the safety and effectiveness of the medication, further studies with larger sample size and longer follow up period is required.

REFFERENCES

[1] Karroum EG, Golmard J-L, Leu-Semenescu S, Arnulf I. Sensations in restless legs syndrome. *Sleep medicine.* **2012**;13(4):402-8.
[2] Pereanu M. Restless Legs Syndrome. *Acta Medica Transilvanica*. **2014**;19(3).
[3] Picchietti D, Bruni O, de Weerd A. International Restless Legs Syndrome Study Group (IRLSSG). Pediatric restless legs syndrome diagnostic criteria: an update by the International Restless Legs Syndrome Study Group. *Sleep Med*. **2013**;14(12):1253-9.
[4] Hanewinckel R, Maksimovic A, Verlinden VJ, van der Geest JN, Hofman A, van Doorn PA, et al. The impact of restless legs syndrome on physical functioning in a community-dwelling population of middle-aged and elderly people. *Sleep medicine.* **2015**;16(3):399-405.
[5] Patrick L. Restless legs syndrome: pathophysiology and the role of iron and folate. *Alternative Medicine Review.* **2007**;12(2):101-13.
[6] Bliwise DL, Zhang RH, Kutner NG. Medications associated with restless legs syndrome: a case–control study in the US Renal Data System (USRDS). *Sleep medicine.* **2014**;15(10):1241-5.
[7] Lin CH, Wu VC, Li WY, Sy HN, Wu SL, Chang CC, et al. Restless legs syndrome in end-stage renal disease: a multicenter study in Taiwan. *European Journal of Neurology.* **2013**;20(7):1025-31.
[8] Sh M, Sh M, Kamali P. Frequency of sleep disorder and restless legs syndrome in patients referring to hemodialysis units in university hospitals in Tehran in 2003. *Medical Science Journal of Islamic Azad Univesity-Tehran Medical Branch*. **2005**;15(1):27-30.
[9] Szentkiralyi A, Molnar MZ, Czira ME, Deak G, Lindner AV, Szeifert L, et al. Association between restless legs syndrome and depression in patients with chronic kidney disease. *Journal of psychosomatic research.* **2009**;67(2):173-80.
[10] Tuncel D, Orhan FÖ, Sayarlioglu H, Isık IO, Utku U, Dinc A. Restless legs syndrome in hemodialysis patients: association with depression and quality of life. *Sleep and Breathing.* **2011**;15(3):311-5.

[11] Molnar MZ, Novak M, Mucsi I. Management of restless legs syndrome in patients on dialysis. *Drugs.* 2006;66(5):607-24.
[12] Brindani F, Vitetta F, Gemignani F. Restless legs syndrome: differential diagnosis and management with pramipexole. *Clinical interventions in aging*. **2009**;4:305.
[13] Lipford MC, Silber MH. Long-term use of pramipexole in the management of restless legs syndrome. *Sleep medicine*. **2012**;13(10):1280-5.
[14] Khajehdehi P, Mojerlou M, Behzadi S, Rais-Jalali GA. A randomized, double-blind, placebo-controlled trial of supplementary vitamins E, C and their combination for treatment of haemodialysis cramps. *Nephrology Dialysis Transplantation*. **2001**;16(7):1448-51.
[15] Zhang K-Y, Zuo L. Vitamin C supplementation in patients on maintenance dialysis. *World J Clin Urol*. **2014**;3(3):344-50.
[16] Skidmore F, Drago V, Foster P, Heilman K. Bilateral restless legs affecting a phantom limb, treated with dopamine agonists. *Journal of Neurology, Neurosurgery & Psychiatry*. **2009**;80(5):569-70.
[17] Handelman GJ. Vitamin C neglect in hemodialysis: sailing between Scylla and Charybdis. *Blood purification.* **2006**;25(1):58-61.
[18] Zhang K, Dong J, Cheng X, Bai W, Guo W, Wu L, et al. Association between vitamin C deficiency and dialysis modalities. *Nephrology*. **2012**;17(5):452-7.
[19] Aggarwal S, Dodd S, Berk M. Restless leg syndrome associated with atypical antipsychotics: current status, pathophysiology, and clinical implications. *Current drug safety.* **2015**;10(2):98-105.
[20] Wang S, Schram I, Sund R. Determination of plasma ascorbic acid by HPLC: method and stability studies. *European journal of pharmaceutical sciences.* **1995**;3(4):231-9.
[21] Miyata T, Wada Y, Cai Z, Iida Y, Horie K, Yasuda Y, et al. Implication of an increased oxidative stress in the formation of advanced glycation end products in patients with end-stage renal failure. *Kidney international*. **1997**;51(4):1170-81.
[22] Demirci MS, Demirci C, Ozdogan O, Kircelli F, Akcicek F, Basci A, et al. Relations between malnutrition–inflammation–atherosclerosis and volume status. The usefulness of bioimpedance analysis in peritoneal dialysis patients. *Nephrology Dialysis Transplantation.* **2011**;26(5):1708-16.
[23] Stenvinkel P, Alvestrand A, editors. Review Articles: Inflammation in End-stage Renal Disease: Sources, Consequences, and Therapy. Seminars in dialysis; **2002**: Wiley Online Library.
[24] Tarng D-C, Liu T-Y, Huang T-P. Protective effect of vitamin C on 8-hydroxy-2′-deoxyguanosine level in peripheral blood lymphocytes of chronic hemodialysis patients. *Kidney international*. **2004**;66(2):820-31.
[25] Finkelstein FO, Juergensen P, Wang S, Santacroce S, Levine M, Kotanko P, et al. Hemoglobin and plasma vitamin C levels in patients on peritoneal dialysis. *Peritoneal Dialysis International.* **2011**;31(1):74-9.
[26] Attallah N, Osman-Malik Y, Frinak S, Besarab A. Effect of intravenous ascorbic acid in hemodialysis patients with EPO-hyporesponsive anemia and hyperferritinemia. *American journal of kidney diseases.* **2006**;47(4):644-54.
[27] Allen R, Barker P, Wehrl F, Song H, Earley C. MRI measurement of brain iron in patients with restless legs syndrome. *Neurology*. **2001**;56(2):263-5.
[28] Sun Y-MJ, Hoang T, Neubauer JA, Walters AS. Opioids protect against substantia nigra cell degeneration under conditions of iron deprivation: a mechanism of possible relevance to the Restless Legs Syndrome (RLS) and Parkinson's disease. *Journal of the neurological sciences.* **2011**;304(1):93-101.
[29] Earley CJ, Connor J, Garcia-Borreguero D, Jenner P, Winkelman J, Zee PC, et al. Altered Brain iron homeostasis and dopaminergic function in Restless Legs Syndrome (Willis–Ekbom Disease). *Sleep medicine*. **2014**;15(11):1288-301.
[30] Erikson KM, Jones BC, Hess EJ, Zhang Q, Beard JL. Iron deficiency decreases dopamine D 1 and D 2 receptors in rat brain. *Pharmacology Biochemistry and Behavior.* **2001**;69(3):409-18.
[31] Erikson KM, Jones BC, Beard JL. Iron deficiency alters dopamine transporter functioning in rat striatum. The *Journal of nutrition.* **2000**;130(11):2831-7.
[32] Yang C, Hsu S, Wu M, Hsu S, Chien C-T. Effects of vitamin C infusion and vitamin E-coated membrane on hemodialysis-induced oxidative stress. *Kidney international.* **2006**;69(4):706-14.
[33] Zhang K, Liu L, Cheng X, Dong J, Geng Q, Zuo L. Low levels of vitamin C in dialysis patients is associated with decreased prealbumin and increased C-reactive protein. *BMC nephrology*. **2011**;12(1):1.
[34] Sagheb MM, Dormanesh B, Fallahzadeh MK, Akbari H, Nazari SS, Heydari ST, et al. Efficacy of vitamins C, E, and their combination for treatment of restless legs syndrome in hemodialysis patients: a randomized, double-blind, placebo-controlled trial. *Sleep medicine.* **2012**;13(5):542-5.
[35] Miranda M, Kagi M, Fabres L, Aguilera L, Alvo M, Elgueta L, et al. Pramipexole for the treatment of uremic restless legs in patients undergoing hemodialysis. *Neurology*. **2004**;62(5):831-2.
[36] Pellecchia MT, Vitale C, Sabatini M, Longo K, Amboni M, Bonavita V, et al. Ropinirole as a treatment of restless legs syndrome in patients on chronic hemodialysis: an open randomized crossover trial versus levodopa sustained release. *Clinical neuropharmacology.* **2004**;27(4):178-81.

[37] Silindir M, Ozer AY. The benefits of pramipexole selection in the treatment of Parkinson's disease. *Neurological Sciences.* **2014**;35(10):1505-11.