Role of levothyroxine suppressive therapy for benign cold nodules of thyroid: a randomized, double-blind, placebo-controlled clinical trial

Bagher Larijani†, Mohammad Pajouhi, Mohammad Hasan Bastanhagh, Alireza Sadjadi, Shahriar Aghakhani, Farhad Zare, Nahid Sedighi, Mohammad Reza Eshraghian, Amir Hossein Nadjafi, Mohammad Reza Amini, Hossein Adibi & Seyed Mohammad Akrami

†Author for correspondence Tehran University of Medical Sciences, Endocrinology and Metabolism Research Center, 5th Floor, Shariati Hospital, North Kargar Avenue, Tehran, 14114, Iran Tel.: +98 218 026 902 Fax: +98 218 029 399 emrc@sina.tums.ac.ir

Introduction: There is no consensus on the appropriate management of benign cold nodules of the thyroid gland. This study addresses the problem in an iodine-deficient area, evaluating the efficacy of levothyroxine suppression therapy on a 2-year course. **Methods:** A total of 58 patients affected with benign cold nodules of the thyroid were enrolled. With a double-blind placebo-controlled design, levothyroxine (1.5–2 μg/kg/day) was delivered to the 31 cases over 2 years. The consequences of this treatment were compared with 27 controls. Nodule size was measured with high-resolution ultrasonography. **Results:** In the treatment group, the mean volume on baseline was 12.8 ± 11.9 ml and changed to 9.4 ± 9.8, 12.4 ± 16.7 and 10.8 ± 9.7 ml in months 6, 12 and 24, respectively. In the placebo group, these figures were 13.0 ± 10.2, 11.5 ± 8.0, 11.7 ± 13.6 and 11.6 ± 8.5 ml, respectively. No significant difference between the two groups was observed. **Conclusion:** Thyroid-stimulating hormone suppression with levothyroxine for 2 years was not effective in reducing the size of benign cold nodules of the thyroid gland.

Keywords: cold nodule, levothyroxine, suppressive treatment, thyroid

Nodular diseases of the thyroid gland are among the most common endocrine disorders. It has been reported that 4 to 7% of all American adults have palpable thyroid nodules [1–3]. The rates are even higher in endemic goiter areas [3–5]. However, the management of a thyroid nodule has remained a challenging issue, with no consensus on the most appropriate course of action. It seems that differences in iodine intake, histologic features and the slow and unpredictable growth patterns of nodules are partly responsible for the result discrepancy of studies looking into the issue [6–9]. Suppressive therapy was first recommended by an uncontrolled study in 1960 [10]. Later, the efficacy of this therapy was suspected by controlled trials benefiting from more precise measurement techniques [11–17]. Until fairly recently, Iran was categorized as an area with clear indications of iodine deficiency [18–20]. In a previous report, the authors indicated the inefficacy of thyroid-stimulating hormone (TSH) suppression in significantly reducing nodule size [21]. However, the rather short duration of the study could have led to this finding. Thus it was decided to extend the trial for another year. This research represents a double-blind clinical-controlled trial on the efficacy of suppressive treatment with levothyroxine for 2 consecutive years in an endemic goiter area, Iran.

Materials & methods

The randomized clinical trial was conducted over a 2-year period. A total of 62 patients were enrolled. All had a single palpable thyroid nodule on physical examination and cytology consistent with benign nature of the nodule on fine needle aspiration biopsy (FNAB). Fine-needle biopsy was taken using a 25-gauge needle without local anesthesia. All cytologic studies were performed by a single cytopathologist at the department of pathology in Shariati Hospital. Patients with suspicious or malignant FNAB results were not considered eligible. Also disqualified from the study were patients:

- With a history of levothyroxine consumption, at least in the preceding year
- With abnormal levels of thyroxine (T4), triiodothyronine (T3) and TSH
- With more than one palpable nodule on physical examination
- Who are pregnant
- With a history of cardiovascular disease
- Who were aged 15 years or younger
- Who were aged 60 years or older

Patients were randomly assigned to either the levothyroxine group or the placebo group, with the use of a random number table. A total of 58 patients of the primary enrolled patients completed the second year of study (31 cases and 27 controls). One of the four dropouts was a middle-aged woman who underwent surgery by choice.

Thyroid hormone profiles were determined at the beginning of the study, 6 weeks later and then on a 3-monthly basis. TSH level was measured by a sensitive immunoradiometric (IRMA) method (Kavoshyar, Tehran, Iran;

Future Drugs Ltd

Reference intervals: 0.3–5 mIU/ml). Complete TSH suppression was the goal (<0.1 mIU/ml). Given the sensitivity of the assay used at the time, the thyroid-releasing hormone (TRH) suppression test was applied to ten randomly selected patients in each group so as to ensure adequate suppression of TSH (synthetic TRH, 400 µg after week 6).

Both clinical and ultrasonographic studies were applied blindly. The patients were visited on a monthly basis at the endocrinology clinic. The size of nodules was measured by ultrasonography at the beginning and at 6, 12 and 24 months during the study period. A single sonologist performed all ultrasonographic studies with a real-time instrument (Kretz) and a medium-resolution 7.5-megahertz linear probe with the patients lying supine. The three diameters of each nodule (longitudinal [L], transverse [T] and anteroposterior [AP]) were measured. The volume of the nodules was then calculated using the spherical ellipsoid formula:

$$Volume = \frac{3.14}{6 \times T \times L \times AP}$$

In each session, measurements were performed twice, and the mean measurement was reported to decrease intraobserver variation. In patients, who had more than one nodule, the largest one was selected and further measurements were performed on that nodule.

To compare the quantitative variables, we used Student's t-test. Each group was evaluated separately by the paired t-test to compare each measurement with the basal size. To analyze changes in nodule size over time, a repeated measures ANanlysis Of VAriance (ANOVA) was used. Differences at $p < 0.05$ were considered significant. The two possible treatments (surgical and medical) and their advantages and disadvantages were described to each patient. The attending physician and sonographer were blind to the treatment protocol. Informed consent was obtained from all patients and the study was sanctioned by the responsible ethics committee. At the end of the study, all patients who had detectable nodules were referred to an endocrinologist for appropriate treatment measures.

Results

Table 1 summarizes the clinical and laboratory findings of the 58 subjects of our study (31 cases and 27 controls). In the treatment group, mean TSH was 1.7 ± 0.09 mIU/ml at baseline and 0.18 ± 0.3 mIU/ml after 6 weeks ($p < 0.001$). The figures in the control group were 0.92 ± 0.8 at baseline and 0.78 ± 0.7 mIU/ml 6 weeks later.

Hormonal alterations in both groups are shown in Table 2. Evidence of suppression was present in all subjects who remained in the study by the end of the second year. In the treatment group, the mean nodule volume was 12.8 ± 11.9 ml at baseline, which decreased to 9.4 ± 9.8 ml after 6 months ($p < 0.003$). However, at month 12 this increased again to 12.4 ± 16.7 ml, where no significant difference existed with the baseline size ($p > 0.05$). At month 24, mean nodule size was 10.8 ± 9.7 ml, again not significantly different from the baseline value ($p > 0.05$).

In the placebo group the mean nodule volume was 13.02 ± 10.2 ml at baseline, which was equivalent to the mean nodule size of the treatment group at baseline (12.8 ± 11.9 ml; $p > 0.05$). At month 6 the size decreased to 11.55 ± 8.0 ml ($p < 0.003$). In addition to the treatment group showing an increase in nodule size, an increase of 11.7 ± 13.6 ml was observed in the placebo group at month 12 – although this was not significantly different from baseline

Table 1. Clinical and laboratory characteristics of cases and controls at the beginning of the trial.

	Levothyroxine group	Control group	p-value	Normal values
Cases (n)	31	27		
Sex (F/M)	25/6	20/7		
Age (years)	34.4 ± 9.4	37.1 ± 11.8	>0.05	
TSH (mIU/ml)	1.7 ± 1.0	0.9 ± 0.8	>0.05	0.2–5.0
T_3 (ng/dl)	129.4 ± 46.0	132.6 ± 41.0	>0.05	80–230
T_4 (µg/dl)	8.7 ± 2.0	8.5 ± 2.8	>0.05	4.5–12.8
Nodule volume (ml)	12.8 ± 11.9	13.2 ± 10.0	>0.05	

F/M: Female/male; T_3: Triiodothyronine; T_4: Thyroxine; TSH: Thyroid stimulating hormone.

Table 2. Hormonal changes of levothyroxine and control groups.

	Levothyroxine group			Control group		
	Baseline (mean ± SD)	*6 weeks (mean ± SD)*	*p-value*	*Baseline (mean ± SD)*	*6 weeks (mean ± SD)*	*p-value*
TSH (mIU/ml)	1.7 ± 1.09	0.18 ± 0.3	<0.001	0.9 ± 0.8	0.8 ± 0.7	>0.05
T_4 (µg/dl)	8.7 ± 2.00	10.5 ± 1.5	>0.05	8.4 ± 2.8	9.2 ± 1.7	>0.05
TSH after TRH stimulation test*		0.8 ± 0.2			8.2 ± 3.8	

**TRH test was given to only ten participants in each group.*

SD: Standard deviation; T_4: Thyroxine; TRH: Thyroid releasing hormone; TSH: Thyroid stimulating hormone.

($p > 0.05$). At month 24, mean nodule size was 11.6 ± 8.5 ml, and was neither significantly different from the baseline value ($p > 0.05$), nor the treatment group at the same time. These observations are summarized in Table 3. A total of 15 patients had more than one nodule, with the largest nodule in these patients being followed. All smaller nodules were less than 1 cm.

As shown in Table 4, the participants were divided into three categories based on the nodules' decrease in size:

- Complete responders: 50% or higher decrease in nodule volume
- Partial responders: less than 50% decrease in nodule volume
- Nonresponders: constant or increase in nodule volume

Repetitive FNAB in the nonresponder group did not show any abnormal cytologic finding.

Discussion

Diagnosis and treatment of cold thyroid nodules has remained a challenging issue in the field of internal medicine – the possibility of malignant transformation of these nodules over years has made the issue even more critical. While sample follow up of patients is suggested by some internists, suppressive therapy with levothyroxine is recommended by others. Medical management is suggested in more than 50% of the patients with single nodules who have benign FNAB findings and do not need surgery [3,13].

As thyrotropin can stimulate growth events in the thyroid gland, it is logical to assume that its suppression may arrest nodular tissue growth [22]. There are reports indicating significant decrease in the nodule size [22,23] or higher frequency of regression after a year of TSH suppression [24]. In contrast, several studies have failed to show a significant reduction after the introduction of levothyroxine suppressive therapy to these patients [13–15]. In a controlled trial, with follow-up after 5 years, Papini and colleagues came to the conclusion that long-term TSH suppression was ineffective to induce significant nodule volume reduction, but levothyroxine treatment had prevented any further increase in nodule volume or emergence of new nodules [9]. The success rate of levothyroxine suppressive therapy of thyroid nodules has ranged between 0 and 68% in previous studies [2]. This can be attributed to imprecise definition of the nodules being treated, failure to document suppression of thyrotropin [11], imprecise estimation of nodules size or lack of a placebo-control group [13].

The current study has used meticulous means to compare the placebo and levothyroxine groups. All measurements were done by high resolution ultrasonography, and suppression of TSH was confirmed by the TRH stimulation test. The observed initial decrease in the nodule size in the current study, which might have occurred secondary to the resorption of fluid in cystic nodules, was significant in both cases and controls, although somewhat more marked in

Table 3. Nodule volumes at baseline, 6, 12 and 24 months in levothyroxine and control groups.

	Baseline (mean ± SD)	6 months (mean ± SD)	p-value	12 months (mean ± SD)	p-value	24 months (mean ± SD)	p-value
Levothyoroxine group	12.8 ± 11.9	9.4 ± 9.8	0.003	12.4 ± 16.7	>0.05	10.8 ± 9.7	>0.05
Control group	13.0 ± 10.2	11.5 ± 8.0	0.003	11.7 ± 13.6	>0.05	11.6 ± 8.5	>0.05

SD: Standard deviation.

Table 4. Frequencies of response categories in levothyroxine and control groups at 2 years.

	Levothyroxine group	Control group
Complete responders	6 (18.7%)	3 (13.3%)
Partial responders	9 (28.1%)	7 (26.6%)
Nonresponders	16 (53.1%)	17 (60.0%)
Total	31 (100.0%)	27 (100.0%)

the placebo group. Nevertheless, measurements on months 12 and 24 indicated that the volume of the nodules had returned to baseline. No significant difference with regards to the nodule size was observable on months 12 and 24.

Ramelli and colleagues have proposed two possible mechanisms for the development of thyroid nodules – excessive accumulation of colloid and proliferation of thyroid follicles in the nondistensible connective tissue [25]. Resorption of colloid or follicular necrosis causes a reduction in the blood supply, eventually resulting in fibrosis and degeneration of the nodule. In this setting, levothyroxine suppressive therapy will not influence the pathologic processes within the nodule [26,27]. A number of other factors, including epidermal growth factor [28], insulin-like growth factor [29] and thyroid stimulating immunoglobulins [29], have been suggested to induce the growth of thyroid nodules. However it remains to future studies to verify whether such mechanisms really exist. Vermiglio and colleagues compared the effects of 12 months of thyrotropin suppressive levothyroxine therapy in terms of initial cytological features. They observed decrease in size of nodules in a third of patients, irrespective of their cytologic features. They also reported a trend towards an augmentation of hypercellular, adenomatous and suspicious characteristics in increasing nodules. Hence they advised repeat FNAB should be used for thyroid nodules which increase in volume despite levothyroxine therapy [30].

In our study, cytological re-evaluation of months 12 and 24 did not show any change. On the whole it seems that, in the absence of an implicating change, repeated FNAB in the follow-up of benign thyroid nodules would be of limited value. Many previous reports were neither conducted in a randomized nor double-blind fashion. The two exceptions were conducted by Gharib and colleagues and Shimaoka and colleagues; however, TSH suppression was only conducted by Gharib and colleagues [13,31].

More recently, Papini and colleagues conducted a 5-year clinical trial to study long-term changes in thyroid cold nodules after suppressive therapy. They reported less frequent new nodules and more frequent nodule shrinkage in patients with complete TSH suppression than in the controls. They concluded that long-term TSH suppression could induce volume reduction in only a subgroup of thyroid nodules, but effectively prevent the appearance of new lesions and increases in nodule and thyroid volume [9]. Zelmanovitz and colleagues also observed that suppressive T_4 treatment led to a reduction in volume and prevented the growth of nodules in a higher proportion of patients than the placebo group, although this difference did not reach statistical significance. They then analyzed their data together with the results of six other similar trials in a meta-analysis, and showed that suppressive T_4 treatment was effective in decreasing the volume and impeding the growth of solitary thyroid nodules [32].

It is clear that more evidence from other studies will be necessary to further clarify the subject. Nevertheless, possible changes in the natural history of nodular goiter related to prolonged TSH suppression can be accompanied by unfavorable side effects of levothyroxine suppressive therapy [33–35]. In this line, some studies which have compared low- or high-level TSH suppression, have advised low-level TSH suppression if one considers levothyroxine suppressive therapy to reduce thyroid nodule size given the equal effectiveness of the two methods [36].

In conclusion, suppressive therapy with levothyroxine for 2 years failed to reduce the size of benign cold thyroid nodules. Moreover, sufficient suppression of TSH, as an effective factor in the growth of thyroid, produced no significant change in the natural course of the benign cold thyroid nodules.

Acknowledgment

The authors would like to express their gratitude to V Fatourehchi from the Department of Endocrinology, Mayo Clinic for his indispensable comments to improve the final draft. Our thanks also go to K Abulamaali and all of our colleagues at the Endocrinology & Metabolism Research Center for their valuable assistance.

Bibliography

1. Vander JB, Gaston EA, Dawber TR. The significance of nontoxic thyroid nodules. Final report of a 15-year study of the incidence of thyroid malignancy. *Ann. Intern. Med.* 69, 537–540 (1968).
2. Rojeski MT, Gharib H. Nodular thyroid disease. Evaluation and management. *N. Engl. J. Med.* 313, 428–436 (1985).
3. Gharib H, Goellner JR. Fine-needle aspiration biopsy of the thyroid: an appraisal. *Ann. Intern. Med.* 118, 282–289 (1993).
4. Azizi F, Kimiagar M, Nafarabadi MT, Yassai M. Current status of iodine deficiency disorders in the Islamic Republic of Iran. *Health. Serv. J.* 8, 23–27 (1990).
5. Azizi F, Miresmaili M Azizi M. The effect of thyroxin therapy on the size of cold thyroid nodules in patients from an iodine deficient area. *Med. J. Islamic Republic of Iran* 6, 161–165 (1992).
6. Studer H, Gerber H, Zbaeren J Peter HJ. Histomorphological and immunohistochemical evidence that human nodular goiters grow by episodic replication of multiple clusters of thyroid follicular cells. *J. Clin. Endocrinol. Metab.* 75, 1151–1158 (1992).
7. Toft AD. Thyroxine therapy. *N. Engl. J. Med.* 331, 174–180 (1994).
8. Asmis LM, Kaempf J, Von Gruenigen C, Kimura ET, Wagner HE, Studer H. Acquired and naturally occurring resistance of thyroid follicular cells to the growth inhibitory action of transforming growth factor-β 1 (TGF-β 1). *J. Endocrinol.* 149, 485–496 (1996).
9. Papini E, Petrucci L, Guglielmi R *et al*. Long-term changes in nodular goiter: a 5-year prospective randomized trial of levothyroxine suppressive therapy for benign cold thyroid nodules. *J. Clin. Endocrinol. Metab.* 83, 780–783 (1998).
10. Astwood EB, Cassidy CE, Aurbach GD. Treatment of goiter and thyroid nodules with thyroid. *JAMA* 174, 459–464 (1960).
11. Schneeberg NG, Stahl TJ, Maldia G, Menduke H. Regression of goiter by whole thyroid or triiodothyronine. *Metabolism* 11, 1054–1060 (1962).
12. Badillo J, Shimaoka K, Lessmann EM, Marchetta FC, Sokal JE. Treatment of nontoxic goiter with sodium liothyronine. A double-blind study. *JAMA* 184, 29–36 (1963).
13. Gharib H, James EM, Charboneau JW, Naessens JM, Offord KP, Gorman CA. Suppressive therapy with levothyroxine for solitary thyroid nodules. A double-blind controlled clinical study. *N. Engl. J. Med.* 317, 70–75 (1987).
14. Cheung PS, Lee JM, Boey JH. Thyroxine suppressive therapy of benign solitary thyroid nodules: a prospective randomized study. *World. J. Surg.* 13, 818–821 (1989).
15. Reverter JL, Lucas A, Salinas I, Audi L, Foz M, Sanmarti A. Suppressive therapy with levothyroxine for solitary thyroid nodules. *Clin. Endocrinol.* 36, 25–28 (1992).
16. Mandel SJ, Brent GA, Larsen PR. Levothyroxine therapy in patients with thyroid disease. *Ann. Intern. Med.* 119, 492–502 (1993).
17. Papini E, Bacci V, Panunzi C *et al*. A prospective randomized trial of levothyroxine suppressive therapy for solitary thyroid nodules. *Clin. Endocrinol.* 38, 507–513 (1993).
18. Nezam-Mafi S. Various aspects of endemic goiter in Iran. *Rev. Med. Moyen. Orient.* 22(2), 199–203 (1965).
19. Azizi F, Kimiagar M, Navai L, Yassai M. Goiter in Tehran and suburbs. Recent progress in thyroidology. *Proceedings of the Third Asia and Oceania Thyroid Association Meeting.* 388–391 (1986).
20. Kimiagar M, Azizi F, Navai L, Yassai M, Nafarabadi T. Survey of iodine deficiency in a rural area near Tehran: association of food intake and endemic goitre. *Eur. J. Clin. Nutr.* 44, 17–22 (1990).
21. Larijani B, Pajouhi M, Bastanhagh MH, Sadjadi AR, Sedighi N, Eshraghian MR. Evaluation of suppressive therapy for cold thyroid nodules with levothyroxine: double-blind placebo-controlled clinical trial. *Endocr. Pract.* 5, 251–256 (1999).
22. Hamberger B, Gharib H, Melton LJ 3rd, Goellner J, Zinsmeister AR. Fine-needle aspiration biopsy of thyroid nodules. Impact on thyroid practice and cost of care. *Am. J. Med.* 73, 381–384 (1982).
23. Reeve TS, Delbridge L, Sloan D, Crummer P. The impact of fine-needle aspiration biopsy on surgery for single thyroid nodules. *Med. J. Aust.* 145, 308–311 (1986).
24. Block MA, Miller JM, Kini SR. The potential impact of needle biopsy on surgery for thyroid nodules. *World. J. Surg.* 4, 737–741 (1980).
25. Ramelli F, Studer H, Bruggisser D. Pathogenesis of thyroid nodules in multinodular goiter. *Am. J. Pathol.* 109, 215–223 (1982).
26. Taylor S. Physiologic considerations in the genesis and management of nodular goiter. *Am. J. Med.* 20, 698–709 (1956).
27. Clark OH. TSH Suppression in the management of thyroid nodules and thyroid cancer. *World. J. Surg.* 5, 39–47 (1981).
28. Westermark KF, Karlwon L, Ericson LE, Westermark B. Epidermal growth factor. A regulator of thyroid growth and function in vitro. In: *Thyroglobulin. The Prothyroid Hormone. Progress in Endocrine Research and Therapy (Volume 2).* MC Eggo, GN Burrow (Eds), Reven Press, NY, USA, 255–262 (1985).
29. Duh QY, Gum ET, Gerend PL, Raper SE, Clark OH. Epidermal growth factor receptors in normal and neoplastic thyroid tissue. *Surgery* 98, 1000–1007 (1985).
30. Vermiglio F, Lo Presti VP, Violi MA *et al*. Changes in both size and cytological features of thyroid nodule after levothyroxine treatment. *Clin. Endocrinol.* 59, 347–353 (2003).
31. Shimaoka K, Sokal JE. Suppressive therapy of nontoxic goiter. *Am. J. Med.* 57, 576–583 (1974).
32. Zelmanovitz F, Genro S, Gross JL. Suppressive therapy with levothyroxine for solitary thyroid nodules: a double-blind controlled clinical study and cumulative meta-analyses. *J. Clin. Endocrinol. Metab.* 83, 3881–3885 (1998).
33. Sheppar MC, Holder R, Franklyn JA. Levothyroxine treatment and occurrence of fracture of the hip. *Arch. Intern. Med.* 162, 338–343 (2002).
34. Larijani B, Gharibdoost F, Pajouhi M *et al.* Effects of levothyroxine suppressive therapy on bone mineral density in premenopausal women. *J. Clin. Pharm. Ther.* 29, 1–5 (2004).
35. Biondi B, Fazio S, Cuocolo A *et al.* Impaired cardiac reserve and exercise capacity in patients receiving long-term thyrotropin suppressive therapy with L-T4. *J. Clin. Endocrinol. Metab.* 81, 4224–4228 (1996).
36. Koc M, Ersoz HO, Akpinar I. Effect of low- and high-dose levothyroxine on thyroid nodule volume: a crossover placebo-controlled trial. *Clin. Endocrinol.* 57, 621–628 (2002).

Affiliations

Bagher Larijani
Tehran University of Medical Sciences,
Endocrinology and Metabolism
Research Center,
5th Floor, Shariati Hospital,
North Kargar Avenue, Tehran, 14114, Iran
Tel.: +98 218 802 6902
Fax: +98 218 802 9399
emrc@sina.tums.ac.ir

Mohammad Pajouhi
Tehran University of Medical Sciences,
Endocrinology and Metabolism
Research Center,
5th Floor, Shariati Hospital,
North Kargar Avenue, Tehran,
14114, Iran
Tel.: +98 218 802 6902
Fax: +98 218 802 9399
emrc@sina.tums.ac.ir

Mohammad Hasan Bastanhagh
Tehran University of Medical Sciences,
Endocrinology and Metabolism
Research Center,
5th Floor, Shariati Hospital,
North Kargar Avenue, Tehran,
14114, Iran
Tel.: +98 218 802 6902
Fax: +98 218 802 9399
emrc@sina.tums.ac.ir

Alireza Sadjadi,
Tehran University of Medical Sciences,
Endocrinology and Metabolism
Research Center,
5th Floor, Shariati Hospital,
North Kargar Avenue, Tehran,
14114, Iran
Tel.: +98 218 802 6902
Fax: +98 218 802 9399
emrc@sina.tums.ac.ir

Shahriar Aghakhani, Researcher
Tehran University of Medical Sciences,
Endocrinology and Metabolism
Research Center,
5th Floor, Shariati Hospital,
North Kargar Avenue, Tehran,
14114, Iran
Tel.: +98 218 802 6902
Fax: +98 218 802 9399
emrc@sina.tums.ac.ir

Farhad Zare,
Tehran University of Medical Sciences,
Endocrinology and Metabolism
Research Center,
5th Floor, Shariati Hospital,
North Kargar Avenue, Tehran,
14114, Iran
Tel.: +98 218 802 6902
Fax: +98 218 802 9399
emrc@sina.tums.ac.ir

Nahid Sedighi
Tehran University of Medical Sciences,
Shariati Hospital, North Kargar Avenue,
Tehran, 14114, Iran
Tel.: +98 218 802 6902
Fax: +98 218 802 9399
emrc@sina.tums.ac.ir

Mohammad Reza Eshraghian
Tehran University of Medical Sciences,
Department of Epidemiology
and Biostatistics,
School of Public Health,
North Kargar Avenue, Tehran,
14114, Iran
Tel.: +98 218 802 6902
Fax: +98 218 802 9399
emrc@sina.tums.ac.ir

Amir Hossein Nadjafi,
Tehran University of Medical Sciences,
Endocrinology and Metabolism Research Center,
5th Floor, Shariati Hospital,
North Kargar Avenue, Tehran,
14114, Iran
Tel.: +98 218 802 6902
Fax: +98 218 802 9399
emrc@sina.tums.ac.ir

Mohammad Reza Amini,
Tehran University of Medical Sciences,
Endocrinology and Metabolism
Research Center,
5th Floor, Shariati Hospital,
North Kargar Avenue, Tehran,
14114, Iran
Tel.: +98 218 802 6902
Fax: +98 218 802 9399
emrc@sina.tums.ac.ir

Hossein Adibi
Tehran University of Medical Sciences,
Endocrinology and Metabolism
Research Center,
5th Floor, Shariati Hospital,
North Kargar Avenue, Tehran,
14114, Iran
Tel.: +98 218 802 6902
Fax: +98 218 802 9399
emrc@sina.tums.ac.ir

Seyed Mohammad Akrami
Tehran University of Medical Sciences,
Endocrinology and Metabolism
Research Center,
5th Floor, Shariati Hospital,
North Kargar Avenue, Tehran,
14114, Iran
Tel.: +98 218 802 6902
Fax: +98 218 802 9399
akramism@sina.tums.ac.ir