http://www.pjbs.org

PJBS

ISSN 1028-8880

Pakistan Journal of Biological Sciences

ANSInet
Asian Network for Scientific Information
308 Lasani Town, Sargodha Road, Faisalabad - Pakistan

Pakistan Journal of Biological Sciences 13 (11): 556-562, 2010
ISSN 1028-8880

The State of Serum Lipids Profiles in Sub-Clinical Hypothyroidism: A Review of the Literature

Azad Reza Mansourian
Biochemistry and Metabolic Disorder Research Center,
Golestan University of Medical Sciences, Gorgan Medical School, Gorgan, Iran

Abstract: Thyroid disorders usually associated with lipid abnormalities. Overt hypothyroidism is a state with thyroid hormone deficiency. Sub clinical hypothyroidism is defined as condition, in which thyroid stimulating hormone concentration elevated when serum thyroid hormones are at normal levels. Whether sub-clinical hypothyroidism associated with lipid alteration, it is the main concept behind this study. Although, in this study, we found cases with normal thyroxin and elevated thyroid stimulating hormone are common, but whether the sub-clinical hypothyroidism finally converted to overt hypothyroidism are not universally accepted. The findings also indicated subjects with sub-clinical hypothyroidism usually are accompanied with dyslipidemia and in general the total cholesterol level is higher among sub-clinical hypothyroid patients, with eventual risk of arthrosclerosis. This study indicated that there is not a common findings to support the benefit of thyroxin therapy in sub-clinical hypothyroidism. It is concluded that it seems sub-clinical hypothyroidism is a common thyroid abnormality which can be diagnosed by the medical diagnostic laboratory through thyroid function test and it is mainly accompanied with lipid disorder.

Key words: Thyroid, hypothyroid, sub-clinical hypothyroid, thyroid stimulating hormone, thyroxin, lipid disorder

INTRODUCTION

Anatomically thyroid gland is located at front section of the neck. The thyroid hormones thyroxin (T4) and triidothyronine (T3) interfere with the body metabolism as whole. The over activity, under activity of the thyroid gland are defined as hyperthyroidism or hypothyroidism, respectively.

In hypothyroidism which may be caused by thyroid nodules and grave disease which is due to autoimmunity in the thyroid gland it is resulting in elevation of thyroid hormones concentration with subsequent alteration in metabolism of many consequences, among all are: under weight, anxiety and hypertension.

In hypothyroidism, the thyroid gland produce less amount of thyroid hormone, such subjects eventually will lead to have lower metabolic rate and clinical manifestation such as over weight, fatigue, hypotension and depression. The symptoms of either hyperthyroidism or hypothyroidism can put the patient life at risk, therefore the diagnosis and management of thyroid abnormalities is a curtail task for the clinicians as well as medical diagnostic laboratories word-wide. Laboratory measurements of Thyroid Stimulating Hormone (TSH) and thyroxin (T4) and tri-idothyronine (T3) are the key hormones in helping the clinicians to diagnose the thyroid patient abnormality. In general TSH and T4 play an even bigger role in the diagnosis of either hyperthyroidism or hypothyroidism. On condition of low TSH, high T4 and high TSH, low T4 the diagnosis can be either overt hyperthyroidism or hypothyroidism respectively.

The other clinically mainly undiagnosed thyroid abnormalities are either sub-clinical, hyperthyroidism or sub-clinical hypothyroidism which usually can be diagnosed on the bases of laboratory blood test results. The sub-clinical hyperthyroidism and sub-clinical hypothyroidism are diagnosed when the T4, T3, serum concentrations are at normal range with low and high TSH serum levels respectively. Whether sub-clinical thyroid dysfunction accompanied with any metabolic disorders, it is remain to be answered and it is not fully understood. Thyroid disorder can be correlated with other metabolic abnormalities among all are dyslipidemia, cardiovascular, liver diseases and anemia.

Our main concern in this study was to clarify the state of dyslipidemia among sub-clinically hypothyroid patients with eventual arthrosclerosis.

This study was carried out at Biochemistry and Metabolic Disorder Research Center of the Golestan University of Medical Sciences, in Northern Iran. The related articles on thyroid dysfunctions accompanied with dyslipidemia were reviewed.

Particular attention was paid on hypercholesterolemia and low density lipoprotein-cholesterol, associated with sub-clinical hypothyroidism and the consequence of lipid disorder in sub clinically hypothyroid patients was examined.

HYPOTHYROIDISM AND SERUM LIPID ALTERATION

It is universally accepted that there is a correlation of lipid profile alteration among hypothyroidism patients and since half century ago There were documented studies, on whether the dyslipidemia in hypothyroidism may finally lead to cardiovascular diseases (Bastenie *et al*., 1967).

In the middle of 20th century when the thyroid hormone assessment was not as easy as lipid measurement, the serum lipid profile and in particular serum cholesterol level was the major point for diagnosing thyroid hormone insufficiency (Flower and Swale, 1967). It is also important that on considering thyroid hormonal status the reference intervals in each particular region should be separately estimated to avoid the misdiagnosis, (Mansourian *et al*., 2010; Shahmohamadi *et al*., 2008). The normal range of thyroid hormones should also have to be assessed at different condition of an individual to avoid the miss-conduct of thyroid hormones interpretations. There are many reports of metabolic disorders among pregnant women, such as nausea and vomiting in early pregnancy, which is due to the thyroid hormone alteration and perhaps the excessive requirements of thyroid hormone during pregnancy, the author of this review and his colleagues conducted a study to follow the patterns of changes of thyroid hormonal level during pregnancy and it was found that it is of great importance to assess carefully the references ranges of normal for this phase of life (Shahmohamadi *et al*., 2008). On the base of latter studies it can be argued that during pregnancy the women should have been cared for lipid disorders to prevent the possible adverse effects lipid alterations. One other matter which should evaluated before going into a dramatic series of test among hypothyroid patients is the urinary iodine concentration measurements. We have carried out a survey of urinary iodine concentration in our region and we found that about 15.7% of the sample population in our study were iodine deficient and should be assessed for goiter prevalence, such population might have been checked for dyslipidemia, (Mansourian *et al*., 2007), because there are various reports indicating the dyslipidemia among subjects with hypothyroidism. There also reports of lipid disorder among sub-clinical hypothyroidism as well as overt hypothyroidism in sub-clinical and hypothyroidism, the main dyslipidemia is due to hypercholesterolemia, In this scenario, hypercholesterolemia, mainly elevated by increased level of low density lipoprotein (Lithell *et al*., 1981; Nikkila and Kekki, 1973; Hazzard and Bierman, 1972; Arem *et al*., 1995; De Bruin *et al*., 1993; Pazos *et al*., 1995; O'Brien *et al*., 1993; Muls *et al*., 1984; Agdeppa *et al*., 1979). Lipid peroxidation in the serum of hypothyroid patients patients were studied by author of this study and his colleagues and it has been found that hypothyroidism enhance lipid peroxidation with subsequent free radical production, which lead to tissue damages. As it was mentioned above in hypothyroidism serum lipid levels are elevated and therefore the precursor for production of free radicals are available, a matter which should have been taken seriously (Marjani *et al*., 2008).

SUB-CLINICAL HYPOTHYROIDISM AND LIPID ALTERATION

Sub clinical hypothyroidism which is called mild hypothyroidism is condition where the thyroid gland produce normal amount of thyroxin and tri iodothyronine, but thyroid stimulating hormone slightly elevated, from the upper limit of normal range (7-10 mU L^{-1}). This status of thyroid hormone usually presented at older age and is more common among women (Mansourian *et al*., 2008). This type of thyroid disorders, usually are not observed among younger subjects (Tunbridge *et al*., 1985; Danese *et al*., 2000).

This type of thyroid disorder although is not commonly occurred, but its incidence higher than hyperthyroidism. Sub-clinical hypothyroidism case finding is easy task compared to the sub-clinical hyperthyroidism. As it is imply from the definition of sub-clinical hypothyroidism, subjects with such thyroid disorder do not show particularly symptom of overt hypothyroidism and the patient specifically do not show a clinical picture representing thyroid hormone deficiency.

This form of hypothyroidism usually is diagnosed on the thyroid function test in the medical diagnostic laboratories. The sub-clinical patients inhibit elevated serum Thyroid Stimulating Hormone (TSH), while at the same time thyroxin (T4) and tri iodothyronine (T3) may remain within normal range (Danese *et al*., 2000; Samuels, 1998). The upper limit of TSH concentration varies according to some studies and therefore the level at which laboratory introduces a subject with sub-clinical hypothyroidism many differ by different definition of upper limit of reference intervals for TSH serum concentration. In some study subjects with TSH concentration up to 10 mu L^{-1} and normal thyroid

hormone of T4 and T3 considered to be sub-clinically hypothyroidism (Cooper, 2001; Topliss and Eastman, 2004). In other study the TSH upper limit for the definition of sub-clinical hypothyroidism was considered about 7 mu L^{-1} (Kanaya *et al*., 2002). It seems very important to finalize the cut-off point for the definition of elevated TSH before considering a patient for sub-clinical hypothyroidism disorder, because, in this type of thyroid disorder it is the laboratory thyroid hormone results which can be a base for the clinician to follow up the patient for thyroid disorder.

This review article conducted a study on the serum lipid level alteration in sub clinical hypothyroid patients in northern Iran. Which was carried out on the data base of Danesh Medical Diagnostic Laboratory in Gorgan, northern Iran and found there is a correlation of dyslipidemia of total cholesterol and low density lipoprotein-cholesterol among sub-clinical hypothyroidism even with TSH upper limit of normal about 6 mu L^{-1} (Mansourian *et al*., 2008).

The sub-clinical patients in our study were those subject which their upper limit of TSH level was considered to be 6.4 mU L^{-1} which very similar to study of biracial population (Kanaya *et al*., 2002). The upper limit of TSH many has been a concept of studies, with conflicting results. In one study even suggested the patients with TSH level of more than 2 mu L^{-1} was to be considered a risk factor for subsequent hypothyroidism, although the upper limit of reference intervals should be kept about 0.4-5 mu L^{-1} (Baloch *et al*., 2003).

As whole although there are not a universally agreed border line at what upper limit of TSH reference rang, a subject has to be considered as sub-clinically hypothyroidism, but on the bases of many articles existed in the literature, when the TSH concentration elevated to more than upper limit of normal range with subsequent dyslipidemia, at that point the individual can be further considered for sub-clinical hypothyroidism. Therefore according to what was mentioned above the TSH upper limit normal of normal can be considered as base line for identifying the sub-clinical hypothyroidism patient and due to this definition, the degree of sub-clinically hypothyroidism can be varied in various parts of the world due to the definition of reference range intervals and upper limit of normal in one society and the laboratory kit manufacturer of TSH and it depends to the TSH upper limit border line which an individual can be diagnosed as sub-clinically hypothyroidism. Age, gender and ethnicity are other factors which related to the higher incidence of sub-clinical hypothyroidism (Hollowell *et al*., 2002; Canaris *et al*., 2000).

The author in separate study in northern Iran found that the women are at higher risk of sub-clinical hypothyroidism and it is more common in older age (Mansourian *et al*., 2008).

The other risk factor involved in prevalence of sub-clinical hypothyroidism is the thyroid autoimmunity (Baskin *et al*., 2002; Vanderpump *et al*., 1996; Singer *et al*., 1995).

LIPID PROFILE IN SUB-CLINICAL HYPOTHYROIDISM

It is universally accepted that overt hypothyroidism associated with elevation of serum lipid profile and total cholesterol. Particularly low density lipoprotein-cholesterol (Galesnu *et al*., 2004; Vala, 2001; Elder *et al*., 1990; Staub *et al*., 1992; O'Brien *et al*., 1993; Caraccio *et al*., 2002). The reason why sub-clinical hypothyroidism also should be a matter for further investigation, it is due to dyslipidemia which is associated with this type of thyroid disorder with nearly the same pattern of dyslipidemia, but still there are a lot of conterersial arguments about whether sub-clinical hypothyroidism constantly and universally associated with lipid disorder. Some report argued (Danese *et al*., 1996; Roti *et al*., 1993), that the sub-clinical hypothyroidism associated with dyslipidemia of increased concentration of total cholesterol and particularly LDL-cholesterol (Miura *et al*., 1994; Kung *et al*., 1995; Yildirimkaya *et al*., 1996; Efstathiadou *et al*., 2001; Luboshitzky *et al*., 2002; Caraccio *et al*., 2002), but there are also some other investigation, which they do not support the latter findings (Althaus *et al*., 1988; Caron *et al*., 1990; Bonger *et al*., 1993; Meier *et al*., 2001).

Few studies which concentrated on large cross-sectional investigation, reported that there was not any significant differences among total cholesterol or LDL-cholesterol between individuals with sub-clinical hypothyroidism and healthy subjects (Tunbridge *et al*., 1977; Parle *et al*., 1992; Geul *et al*., 1993; Lindemann *et al*., 1999; Pirich *et al*., 2000), on the other hand some cross-sectional studies reported elevation of total cholesterol and low density lipoprotein cholesterol (LDL-c) among sub-clinical hypothyroid patient, there are also studies, that reported even total cholesterol of female subjects with sub-clinical hypothyroidism was even lower than euthyroid women (Jung *et al*., 2003; Hak *et al*., 2000), but this is type of report is very rare and can not been taken seriously and the author of this review article also already reported that the lipid profile in women with sub-clinical hypothyroid elevated, compared to euthyroid females (Mansourian *et al*., 2008).

There are also some report indicating in addition to total cholesterol and LDL-cholesterol lipoprotein (a) concentration is also increased (Kung *et al*., 1995).

Other study on the state of lipoprotein reported apolipoprotein (b) and lipoprotein (a) increased in sub-clinical hypothyroid subjects with no significant alteration of triglycerides and high density lipoprotein cholesterol but with significant increase of total cholesterol and low density lipoprotein (Efstathiadou *et al*., 2001).

In another study on the state of lipid profile alterations in sub-clinical hypothyroidism, it was concluded that in sub-clinical hypothyroidism, serum cholesterol and triglycerides concentration were increased also the patients with this type of thyroid disorder inhibited the higher ratios of total cholesterol/HDL and LDL/HDL, this latter study indicated that Apo lipoprotein (b) is also increased on the same patients (Cabral *et al*., 2004).

As whole although overt hypothyroidism is frequently related with lipid disorder and it is universally agreed and it is well documented in the literatures, but dyslipidemia among sub-clinical hypothyroidism are not fully and comprehensively agreed on, but thoroughly literatures review in this present study it is indicated that in particular state of sub-clinical hypothyroidism, when the TSH level exceed about (7-10 mU L^{-1}) significant elevation in total cholesterol and low density lipoprotein cholesterol are occurred, some other studies even suggested that Patients with elevated cholesterol should examined further for thyroid function assessments (Duntas, 2002; Cooper, 1998; Helfand and Redfern, 1998).

ADVERSE CONSEQUENCE OF DYSLIPIDEMIA IN SUB-CLINICAL HYPOTHYROIDISM

Overt hypothyroidism believed to play an important role in the development of arthrosclerosis, which is enhanced by the presence of hypercholesterolemia, which is the consequence of thyroid hormone deficiency with ultimate reduction in the activity of lipoprotein lipase (Galesnu *et al*., 2004; Vala, 2001).

It is not absolutely indicated whether, the sub-clinical hypothyroidism is also correlated with cardiovascular disease. There are some reports indicating that the intensity of sub-clinical hypothyroidism at some point enhance the cardiovascular abnormality with subsequent arthrosclerosis due to dyslipidmia (Hak *et al*., 2000; Tunbridge *et al*., 1977; Lindeman *et al*., 2003; Kahaly, 2000).

It is not also clearly well documented whether levothyroxine therapy has shown to have some effect for the treatment of arthrosclerosis and dyslipidemia in sub-clinical hypothyroid subjects. The studies in this area are contradictory. There are some report in favor of thyroxin administration to treat dyslipidemia with consequence of cardiovascular disease prevention (Caraccio *et al*., 2002; Milionis *et al*., 2003; Ayala *et al*., 2000). But On the other hand various studies concluded hormone therapy do not lead to overall improvement of dyslipidemia and its related risk factor in sub-clinical hypothyroid subjects. It is uncertain what would be the consequence of untreated subjects and there is untreated sub-clinical hypothyroid subjects always encountering the cardiovascular failure. There are argument in favor of treating the sub-clinically hypothyroid patients with ultimate improvement in dyslipidemia (Canaris *et al*., 2000; Cooper *et al*., 1984; Muls *et al*., 1984), but on the other hand other studies are not supporting the latter findings and arguing that thyroxin therapy do not improve the patient conditions (Bemben *et al*., 1994; Lindemann *et al*., 1999; Zulewski *et al*., 1997).

CONCLUSIONS

The main points of conclusion derived from the present study are as follow:

- Sub-clinical hypothyroid patients have elevated thyroid stimulating hormone (TSH) with normal thyroxine (T4) and triiodothyronine (T3) levels associated with hypercholesterolemia and elevated low density lipoprotein cholesterol
- Although, the border line of upper limit of normal differ in various studies and at one point the investigator advised the TSH upper limit of normal should be lowered to as 2.5 mU L^{-1}, but such low limit is generally unacceptable and TSH upper limit of about (7-10 mU L^{-1}) is considered as acceptable upper limit of border line range and patients more than latter TSH concentration should be defined as sub-clinical hypothyroid subjects
- The clinical manifestations of patients with sub-clinical hypothyroidism clinically are not diagnosed by the physician and it is the laboratory upper limit of normal rang for TSH which ultimately recognizes a patient with sub-clinical hypothyroidism
- It seems necessary that subjects with laboratory report of hypercholesterolemia should be also further examined and tested for serum thyroid hormones measurements and particularly the evaluation of thyroid stimulating hormone (TSH) should be reassessed carefully

- Although, there are tremendous recommendations in favor of hormonal replacement therapy in sub-clinical hypothyroidism to correct dyslipidmia, there are also some reports which are against thyroxine therapy in sub-clinically hypothyroid patients

REFERENCES

Agdeppa, D., C. Macaron,T. Mallik and N.D. Schnuda, 1979. Plasma high density Lipoprotein cholesterol concentration in thyroid disease. J. Clin. Endocrinol. Metab., 49: 726-729.

Althaus, B.U., J.J. Staub, A.L. Ryff-DeLeche, A. Oberhansli and H. Staheline, 1998. B.LDL/HDL-changes in subclinical hypothyroidism: Possiblerisk factors for coronary heart disease. Clin. Endocrinol., 28: 157-163.

Arem, R., D.A. Escalante, N. Arem, J.D. Morrisett and W. Patsch, 1995. Effect of l-thyroxine therapy on lipoprotein fractions in overt and subclinical hypothyroidism with special reference to lipoprotein(a). Metabolism, 44: 1559-1563.

Ayala, A.R., M.D. Danese and P.W. Ladenson, 2000. When to treat mild hypothyroidism. Endocrinol. Metab. Clin. North Am., 29: 399-415.

Baloch, Z., P. Carayon, B. Conte-Devolx, L.M. Demers and U. Feldt-Rasmussen *et al*., 2003. Laboratory medicine practice guidelines: Laboratory support for the diagnosis and monitoring of thyroid disease. Thyroid, 13: 3-126.

Baskin, H.G., R.H. Cobin, D.S. Duick, H. Gharib, M.M. Kaplan and R.L. Segal, 2002. American Association of Clinical Endocrinologist medical guidelines for the evaluation and treatment of hyperthyroidism and hyperthyroidism. Endor. Pract., 8: 457-469.

Bastenie, P.A., L. Vanhaelst and P. Neve, 1967. Coronary-artery disease in hypothyroidism. Lancet, 290: 1221-1222.

Bemben, D.A., R.M. Hamm, L. Morgan, P. Winn, A. Davis and E. Barton, 1994. Thyroid disease in the elderly, part 2: Predictability of subclinical hypothyroidism. J. Fam. Pract., 38: 583-588.

Bonger, U., H.R. Arntz, H. Peters and H. Schleusener, 1993. Subclinical hypothyroidism and hyperlipidemia: Indiscriminate 206 thyroxine treatment not justified. Acta Endocrinol., 28: 202-206.

Cabral, M.D., A.J.L. Costa, M. Santos and M. Vaisman, 2004. Lipid profile alterations in subclinical hypothyroidism: The endocrinologist. Endocrinologist, 14: 121-125.

Canaris, G.J., N.R. Manowitz, G. Mayor and E.C. Ridgway, 2000. The colorado thyroid disease prevalence study. Arch. Intern. Med., 160: 526-534.

Caraccio, N., E. Ferrannini and F. Monzani, 2002. Lipoprotein profile in subclinical hypothyroidism: Response to levothyrosine replacement, a randomized placebo-controlled study. J. Clin. Endocrinol. Metab., 87: 1538-1553.

Caron, P., C. Calazel, H.J. Parra, M. Hoff and J.P. Louvet, 1990. Decreased HDL cholesterol in subclinical hypothyroidism: The effortof L-thyroxine therapy. Clin. Endocrinol., 33: 519-523.

Cooper, D.S., R. Halpern, L.C. Wood, A.A. Levin and E.C.L. Ridgway, 1984. Thyroxine therapy in subclincal hypothyroidism: A double-blind, placebo-controlled trial. Ann. Intern. Med., 101: 18-24.

Cooper, D.S., 1998. Subclinical thyroid disease: A clinician's perspective. Ann. Intern. Med., 129: 135-138.

Cooper, D.S., 2001. Subclinical hypothyroidiam. N. Engl. J. Wed., 345: 260-265.

Danese, M.D., N.R. Powe, C.T. Sawin and P.W. Ladenson-Jama, 1996. Screening for mild thyroid failure at the periodic examination: A decision and cost-effectiveness analysis. Am. Med. Assoc., 276: 285-292.

Danese, M.D., P.W. Landenson, C.L. Meinert and N.R. Powe, 2000. Effect of thyroxine therapy on serum lipoprotrin in patients with mild thyroid failure: A quantitative review of literature. J. Clin. Endocrinal. Metab., 85: 2993-3001.

De Bruin, T.W., H. van Barlingen, M. van Linde-Sibenius Trip, A.R. van Vuurst de Vries, M.J. Akveld and D.W. Erkelens, 1993. Lipoprotein(a). and apolipoprotein B plasma concentration in hypothyroid euthyroid and hyperthyroid subjects. J. Ciln. Endocrinol. Metatab., 76: 121-126.

Duntas, L.H., 2002. Thyroid disease and lipids. Thyroid, 12: 287-293.

Efstathiadou, Z., S. Bitsis, H.J. Milionis, A. Kukuvitis, E. Bairaktari, M. Elisaf and A. Tsatsoulis, 2001. Lipid profile in subclinical hypothyroidism: is L-thyroxine substitution beneficial? Eur. J. Endocrinol., 145: 705-710.

Elder, J., A. McLelland. D.S. O'Reilly, C.J. Packard, J.J. Series and J. Shepherd, 1990. The relationship between serum cholesterol and serum thyrotropin, thyroxine and tri-iodothyronine concentrations in suspected hypothyroidism. Ann. Clin. Biochem., 27: 110-113.

Flower, P.S. and J. Swale, 1967. Premyxoedema and coronary-artery disease. Lancet, 1: 1077-1079.

Galesnu, C., N. Lisnic, R. Teslaru, L. Apostu and E. Zbranca, 2004. Lipid profile in a group of hypothyroid patients vs treated hypothyroid patients. Rev. Med. Chir. Soc. Med. Nat. Lasi., 108: 554-560.

Geul, K.W., I.L. van Sluisveld, D.E. Grobbee, R. Docter and A.M. de Bruyn *et al*., 1993. The importance of thyroid microsomal antibodies in the development of elevated serum TSH in middle-aged women: Associations with serum lipids. Clin. Endoorinol., 39: 275-280.

Hak, A.E., H.A. Pols and T.J. Visaer, 2000. Subclinical hypothyroidism is an independent risk fartor for arthreosclerosis and myocardial infarction in elderly women: The rotterdam study. Ann. Intern. Med., 132: 270-278.

Hazzard, W.R. and E.L. Bierman, 1972. Aggravation of broad-disease (type 3 hyperlipoproteinemia) by hypothyroidism. Arch. Intern. Med., 130: 822-828.

Helfand, M. and C.C. Redfern, 1998. Screening for thyroid disease: An update. Ann. Intern. Med., 129: 144-158.

Hollowell, J.G., N.W. Staehling, W.D. Flanders, W.H. Hannon, E.W. Gunter, C.A. Spencer and L.E. Braverman, 2002. Serum TSH, T4 and thyroid autoantibody in United States population (1985-1994): National Health and Nutrition Examination Survey (NHANESM). J. Clin. Endocrinol. Metab., 87: 489-499.

Jung, C.H., K.C. Sung, H.S.S. Shin, F.J. Rhee and W.Y. Lee *et al*., 2003. Thyroid dysfunction and their relation to cardiovascular risk factors such as lipid profile, hsCRP and waist hip ratio in Korea. Korean J. Intern. Med., 18: 146-153.

Kahaly, G.J., 2000. Cardiovaseular and atherogenic aspects of subclinical hypothyroidism. Thyroid, 10: 665-679.

Kanaya, A.M., F. Harris, S. Volpato, E.J. Pérez-Stable, T. Harris and D.C. Bauer, 2002. Association between thyroid dysfunction and total cholesterol level in an older biracial population: the health, aging and body composition study population: The health aging and body composition study. Arch. Intern. Med., 162: 773-779.

Kung, A.W.C., R.W.C. Pang E.D. Janus, 1995. Elevated serum lipoprotein(a) in subclinical hypothyroidism. Clin. Endocrinol., 43: 445-449.

Lindemann, R.D., D.S. Srhade, A. la Rur, L.J. Romero and H.C. Iiang *et al*., 1999. Subclinical hypothyroidism in a biethnic, urban community. J. Am. Geriatr. Soc., 47: 703-709.

Lindeman, R.D., L.J. Romero, D.S. Schade, S. Wayne, R.N. Baumgartner and P.J. Garry, 2003. Impact of subclinical hypothyroidism on serum total homocysteine concentrations, the prevalence of coronary heart disease (CHD) and CHD risk factors in the New Mexico Elder Health Survey. Thyroid, 13: 595-600.

Lithell, H., G. Boberg, K. Hellsing, S. Ljunghall, G. Lundqvist, B. Vessby and L. Wide, 1981. Serum lipoprotein and apolipoprotein concentrations and tissue lipoprotein-lipase activity in overt and subclinical hypothyroidism: The effect of substitution therapy. Eur. J. Clin. Invest., 11: 3-10.

Luboshitzky, R., A. Aviv. P. Herer and L. Lavie, 2002. Risk factors for cardiovascular disease in women with subclinical hypothyroidism. Thyroid, 12: 421-425.

Mansourian, A.R., E.O. Ghaemi, A.R. Ahmadi, A. Saifi, A.V. Moradi and S. Bakhshandeh-Nosrat, 2007. A survey of urinary iodine concentration in South-east of Caspian Sea in Northern, Iran. Pak. J. Biol. Sci., 10: 2166-2171.

Mansourian, A.R., E. Ghaemi, A.R. Ahmadi, A. Marjani, A. Saifi and S. Bakhshandehnosrat, 2008. Serumlipid level alterations in sub clinical hypothyroid patients in Gor-gan (South East of Caspian Sea), J. Chinese Clin. Med., 3: 206-210.

Mansourian, A.R., A.R. Ahmadi, H.R. Mansourian, A. Saifi, A. Marjani, G.R. Veghari and E. Ghaemi, 2010. Maternal thyroid stimulating hormone levels during the first trimester of pregnancy at the south-east of the Caspian Sea In Iran. J. Clin. Diagnostic Res., http://www.jcdr.net/article_fulltext.asp?issn=0973-709x&year=2010&month=May&volume=&issue=&page=&id=719

Marjani, A., A.R. Mansourian, E.O. Ghaemi, A. Ahmadi and V. Khori, 2008. Lipid peroxidation in the serum of hypothyroid patients(In Gorgan-South East of Caspian Sea). Asian J. Cell Biol., 3: 47-50.

Meier, C., J.J. Staub, C.B. Roth, M. Guglielmetti and M. Kunz *et al*., 2001. TSH-controlled L-thyroxine therapy reduces cholesterol levels and clinical symptoms in subclinical hypothyroidism: A double blind, placebo-controlled trial (Basel Thyroid Study). J. Clin. Endocrinol. Metab., 86: 4860-4866.

Milionis, H.J., Z. Efstathiadou, A.D. Tselepis, E.T. Bairaktari, L.D. Tsironis, A. Tsatsoulis and M.S. Elisaf, 2003. Lipoprotein (a) levels and apolipoprotein (a) isoform size in patients with subclinical hypothyroidism: Effect of treatment with levothyroxine. Thyroid, 13: 365-369.

Miura, S., M. Litaka, H. Yoshimura, S. Kitahama and N. Fukasawa *et al.*, 1994. Disturbed Lipidmetabolism in patients with subclinicalhypothyroidism: Effect of L-thyroxine therapy. Int. Med., 33: 413-417.

Muls, E., M. Rossenen, V. Blaton, E. Lesaffre, G. Lamberigts and P. de Moor, 1984. Serum lipids and apolipoproteins AI, AII and B in primary hypothyroidism before and during treatment. Eur. J. Clin. Invest., 14: 12-15.

Nikkila, E. and M. Kekki, 1973. Plasma triglyceride metabolism in thyroid disease. J. Clin. Invest., 51: 2103-2114.

O'Brien, T., S.F. Dinneen, P.C. O'Brien and P.J. Palumbo, 1993. Hyperlipidemia in patients with primary and secondary hypo-thyroidism. Mayo Clin. Proc., 68: 860-866.

Parle, J.V., J.A. Franklyn, K.W. Cross, S.R. Jones and M.C. Sheppard, 1992. Circulating lipids and minor abnormalities of thyroid function. Clin. Endocrinol., 37: 411-414.

Pazos, F., J.J. Alvarez, J. Rubies-Prat, C. Varela and M.A. Lasuncion, 1995. Long term thyroid replacement therapy and levels of lipoprotein (a) and other lipoproteins. J. Clin. Endocrinol. Metab., 80: 562-566.

Pirich, C., M. Mullner and H. Sinzinger, 2000. Prevalance and relevance of thyroid dysfunction, in 1922 cholesterol screening participants. J. Clin. Epidemiol., 53: 623-629.

Roti, E., R. Minelli, E. Gardini and L.E. Braverman, 1993. The use and misuse of thyroid hormone. Endocrine Rev., 14: 401-423.

Samuels, M.H., 1998. Subclinical thyroid disease in the elderly. Thyroid, 9: 80-80.

Shahmohamadi, F., A.R. Mansourian and H. Mansourian, 2008. Serum thyroid hormoe level in women in early pregnancy. J. Med. Sci., 8: 507-510.

Singer, P.A. D.S. Cooper. E.G. Levey, P.W. Ladenson and L.E. Braverman *et al.*, 1995. Treatment guidelines for patients with hyperthyroidism and hyperthyroidism. JAMA., 273: 808-812.

Staub, J.J., B.U. Althaus, H. Engler, A.S. Ryff and P. Trabucco *et al.*, 1992. Spectrum of subclinical and overt hypothyroidism: Effect on thyrotropin prolactin and thyroid reserve and metabolic impact on peripheral target tissues. Am. J. Med., 92: 631-642.

Topliss, D.J. and C.J. Eastman, 2004. Diagnosis and management of hyperthyroidism and hypothyroidism. Med. J. Aust., 180: 186-194.

Tunbridge, W.M., D.C. Evered, R. Hall, D. Appleton and M. Brewis *et al.*, 1977. Lipid profiles and cardiovascular disease in the Whickham area with particular reference to thyroid failure. Clin. Endocrinol. (Oxf)., 7: 495-508.

Tunbridge, W.M., D.C. Evered, R. Hall, D. Appleton and M. Brewis *et al.*, 1985. The aspectrum of thyroid disease in a community: The Whickhum survey. Clin. Endocrinol., 7: 481-483.

Vala, B.S., 2001. Endocrinology and the Heart. In: Cardioloz, Carwford, M.H. and J.P. di Marco (Eds.). 1st Edn., Mosby, London, pp: 8.4.1.

Vanderpump, M.P.J., J.A.O. Ahiquist, J.A. Franom and R..N. Clayton, 1996. Consensus statement for good practice in the management of hypothyroidism and hypothyroidism. Brit. Med. J., 313: 539-544.

Yildirimkaya, M., M. Ozata, K. Yilmaz C. Kiline, M.A. Gundogen and T. Kutluay, 1996. Lipoprotein(a)concentration in subclinical hypothyroidism before and after levo-thyroxine therapy. Endocr. J., 43: 731-736.

Zulewski, H., B. Muller, P. Exer, A.R. Miserez and J.J. Staub, 1997. Estimation of tissue hypothyroidism by a new clinical score: evaluation of patients with various grades of hypothyroidism and controls. J. Clin. Endocrinol. Metab., 82: 771-776.