

A Review on Cardiovascular Diseases Originated from Subclinical Hypothyroidism

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Abstract: Thyroid hormones play an important role on the cardiovascular systems and thyroid disorder ultimately have a profound adverse effects on myocardium and vascular functions. There are extensive reports on the role of overt thyroid dysfunction which adversely can modify the cardiovascular metabolism but even at the present of some controversial reports, the subclinical thyroid disorders are able also to manipulate cardiovascular system to some extent. The aim of this study is to review the cardiovascular disorders accompanied with subclinical hypothyroidism. It is concluded that adverse effect of thyroid malfunction on myocardium and vascular organs are through the direct role of thyroid hormone and dyslipidemia on heart muscle cells at nuclear level and vascular system, respectively. It seems many cardiovascular disorders initially would not have been occurred in the first place if the thyroid of affected person had functioned properly, therefore thyroid function tests should be one of a prior laboratory examinations in cardiovascular disorders.

Key words: Thyroid, heart, hypothyroidism

INTRODUCTION

Cardiovascular disorders are among most important diseases which in many cases eventually leading to death. There are huge reports on the heart diseases with eventual fatal outcome and there are intensive studies and efforts underway to find the causative factors (Hoyert *et al.*, 2005; Pahor *et al.*, 1999).

Among the major cause of heart failure one should pay particular attention on the role played by thyroid hormones, whether thyroid over or underproduction, in either cases the thyroid hormone of thyroxin (T_4) and triiodothyronine (T_3) in particular, are responsible for associated cardiovascular disorders originated from excess or deficiency of thyroid hormones (Klein, 1990). Although, the role of overt thyroid dysfunction on the cardiovascular systems are well established but there are also extensive investigation about the heart metabolic disorders originated from subclinical thyroid malfunction. In subclinical thyroid disorders, although, thyroid hormones T_4 and T_3 are at normal level but Thyroid Stimulating Hormone (TSH), are either suppressed or elevated in subclinical hyperthyroidism and subclinical hypothyroidism, respectively (Westerink *et al.*, 2011; Wilson and Curry Jr., 2005; Fazio *et al.*, 2004; Trbojevic, 2003; Weissel, 2001; Roffi *et al.*, 2005; Schmidt-Ott and Aschim, 2006; Dorr and Voolzke, 2005; Voolzke *et al.*, 2007; Biondi *et al.*, 2002a; Hak *et al.*, 2000; Mansourian, 2010a, b, c; Mansourian *et al.*, 2008; Mansourian, 2011a). What relay behind thyroid hormone

is protein production which is originated from this fact that either of thyroid hormones following binding to their receptor within the nucleus subsequently stimulate a specific genetic system to produce a particular protein (Dillmann, 1990; Everts *et al.*, 1996; Brent, 1994).

It seems that those protein responsible for muscle contraction known as myosin and proteins which play a role in calcium regulation through the stimulation of the activity of ATPase enzyme are part of process responsible for cardiac muscle contraction. The cardiomyocytes contraction through the gene expression of proteins responsible for myocytes modulation eventually leading to systo-diastolic contraction, within heart muscle (Dillmann, 1990; Kiss *et al.*, 1994).

There are various studies on the role of thyroid hormone on diastole phase through the activation of Ca^{++} -dependent ATPase enzyme which is responsible for the Ca^{++} -reuptake into the sarcoplasmic reticulum (Dillmann, 1990; Kiss *et al.*, 1994). There are extensive studies on the biochemical process which is played by thyroid hormone on the heart muscles and it is believed that thyroid hormone eventually activate the specific site on the Deoxy Nucleic Acid (DNA) within the nucleus and eventually a particular ribonucleic acid synthesized prior to a biosynthesis of a specific protein through the initial stimulation of particular gene type on the DNA of cardiac muscle cell (Brent, 1994). It seems that following gene stimulation of nuclear DNA and ribonucleic acid (RNA) production, the produced protein play a crucial task in the systole and diastole process within the heart and any

thyroid disorders with ultimate alteration of serum thyroid hormone level eventually modify the normal procedure of cardiac muscle by interference in above protein synthesis and eventual systole-diastole modification from healthy cardiac function (Kiss *et al.*, 1998; Ojamaa *et al.*, 1999; Mansourian, 2011b, c).

Although, the effect of thyroid hormone on cardiac muscles are through the gene modulation of heart muscle cells are well established but there are also reports that thyroid hormone may play a role without DNA and RNA interference, with possible involvement of adrenergic nervous system (Levey and Klein, 1990; Hoit *et al.*, 1997; Ojamaa *et al.*, 2000b; Mansourian, 2011a, b, c). In addition to effect of thyroid hormone on the cardiocytes of heart muscle, there are extensive reports on the role played by thyroid hormone on the heart vascular system as well (Klemperer *et al.*, 1995; Park *et al.*, 1997).

There are also many studies on the key role of thyroid hormone on the heart ischemia and other lesion (Flynn *et al.*, 2006) and the process of heart signaling and remodeling produced by thyroid hormone (Iervasi *et al.*, 2003; Morkin *et al.*, 2002; Ojamaa *et al.*, 2000a; Morkin *et al.*, 2004; Mackay and Mochly-Rosen, 1999; Novitzky *et al.*, 1991).

Due to various effect of thyroid hormone on cardiovascular system and heart diseases originated from thyroid dysfunction particularly among older population and in some physiological condition such as pregnancies, many investigations on this area of research have been carried out, to draft documented reports on how cardiovascular disorders which are among leading cause of morbidity and mortality can be affected by thyroid hormones and in which way the disorder of thyroid gland eventually modify routine procedure of cardiovascular systems. From what it was mentioned earlier, it seems that thyroid hormones are responsible for the cardiocyte contraction, the structure and well being of heart, diastole-systolic characteristics (Mitrou *et al.*, 2011; Morganti *et al.*, 2005; Lieutaud, 1999; Mansourian, 2010d, e, f; Mansourian and Ahmadi, 2010; Mansourian *et al.*, 2007).

Although, the role of overt thyroid disorder on heart metabolism have been properly documented, it seems subclinical thyroid dysfunction, also playing profound effects on cardiovascular system. Subclinical hypothyroidism most probably related to heart diastolic, systolic abnormalities with subsequent atherosclerosis, with eventual myocardium dysfunction, leading to myocardial infarction. The heart abnormalities followed by subclinical hypothyroidism can be reversed when the thyroid dysfunction treated which is a further evidence for the role of thyroid disorders on cardiovascular diseases (Hak *et al.*, 2000; Imaizumi *et al.*, 2004;

Mya and Aronow, 2003; Kvetny *et al.*, 2004; Lindeman *et al.*, 2003; Grimes and Schulz, 2002; Mansourian *et al.*, 2008; Mansourian, 2010a, c). There are also controversial findings which are in disagreement with later statement (Vozzke *et al.*, 2007; Dorr and Voolzke, 2005; Schmidt-Ott and Aschim, 2006).

The available data also contradict each other on whether sub-clinical hypothyroidism treatment particularly for older subjects eventually do any good to prevent the cardiovascular disorders. There are various reports indicating, that thyroid diseases including subclinical type are partly responsible for cardiovascular disorders among elderly population but with caution consideration (Sawin *et al.*, 1994; Walsh *et al.*, 2005; Rodondi *et al.*, 2005; Hak *et al.*, 2000; Parle *et al.*, 2001; Mitrou *et al.*, 2011; Morganti *et al.*, 2005; Mansourian *et al.*, 2007, 2008). There are also studies indicating that the subclinical type of hypothyroidism is among the most common forms of thyroid disorders, various studies around the world, universally are in agreement that the prevalence of subclinical hypothyroidism is more common among, females than males (Rosenthal *et al.*, 1987; Sawin *et al.*, 1979; Hak *et al.*, 2000; Parle *et al.*, 1991; Tunbridge *et al.*, 1977; Bagchi *et al.*, 1990; Kanaya *et al.*, 2002; Mansourian *et al.*, 2008; Mansourian, 2010a, b, c; Levy, 1991).

On the correlation of subclinical hypothyroidism and cardiovascular diseases, there are not universally agreed point of views, there are reports of agreement and disagreement on the state of subclinical hypothyroidism and its association with hypercholesterolemia and cardiovascular diseases (Chu and Crapo, 2001; Hak *et al.*, 2000; Parle *et al.*, 2001; Imaizumi *et al.*, 2004; Rodondi *et al.*, 2005; Parle *et al.*, 2001; Cappola and Ladenson, 2003; Rodondi *et al.*, 2005; Surks *et al.*, 2004; Helfand, 2004; Fried *et al.*, 1991; Mansourian, 2010a).

Subclinical hypothyroidism: Subclinical hypothyroidism is the thyroid disorders which is accompanied with normal serum level of thyroid hormone T₄ and T₃ but elevated Thyroid Stimulating Hormone (TSH) which is a pituitary hormone (Roffi *et al.*, 2005; Mansourian, 2010a; Schmidt-Ott and Aschim, 2006; Dorr and Voolzke, 2005). In practice the sub-clinical hypothyroidism considered to be the mild form of hypothyroidism and usually can be presented among some individuals of older age, particularly among women (Mitrou *et al.*, 2011; Mansourian *et al.*, 2008; Danese *et al.*, 2000; Levy, 1991; Mitrou *et al.*, 2011; Mansourian, 2010a). One of significant of such thyroid disorder arises from the fact that, the sub-clinical condition can be observed among subjects in

healthy society without any clinical syndrome (Tunbridge *et al.*, 1977; Hollowell *et al.*, 2002) but can be diagnosed on routine clinical setting which should be accompanied by serum hormone measurements by laboratory examination, on condition of elevated thyroid stimulating hormone which is released by the pituitary gland but normal range of thyroid hormones in which the subclinical hypothyroidism is confirmed (Danese *et al.*, 2000; Biondi and Cooper, 2008; Tunbridge *et al.*, 1977; Hollowell *et al.*, 2002; Mansourian, 2010a; Mansourian *et al.*, 2008).

Sub-clinical hypothyroid and cardiovascular function:

Before entering into discussion about the adverse consequence of sub-clinical hypothyroidism one should postulate the Thyroid Stimulating Hormone (TSH) upper threshold in the designated laboratory setting. There are various reports in this area of medical examination, ranging from 7 and 10 $\mu\text{U L}^{-1}$ with normal serum level of thyroid hormone of thyroxine and triiodothyronine (Duntas, 2001; Surks *et al.*, 2004; Mansourian and Ahmadi, 2010).

Gender and age are related factors which should be considered in evaluating and defining this sort of thyroid dysfunction and therefore they are important in defining the type of thyroid disorders (Parle *et al.*, 1991; Boelaert and Franklyn, 2005). There are various disorders and clinical manifestation associated with sub-clinical thyroid disorders, including dyslipidemia and cardiovascular diseases (Biondi and Cooper, 2008; Duntas and Wartofsky, 2007; Li *et al.*, 2010; Mansourian, 2010a). There are various reports on the scale of risk factors with eventual undesired outcome, of subclinical thyroid disorders with subsequent fatal scenario (Dorr and Voolzke, 2005; Rodondi *et al.*, 2006; Voolzke *et al.*, 2007; Mansourian, 2010a, b, c).

Although, there are many studies in favor of treating the subclinical thyroid disorders, there are also contradictory suggestion in this regards and the eventual picture in this area of research is not clear cut, procedure (Voolzke *et al.*, 2007; Surks *et al.*, 2004; Mansourian *et al.*, 2007), but the importance of subclinical hypothyroidism and its role on cardiovascular dysfunction and related factor such as serum lipid alteration and blood coagulation pathways and other disorder leading to over all heart dysfunction are debatable topics in the vast amount of literatures (Boelaert and Franklyn, 2005; Biondi and Klein, 2004; Biondi *et al.*, 2002a; Sawin, 2002; Sawin *et al.*, 1994; Dorr and Voolzke, 2005; Rodondi *et al.*, 2006).

There are studies indicated that, the extend that cardiovascular get involved depends on the severity of subclinical hypothyroidism which can be evaluated from the upper limit range of thyroid stimulating

hormone in one individual (Walsh *et al.*, 2005; Duntas, 2001; Surks *et al.*, 2004; Karmisholt *et al.*, 2008; Andersen *et al.*, 2003; Vigario *et al.*, 2009; McMillan *et al.*, 2008).

Autoimmunity to thyroid gland is the other determining risk factors of how subclinical hypothyroidism is emerged, therefore the assessment of thyroid enzyme autoantibody, should be carried out simultaneously with thyroid stimulating hormones and thyroxine and triiodothyronine to have a clear picture of how the subclinical hypothyroidism will eventually behave, on the disruption of cardiovascular system and the normal physiological trend of human metabolism (Vigario *et al.*, 2009; McMillan *et al.*, 2008; Mansourian, 2010f). It is a long history since it was realized that dyslipidemia of thyroid disorder, eventually contributed to cardiovascular diseases. The serum lipid profile and the cholesterol in particular was the main index in evaluating the status of thyroid, when the available laboratory techniques were not sensitive enough to measure serum thyroid hormones level. The powerful laboratory methods now a day are practiced in assessment of serum thyroid hormones but on labeling an individual with either forms of hypothyroidism the reference range for each thyroid hormone in various region should be defined on that particular location to protect those healthy subjects with with possible undocumented upper limit for thyroid stimulating hormone, thyroxine and triiodothyronine (Mansourian *et al.*, 2010a; Shahmohammadi *et al.*, 2008; Biondi and Cooper, 2008; Tunbridge *et al.*, 1977; Hollowell *et al.*, 2002; Canaris *et al.*, 2000; Duntas and Wartofsky, 2007; Li *et al.*, 2010; Mansourian *et al.*, 2010b).

Dyslipidemia in subclinical hypothyroidism: There are extensive studies indicating that lipid alteration can be one of eventual risk factors accompanied with thyroid disorder including subclinical hypothyroidism. The low density lipoprotein-cholesterol, particularly is a cholesterol index accompanied with cardiovascular diseases (Hak *et al.*, 2000; Duntas, 2002; Duntas *et al.*, 2002; Mansourian, 2010a, b; Mansourian *et al.*, 2008). There are also reports on the adverse role of atherosclerosis on coagulation pathway and related vasodilation which is stimulated by subclinical hypothyroidism due to its dyslipemic condition (Muller *et al.*, 2001; Lekakis *et al.*, 1997).

There are some confirmatory reports on the role of dyslipidemia and its atherogenesis behavior, by prescribing levothyroxine and subsequent treatment of cardiovascular disorder but this strategy is not universally accepted (Danese *et al.*, 2000; Biondi *et al.*, 2002b; Chu and Crapo, 2001; McDermott and Ridgway, 2001).

It is widely reported that subclinical hypothyroidism is associated with cardio-vascular disease which most probably brought about by alteration of cholesterol and its low density lipoproteins (Mansourian, 2010a, b, c; Mansourian *et al.*, 2008; Boelaert and Franklyn, 2005; Biondi and Klein, 2004; Biondi *et al.*, 2002b; Sawin, 2002; Sawin *et al.*, 1994; Dorr and Voolzke, 2005; Rodondi *et al.*, 2006; Biondi *et al.*, 2002a; Brenta *et al.*, 2003; Taddei *et al.*, 2003; Taddei *et al.*, 2003; Cikim *et al.*, 2004). Additionally, there are many investigation resulted in the crucial role which is reported for thyroid hormone in many other metabolic disorders interestingly the subclinical hypothyroidism probably still can be accountable for similar metabolic disorders/ including part of nervous system contributed to the muscle cells (Petersen *et al.*, 1990).

Although, it seems that serum, triglyceride level increased within the state of hypothyroidism but it is most probable that it is the hypercholesterolemia and particularly the low density lipoprotein derivatives which is responsible for all the adverse effect and particularly the cardiovascular disorders (Petersen *et al.*, 1990; Hall *et al.*, 1993; Franklyn *et al.*, 1998; Mansourian *et al.*, 2008).

It is widely accepted that the sequence event which are responsible for total cholesterol and low density lipoprotein elevation originated from this fact that the receptor generation for low density protein is reduced, most probably due to thyroid disorder which is responsible for the expression of low density lipoprotein receptor with subsequent cardiovascular disease (Scarabottolo *et al.*, 1986; Duntas, 2002).

Various studies indicates that heart disease, related to subclinical hypothyroidism can eventually reversed following putting the heart patient on thyroid replacement therapy which further indicate that, low density lipoprotein receptor gene expression may stimulated after thyroxin prescribed for the subclinical hypothyroidism patients (Biondi and Cooper, 2008; Duntas and Wartofsky, 2007; Razvi *et al.*, 2007; Monzani *et al.*, 2004) although again, this area of research data are not universally homogenized and disagreements among the researchers are existed in how and in which pathway the treatment should be carried out (Biondi and Cooper, 2008; Palmieri *et al.*, 2004; Biondi, 2008; Caraccio *et al.*, 2002; Milionis *et al.*, 2003; Ayala *et al.*, 2000; Cooper *et al.*, 1984; Muls *et al.*, 1984; Bemben *et al.*, 1994; Lindeman *et al.*, 1999; Zulewski *et al.*, 1997; Mansourian, 2010a).

How thyroid hormones affect the heart function: There are many reports on the role of integration of thyroid

hormone integration with cardiovascular systems metabolism and various clinical signs and symptoms of thyroid disorder might stimulate the heart function to some extent. The heart metabolic alternation may happen in either of hyper and hypothyroidism which have been reported in many investigation (Klein, 1990; Dillmann, 1990; Polikar *et al.*, 1993; Klemperer *et al.*, 1996; Mansourian, 2010b, c, e). Thyroid hormones and in particular triiodothyronin (T_3) which mainly can be produced through diiodination of thyroxin (T_4) in the peripheral tissues, can have profound metabolic effect on heart function. The heart metabolism such as rate, optimal productivity and vascular system found to have a direct correlation with overall activity of thyroid hormones (Klein, 1990; Dillmann, 1990; Polikar *et al.*, 1993; Park *et al.*, 1997; Ojamaa *et al.*, 1996; Klemperer *et al.*, 1995), in those subjects with hypothyroidism elevated cardiac rate and resulted tachycardia most often seen among effected patients of thyroid disorders (Biondi *et al.*, 1994; Klein and Ojamaa, 1998a; Graettinger *et al.*, 1959; Mintz *et al.*, 1991; Biondi *et al.*, 1994; Polikar *et al.*, 1993; Cacciatori *et al.*, 1996; Nordyke *et al.*, 1988).

The metabolic alteration of cardiovascular function following hypothyroidism are reverse of what manifested in thyroid over activity but with less severity. The marked clinical manifestation observed in hypothyroid state is bradycardia, with subsequent sequential event (Klein, 1990; Wieshammer *et al.*, 1989; Ojamaa *et al.*, 1996; Klein and Ojamma, 2001; Crowley *et al.*, 1997). There are many reports indicating that following thyroid hormone prescription the clinical manifestation of hypothyroid patients, most notably ranging from bradycardia, hypertension, pulse pressure, cardiac potential are corrected (Klein, 1990; Wieshammer *et al.*, 1989; Ladenson *et al.*, 1992; Klein and Ojamma, 2001; Ojamaa *et al.*, 1999; Crowley *et al.*, 1997; Fredlund and Olsson, 1983).

The reason behind the efficacy of thyroid hormones and particularly T_3 , is through gene expressions of cardiac channels, elevation of oxygen uptake by heart muscle and reducing vascular resistance pathways (Klemperer *et al.*, 1996; Bengel *et al.*, 2000; Park *et al.*, 1997; Ojamaa *et al.*, 1996; Ladenson *et al.*, 1992; Ojamaa *et al.*, 1999).

The manifested cardiovascular and coronary heart disease seen in subclinical hypothyroidism may be related to elevated serum cholesterol and other heart hemodynamic state which can be reversed possibly through thyroid hormones therapy (Bengel *et al.*, 2000; Keating *et al.*, 1961; Biondi *et al.*, 1999).

There are reports also that not only thyroid disorder can modulate cardiovascular system but also heart diseases can adversely effect the thyroid functions. It is

reported that heart malfunction can reduce serum thyroid hormones level and T₃ in particular which can be a topic for further investigations in the heart and thyroid inter-relation metabolism (Franklyn *et al.*, 1984; Hamilton *et al.*, 1990; Klein and Ojamaa, 1998b; Holland *et al.*, 1991; Bettendorf *et al.*, 1997; Saatvedt and Lindberg, 1996; Klemperer *et al.*, 1995).

CONCLUSION

There are various undisputable data originating from many investigations on the unique role play by thyroid hormones on the myocardium and vascular systems leading to the disruption of cardiovascular disorders.

There are extensive investigations stating that clinical manifestation related with cardiovascular disorders, originated from thyroid dysfunction including subclinical hypothyroidism.

On the bases of many investigations which are presented in this review, the modification of thyroid function and alteration of thyroid hormone metabolism, may eventually lead to cardiovascular diseases.

Although, there are extensive data on the role of subclinical hypothyroidism but simultaneously there are also various other reports on the contrary, in which indicating that subclinical hypothyroidism is not a major risk factor for heart and vascular dysfunction.

Dyslipidemia and the elevation of serum cholesterol in particular are the major evidence of subclinical hypothyroidism with eventual myocardium and vascular dysfunction.

There are various reports indicating that it seems subclinical hypothyroidism manifest itself with higher prevalence among elderly and particularly among women and on the bases of this findings, the cardiovascular disease can be more commonly seen among elderly women.

Various studies indicate that the treatment of subclinical hypothyroidism by thyroid hormones replacement therapy eventually prevent related cardiovascular diseases, also there are some reports on the contrary but those reports supporting the hormone replacement therapy to prevent cardiovascular abnormality are in stronger position, in their arguments.

Many cardiovascular disorders would not have been clinically manifested itself in the first place if the thyroid function initially was working properly, therefore laboratory investigation of thyroid assessments is recommended simultaneously with any other examinations for cardiovascular patients to prevent possible misdiagnosis.

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