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A Review on Hyperthyroidism: Thyrotoxicosis under Surveillance

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Abstract: Thyrotoxicosis exhibit collective clinical manifestation, caused by excessive serum thyroid hormones particularly thyroxine. The clinical signs and symptoms included general alteration of metabolic process leading to weight loss fatigue and weakness and some specific disorders such as cardiovascular, neuromuscular reproductive gastrointestinal dermatological and bone disorders. The diagnosis of thyrotoxicosis rely on the thyroid function test carried out by the laboratory serum measurement of thyroxine, triiodothyronine and thyroid stimulating hormones accompanied by other para-medical examinations suggested by clinicians and endocrinologist. In thyrotoxicosis serum level of thyroid hormones and thyroxine in particular elevated accompanied by pituitary thyroid stimulating hormone suppression reaching to undetectable level in severe thyrotoxicosis. Among the most common cause of thyrotoxicosis are, thyroid autoimmunity diseases thyroid toxic, adenoma toxic nodular and multinodular hyperthyroidism. The main aim behind this review is to explore the clinical manifestation, the causative factors, diagnosis, metabolic disorder occur due to thyrotoxicosis.

Key words: Hyperthyroidism, thyrotoxicosis, thyroxine, clinical manifestation, laboratory diagnosis

HYPERTHYROIDISM

Thyroid hormones consist of tetraiodothyronine or generally known as thyroxine (T4) and triiodothyronine (T3), which are the two vital hormone produced by the thyroid gland to regulate metabolism as whole.

In other words the T4 and T3 are responsible for well-being of all metabolic process within the body and are curtail if the various organs within the human body are supposed to work normally, (Dratman and Grodon, 1996) the pituitary hormone, Thyroid Stimulating Hormone (TSH) is a hormone which can stimulate the thyroid hormone by binding to its receptor on the thyroid gland, activating the enzyme adenylate cyclase, on the cell membrane and subsequently synthesizing cyclic AMP in the thyroid gland (Parma *et al.*, 1995). The cyclic AMP through a cascade reactions activating various enzymes with ultimate aim of T4 and T3 production. In healthy subjects there is relation between the serum level of TSH, T4 and T3, if according to the medical laboratory results the latter hormones remain within the normal reference interval the subjects are at euthyroid state and remain healthy (Tolls *et al.*, 1978).

In euthyroid subjects metabolic process remain under the control of healthy thyroid, on conditions the thyroid itself become sick and interathyroid problems leading to either under or over-production of T4 and T3 which is a starting point of for adverse effect of thyroid malfunctions. The side-effect of hypothyroidism in human

have already been reviewed (Mansourian, 2010a, b; Mansourian *et al.*, 2008).

Thyroid gland also has to adapt itself to various metabolic process and it can alter its activity due to the body demand for example the thyroid hormone production changes during a normal pregnancy (Shahmohanmudi *et al.*, 2008; Mansourian, 2010c; Mansourian *et al.*, 2010a, b). As growing fetus and pregnant women require extra thyroid hormone due to existed state. There is an acceptable relation between TSH and T4, T3 serum concentration levels (Mansourian *et al.*, 2008; Mansourian, 2010a) on condition where T4 and T3 concentration reduced TSH concentration raised due to lack of negative feed back when for any reason the production of T4 and T3 elevated the TSH concentration begin to fall and as the scenario of hyperthyroidism further progressed the TSH serum level reach to that level which can not be detected by available laboratory techniques.

Hyperthyroidism therefore is a definition for over production of either T4 or T3 or both (Emerson and Utiger, 1972).

As thyroid hormones concentrations are elevated the adverse effect of T4 and T3. causing the unique presentation of a clinical manifestation within the affected patients best known as thyrotoxicosis. It should be mentioned that hyperthyroidism and thyrotoxicosis are not similar medical term, thyrotoxicosis is a definition given to the clinical signs, symptoms and side effects of either T4, T3 elevation but hyperthyroidism is a definition

given when thyroid gland produce excessive amount of T4 and T3. In other words hyperthyroidism is an stimulator of clinical manifestation well known as thyrotoxicosis (Emrich *et al.*, 1993; Studer *et al.*, 1989; Studer and Ramelli, 1982).

Thyrotoxicosis not only caused by hyperthyroidism but also by drugs based on thyroxine structure such as levothyroxine or even the thyroxine tablet given to treat hypothyroidism (Bogazzi *et al.*, 1999; Mariotti *et al.*, 1982; Kinney *et al.*, 1988; Hedberg *et al.*, 1987; Mansourian, 2010b) but on condition of misdiagnosis or elevated dosage there is a possibility in which hypothyroid patients enter into a clinical presentation which is caused by extra thyroxine based drugs (Vitug and Goldman, 1985; Orgiazzi and Mornex, 1990; Mansourian, 2010a, b).

Thyroid hormones are responsible for the regulation of every single metabolic process within the human body at cellular levels thyroid hormones at normal concentration control the speed of biochemical and physiological reaction at a rate the body requires. As the production of T4 and T3 begin to rise at an abnormal level subsequently the rate of metabolism accelerated with ultimate of some clinical manifestation among all are :abnormality in nervous system anxiety hand tremors irritability heart abnormality due to faster heart beat, excess perspiration sleep disorder skin and hair abnormality intolerance to heat and muscular weakness. The main feature of affected persons is significant weight loss in spit of a acceptable reasonable appetite women menstrual cycle also are another disorder.

In this type of thyroid malfunction, contrary to hypothyroidism, which was accompanied with elevated cholesterol in hyperthyroidism the serum cholesterol level is normal or even lowered (Kim *et al.*, 2009; Mansourian, 2010b; Mansourian *et al.*, 2008; McDermott and Ridgway, 1998).

THYROTOXICOSIS

As it was mentioned in earlier section the term thyrotoxicosis refer to the clinical manifestation caused by abnormally high concentration of thyroid hormones either T4 or T3 and both. Thyrotoxicosis affect both men and women also the incidence of thyrotoxicosis higher among women (Mariotti and Pinchera, 1990; Marjani *et al.*, 2008; Kim *et al.*, 2009) It has been reported that women are 10 times susceptible to afflict thyrotoxicosis than men (Berglund *et al.*, 1996; Karger and Fuhrer, 2008; Cooper, 2003; Streetman and Khanderia, 2003; Schneeberg, 1983; Studer *et al.*, 1989).

Although, thyrotoxicosis is causing by excess amount of thyroid hormones but there are some reasons for the serum elevation of thyroid hormones of T4, T3 . It seems that Graves disease is the most important thyroid disorder ending with thyrotoxicosis (Mansourian, 2010d)

in such disease men and women of all age have the chance of obtaining the disorder with higher incidence among women. Toxic nodular goiter is another cause on the epidemiology of thyrotoxicosis, the incidence of this type is shown to have a direct correlation with age. It seems genetically background, excess iodine within the dietary regiments, exogenous thyroid hormones used as a therapeutic treatment and eventual over treatment may end up with unwanted thyrotoxicosis in addition to multinodular goiter and single toxic adenoma and overtreatment with thyroid hormones as medicines also, causing the thyrotoxicosis (Persani *et al.*, 2000; Kinney *et al.*, 1988), thyroiditis, thyrotoxicosis factita and elevated production of TSH hormone either by pituitary or ectopic production, which are responsible of the synthesis of T4 and T3 are also among the causative factors of inducing thyrotoxicosis . The clinical symptoms of thyrotoxicosis was already explained in hypothyroidism section which include, intolerance to heat weight loss in spite of good appetite, increasing heart palpitation anxiety tremor muscle weakness and fatigues perspiration, reproductive disorder and menstrual abnormality among women (Nayak and Burman, 2006; Maji, 2006; Shimatsu *et al.*, 1999).

THE GENETIC BASIS OF THYROTOXICOSIS

Thyroid hormones of T4 and T3 are produced when TSH binds to its receptor on the thyroid gland with ultimate activation of adenylyate cyclase the enzyme directly responsible for all of the process leading to T4 and T3 (Sergi *et al.*, 1993; Sanno *et al.*, 2001; Smallridge and Smith, 1983), production This process are included form iodine uptake, iodine oxidation, thyroglobulin iodination, coupling reaction of moniodothyronine and diiodothyronins of thyroglobulin ionodiated derivatives to produce T4 and T3. There are some reports indicating toxic adenoma within the thyroid gland genetically triggered by the alteration of proteins located on the cell surface of thyroid gland adjusted to TSH receptor. Also there are also some study indicating that the TSH receptor also can be mutated and due to this mutation all resulting in the enhanced activity of adenylyate cyclase which is an enzyme directly responsible for the production of cyclic adenosine monophosphate (cAMP). The cAMP trigger all the metabolic pathway leading to the synthesis of T4 and T3 (Yovos *et al.*, 1981; Tonachera *et al.*, 2000; Takeshita *et al.*, 1995; Trulzsch *et al.*, 2001; Polak *et al.*, 1991; Persani *et al.*, 2000; Parma *et al.*, 1995, 1997; Duperz *et al.*, 1994; Derwahl *et al.*, 1996; Deleu *et al.*, 2000; Kopp *et al.*, 1995; Lax *et al.*, 1997; Ouchimoura *et al.*, 1982; Nogueira *et al.*, 1999).

The over activation of adenylyate cyclase with subsequent elevation of c-AMP concentration within the

thyroid gland, the production thyroid hormone increased to the level which is considered to be toxic for human metabolism. As it was mentioned the thyrotoxicosis is not similar definition with hyperthyroidism, but as the thyroid hormones concentration begin to rise and it continue to be elevated for while enough to alter the normal pathway of physiological chemistry of human cell and tissues to the level which clinical manifestation of elevated thyroid hormone begin to show itself (Goldstein and Hart, 1983; Parma *et al.*, 1997; Takeshita *et al.*, 1995; Lax *et al.*, 1997; Pinducciu *et al.*, 1998; Holtzapfel *et al.*, 2002).

It has to be mentioned here that although the main concept of toxic adenoma leading to the thyrotoxicosis is genetically based on the gene mutation of proteins involved within the cell membrane of thyroid gland and the TSH receptor, but these findings are not universally similar which have been reported by other studies (Pinducciu *et al.*, 1998; Derwahl, 1996; Parma *et al.*, 1997; Takeshita *et al.*, 1995; Lax *et al.*, 1997; Pinducciu *et al.*, 1998; Nogueira *et al.*, 1999; Trulzsch *et al.*, 2001; Persani *et al.*, 2000).

As it was already stated the other reason for thyrotoxicosis is multinodular or nodular goiter also conducted through a genetically process (Guters *et al.*, 1998; Derwahl and Stunder, 2001).

In contrary to many documented reports on the role played by iodine in hypothyroidism (Mansourian *et al.*, 2007) but there are also some reports that iodine depletion in human eventually may lead to the genetical process which ultimately causing thyroid hyperactivity (Krohn and Paschke, 2002).

On the basis of many reports it should be emphasized that not all the nodules within the thyroid gland supposed to be active and toxic and the probability of nodular toxic incidence can be differed among various population and sub-population and as it was mentioned earlier, this disorder is more common among female than males and also some reports indicating the incidence of nodular is higher at older age compared to younger subjects (Hamburger, 1980; Thomas and Croom, 1987; Bransom *et al.*, 1979).

ASSISTANCE OF MEDICAL DIGNOSTIC LABORATORY FINDINGS

Laboratory can help by detemination of TSH, T4 and T3 or condition of overt thyrotoxicosis either T4 and T3 concentration one of them elevated while TSH serum concentration reduced significantly, the exceptions are when thyroid hormones are elevated accompanied with elevated TSH hormone due to ectopic production of TSH

or pituitary overproduction of TSH due to adenoma within the pituitary gland and finally the adoption of pituitary thyroid axis's resulting from hormonal resistance syndrome. The common form of thyrotoxicosis is T4 thyrotoxicosis although there are rare cases of T3 thyrotoxicosis accompanied with elevated and suppressed, T3 and TSH hormones, respectively.

At present time laboratory measurement of TSH using high profile sensitive TSH technique is a valuable method in identifying and hyperactive thyroid, serum TSH level suppressed to the level which with normal laboratory technique can not be detected. The TSH measurement should be accompanied by simultaneous measurement of T4 and T3 to have a clear picture of a hyperactive thyroid gland in addition to the laboratory diagnosis Nuclear medicine is given a grate assistance in diagnosis and locating the exact site of mudles within the thyroid gland. In overt thyrotoxicosis on clinical examination by clinician and endocrinogist a single sensitive TSH measurement can clearly identify the active thyroid, but simultaneous assessment of T4 and T3 should be accompanied due to the importance of patient proper management. In drawing absolute clinical picture other para- medical examinations particularly thyroid imaging evaluations also should have been taken under careful consideration (Miyakawa *et al.*, 1992; Mariotti *et al.*, 1982; Faber and Gallo, 1994; Bogazzi *et al.*, 1999; Ratchliffe *et al.*, 1986; Franklyn *et al.*, 1994; Horst *et al.*, 1967; Hamburger, 1975; Ross *et al.*, 1984).

VARIOUS TYPES OF DISORDER LEADING TO THYROTOXICOSIS

Toxic adenoma: This cause of thyrotoxicosis was mainly the bases of the text in this review. It is the overproduction thyroid gland due to the autonomous synthesis of thyroid hormones due to a toxic nudles within the thyroid gland (Gorman *et al.*, 1978; Eyre-Brooke and Talbot, 1982). It is a genetically base thyroid disorder due to genetic abnormality in the TSH receptor of thyroid gland (Benoit *et al.*, 1980; Yovos *et al.*, 1981; Bransom *et al.*, 1979; Holtzapfel *et al.*, 1997; Parma *et al.*, 1997; Takeshita *et al.*, 1995) Thyrotoxicosis.

NODULAR AND MULTINODULAR LEADING TO THYROTOXICOSIS

The enlargement of thyroid gland due to any stimulation which eventually lead to hyperplasia of thyroid gland are the causative factors of nodular and multinodular occurrence in the thyroid glad (Taylor, 1953; Becker and Cornette, 1971; Dige-Petersen and Hummer,

1977; Mariotti *et al.*, 1986; Thomas and Croom, 1987) other factor are goitrogenous substances and congenital abnormalities of thyroid gland try to compensate for thyroid hormones by enlargement due to hyperplasia of thyroid gland (Marine, 1924) which initially can be a non-toxic goiter supported by laboratory thyroid function tests of TSH T4 and T3, some experimental study also have been carried out in this area of research (Hamburger, 1980; Peter *et al.*, 1985; Becker and Cornett, 1971; Hedberg *et al.*, 1987).

There are also some studies indicating on the role played by nodular and multinodular goiter on clinical presentation of thyrotoxicosis initiated by toxic goiter. In addition there are many studies based on the over activating nodular and multinodular lesion within thyroid gland which genetically related multinodular (Al-Khafaji *et al.*, 2005; Peter *et al.*, 1985; Kopp *et al.*, 1994; Berghout *et al.*, 1990; Holzapfel *et al.*, 1997).

THYROTICOSIS AND IODINE

Iodine deficiency is one of stimulator factor of nodular and multinodular presentation within the thyroid gland. the mechanism behind this observation coming through the thyroid hyperplasia due to iodine deficiency with reduced synthesis of T4 and T3 (Mansourian *et al.*, 2007).

The disruption of iodine uptake by thyroid gland or iodine deficiency eventually lead to overproduction of TSH by pituitary to compensate the thyroid hormone synthesis through follicle production probably created by excess TSH (Davies and Platzer, 1986; Chanson *et al.*, 1993; Connolly *et al.*, 1970; Holzapfel *et al.*, 1997) eventually leading to the enlargement of thyroid gland medically defined as goiter. There are well documented studies on the status of urinary iodine and direct correlation existed between the thyroid urinary iodine concentration and the thyroid function tests. In other words it can be explained that the low iodine concentration is an indicative of hypothyroidism (Stewart and Vidor, 1976; Stanbury *et al.*, 1988; Leger *et al.*, 1984; Martin *et al.*, 1993; Hintze *et al.*, 1999; Hershman *et al.*, 1988; Derwahl and Studer, 2001; Gabril *et al.*, 1999; Holzapfel *et al.*, 1997; Mansourian *et al.*, 2010a, b), there are also other studies which report on the physiological changes happen during pregnancy with thyroid function tests and iodine requirement alterations. Pregnancy accompanied by extra demand for thyroid hormones and dietary iodine. In fact thyroid hormone demands vary according to the different physiological condition as whole and also at some stage during the normal healthy life, from

childhood through adolescence to adulthood can be fluctuated depending to stage of life (Many *et al.*, 1992; Neumann *et al.*, 1999; Mansourian, 2010c; Mansourian *et al.*, 2007, 2010a).

Thyroid disorder of mainly enlargement of thyroid gland itself with overproduction thyroxine may happen during normal pregnancy which can be due to elevated concentration of Human Chorionic Gonadotrophin (HCG) a hormone normally produced by placenta during pregnancy (Glinoe and Lemone, 1992; Carayon *et al.*, 1980; Cole and Kardana, 1992; Davies *et al.*, 1979; Hoermann *et al.*, 1994) this latter hormone are particularly exist at higher concentration during early phase of pregnancy and in some cases pregnant women physiological condition accompanied with nausea and vomiting and in sever condition the pregnant women requires hospitalization, with all of the unexpected adverse effects. The findings in this area universally reported word wide (Kirkegaard and Faber, 1998; Bogazzi *et al.*, 2001; Gabril *et al.*, 1999; Mansourian 2010c; Shahmohammadi *et al.*, 2008; Mansourian *et al.*, 2010a, b).

There are studies indicating there are some type of hyperthyroidism during pregnancy and some of physiological changes observed during pregnancy such as nausea and vomiting which take place by elevating HCG and subsequent stimulation of TSH, but some other studies believe this thyroid hyperactivity is a necessary requirement of pregnancy (Smits *et al.*, 2002; Rodien *et al.*, 1998; Hershman *et al.*, 1988; Hoermann *et al.*, 1988; Mansourian *et al.*, 2010a, b; Mansourian, 2010c; Shahmohammadi *et al.*, 2008).

CANCER

Although, thyrotoxicosis due carcinoma is a rare condition but it may be seen in metastatic thyroid cancer thyroidal carcinoma mostly is presented among women and therefore it is predominantly sex related disease (Wahner *et al.*, 1966; Anderson *et al.*, 1979; Belfiore *et al.*, 1990; Fujimoto *et al.*, 1972; Kasagi *et al.*, 1994; Mazzaferri, 1990; Orgiazzi *et al.*, 1974; Nakashima *et al.*, 1981; Paul and Sisson, 1990; Sandler *et al.*, 1998; Steffensen and Aunsholt, 1994).

MAIN CAUSES OF THYROTICOSIS AT A GLANCE

In general the main causes of thyrotoxicosis can be summarized as: (1) toxic nodular and multinodular goiter (Symth *et al.*, 1988; Studer and Ramelli, 1982) (2): the administration of thyroid hormones of either of thyroxine

or triiodothyronine which are the main causes of thyrotoxicosis and the rare causes: (3) the administration of iodine by drug based iodide and particularly healthy dietary enriched with iodine and possibly through drug administration (Thorne *et al.*, 1999; Mazson *et al.*, 1984; Mansourian, 2010a; Matrino *et al.*, 1994), (4) Neonatal thyrotoxicosis due to physiological modulation in some pregnancies (5) over production of TSH due to some pituitary adenoma and the failure of negative feed-back existed between thyroid hormones and pituitary. It means by elevation T4 and T3 there should be a negative feed-back by thyroid hormones on pituitary not to secrete extra TSH (Benoit *et al.*, 1980; Hill *et al.*, 1982) but it seems there are some resistance in this metabolic pathway and subsequently TSH secreted by pituitary with even extra concentration of T4 and T3 leading to the hyperthyroidism resulting the thyrotoxicosis (Lamberg *et al.*, 1983; Gershengorn and Weintraub, 1975; Gesundheit *et al.*, 1989); (6) metastatic thyroid cancer. (7) Among other rare cases of thyrotoxicosis are choriocarcinoma and hydatidiform mole, struma ovarii, polycystic fibrous dysplasia (Dowling *et al.*, 1960; Ciccarelli *et al.*, 2004; Anderson *et al.*, 1979; Bransom *et al.*, 1979; Becjer *et al.*, 1963; Hershman and Higgin, 1971; Kenimer *et al.*, 1975; Kempers *et al.*, 1970; Kock *et al.*, 1966; Galton, 1968; Misra *et al.*, 2002; Simkin *et al.*, 1999; Zalel *et al.*, 2000).

DYSLIPIDEMIA AND PROTEIN METABOLISM IN THYROTOXICOSIS

There are well documented reports that hypothyroidism has meaningful correlation with hypothyroidism (Franklyn *et al.*, 1993; O'Brien *et al.*, 1997; Liberopoulos and Elisat, 2002; Mansourian *et al.*, 2008), but other studies indicated that the level of total cholesterol and LDL-cholesterol are lower among hyperthyroid patients compared with hypothyroid and healthy subjects (Kim *et al.*, 2009; De Bruin *et al.*, 1993; Tzotzas *et al.*, 2000; Mansourian *et al.*, 2008; Mansourian, 2010b).

In fact the reports indicated that serum thyroxine concentration has an inverse relation with lipid profiles, but on the other hand it has been found there is a positive correlation between the level TSH and lipid parameters (Kim *et al.*, 2009; Lee *et al.*, 2004; Kutty *et al.*, 1978).

It seems on the bases above findings it can be concluded that in hyperthyroidism and resulting thyrotoxicosis the level of cholesterol, triglyceride and low density lipoprotein cholesterol are all lower when compared with hypothyroid patients and healthy

subjects. It seems that protein and lipid metabolism interchangeably related in thyrotoxicosis. Thyroid hormones affect protein synthesis with subsequent alteration in lipid metabolism. This phenomenon happens through effect on the low density lipoprotein receptor gene which is located on the cell membrane. In the case of thyrotoxicosis gene expression is modulated by thyroid hormones (Shapiro *et al.*, 1997; Biondi *et al.*, 1993).

CONCLUSIONS

- Thyrotoxicosis is resulted from a hyperthyroidism with subsequent biochemical and physiological changes which is caused by excess thyroid hormones of T4 and T3 within human blood circulation
- Thyrotoxicosis mainly is occurred due to excess thyroxine (T4) but T3 thyrotoxicosis due to elevated triiodothyronin (T3) do happen but with very low incidence
- Thyrotoxicosis happens due to toxic adenoma, nodular and multinodular goiter, acute thyroiditis postpartum thyroiditis, autoimmunity related thyroiditis including Hashimoto's thyroiditis, thyrotoxicosis factitia thyrotoxicosis originated from pregnancy and trophoblastic thyrotoxicosis due to a tumor producing thyroid stimulating hormone (TSH)
- Thyrotoxicosis due to pituitary resistance to thyroid hormone T4 and T3 thyrotoxicosis accompanied by excessive production of TSH by the pituitary adenoma
- Thyrotoxicosis due to congenital hyperthyroidism thyrotoxicosis which occurs by thyroid carcinoma and finally thyrotoxicosis due to struma ovarii. It seems from all the causes of thyrotoxicosis of thyroid gland
- Autoimmunity hyperthyroidism, toxic nodular and multinodular thyroiditis, factitious hyperthyroidism occurred by thyroxine (T4) and triiodothyronin (T3) administration are the major and common form of thyrotoxicosis and excessive iodination of dietary regimen or iodide based drugs, neonate hyperthyroidism and overproduction of TSH due to pituitary adenoma and pituitary biochemical resistance by T4 and T3, thyroid cancer, struma ovarii choriocarcinoma are considered to be among rare causes of thyrotoxicosis
- Laboratory examinations of thyroxine (T4) triiodothyronine (T3) and Thyroid Stimulating Hormones (TSH) are important laboratory measurement to diagnose thyrotoxicosis. In

thyrotoxicosis serum thyroxine level is increased although T3 can also be raised with serum TSH suppression and at some time serum TSH level suppressed to the level which can not be detected by laboratory procedures, the laboratory measurement and other paramedical examinations obviously are requested by Clinicians and Endocrinologist following careful clinical examinations of thyroid gland

- Although, there are strong inverse correlation between lipid profile and hypothyroidism but the serum total cholesterol and low density lipoproteins cholesterol (LDL-C) are lower in patients with hyperthyroidism and even healthy subjects
- It seems thyroid hormones modulating the protein synthesis through the alteration of lipoprotein gene of LDL-C receptor on the cell of biological membrane with ultimate enhancing lipoprotein metabolic pathway
- The main clinical manifestation accompanied with thyrotoxicosis are usually affect most organs. In general weight loss fatigue and weakness hyperactivity, irritability depression heat intolerance, sweating and in particular cardiovascular neuromuscular, reproductive, gastrointestinal, dermatological and finally bone disorders are among organ failure in thyrotoxicosis

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