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A Literature Review on the Adverse Effects of Hypothyroidism on Kidney Function

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Abstract: Thyroid produce two important hormone of thyroxine or tetraidothyronine (T4) and triidothyronine (T3), which are involved in whole aspect of metabolism. T4 and T3 play vital role in all biochemical function, growth and development in human body. The basic metabolic pathways in kidney and every organ in human controlled by these hormones. T4 and T3 are involved in kidney function in health and diseases condition therefore the pathophysiology of kidney can be directly influenced and regulated by thyroid hormones. Kidney growth, haemodynamic, blood circulation, tubular, electrolyte balance and glomerular filtration rate (GFR) are among such crucial process. Hypothyroidism which accompanied with reduced thyroid hormone production adversely affect the renal functions, development and eventually leading to reduced weight, kidney vascular disorders, electrolyte, tubular transport imbalances, lower filtration rate and other adverse consequences of hypothyroidism. On other hand kidney diseases can also disrupt the thyroid function metabolism resulting in the subsequent hypothyroidism. It is an interesting subject in how thyroid and kidney in health and diseases closely interacted. For the ideal clinical follow up of either of thyroid and renal diseases the two organs should be simultaneously examined for a proper patient management. Close correlation of thyroid and kidney clinical teams are essential to check the cross reactions and adverse interactions which might be produced between these two vital organs to avoid misdiagnosis either of thyroid or kidney abnormalities.

Key words: Thyroid hormones, hypothyroidism, kidney disorder, renal function test

INTRODUCTION

Thyroid gland produce the two most important hormones tetraidothyronine or thyroxine (T4) and triidothyronine (T3), although the latter hormone can be synthesized in peripheral tissue by diiodination of thyroxine (Mansourian, 2010a). It means that T3 is produced from T4 outside the thyroid gland by diiodinase enzyme. The thyroid hormones play a vital role in various metabolic pathways within the human biochemical reactions and any alteration in the amount of serum thyroid hormones, directly cause metabolic disorders, in various organs and modify the normal metabolic pathways of various organs, including kidney (Mansourian, 2010b-d). Thyroid hormones are crucially required for the proper functioning and normal physiological growth of kidney therefore thyroid disorders have a direct adverse affects on the kidney behavior. It is well documented that thyroid hormones directly modify kidney structure and functions and the relationship between hypothyroidism and kidney is the main topic behind this review. There are extensive studies in this regards, indicating that hypothyroidism play a key adverse role in the kidney structural and functional statues, with ultimate reduction in kidney mass and the alteration in of kidney following, clinical manifestation of hypothyroidism are remarkable of these adverse effects including the reduction of blood circulation and decrease in the filtration rate of kidney (Shin *et al*., 2012; Bradley *et al*., 1972, 1974; Katz *et al*., 1975; Michael *et al*., 1972).

The metabolism of sodium and other electrolyte in the kidney is decreased, (Michael *et al*., 1972; Katz and Lindheimer, 1973; Asmah *et al*., 1997; Hauger-Klene *et al*., 1977). In general every aspect of the renal function is affected in some way during hypothyroidism. The other main function of kidney such as renal concentration and dilution abilities of renal function also worsen to the some extend (Ponsoye *et al*., 2012; Holmes and Discala, 1970; Michael *et al*., 1976; DiScala and Kinney, 1971; Acker *et al*., 2002). Myexdema can not only adversely affect the renal function, but, it seems hypothyroidism also play a negative key role on the structure of kidney, with ultimate reduction in the kidney mass (Bradley *et al*., 1974; Katz *et al*., 1975; Fregly and Hood, 1959; Scammell and Fregly, 1981; Mansourian, 2010a-d; Waring and Moonie, 2011). Also, there are various studies on the role of hypothyroidism on renal function, but the structural studies on the kidney function following the decrease in proximal and distal tubules length in hypothyroidism are also among such modification of kidney structure which is well document (Bradley *et al*., 1972, 1974; Mooraki *et al*., 2003; Singh *et al*., 2006; Nikolaeva and Pimenov, 2002).

It can be postulated that such structural changes of kidney, may eventually lead toward to some renal abnormalities including, the reduction of plasma sodium, over hydration, metabolic acidosis, deceased concentration of renine with ultimate disruption of electrolyte imbalance. It seems hypothyroidism play an important role in the physio-biochemical function of kidney, but thyroid hormone play an important role on the kidney formation during fetus life as well (Satav and Katyare, 1982; Katyare *et al*., 2007; Kim *et al*., 2012; Hataya *et al*., 2012; DiScala and Kinney, 1971; Fregly and Hood, 1959; Scammell and Fregly, 1981; Lo *et al*., 1981; Garg *et al*., 1982).

The main concept behind this review article is to elaborate how hypothyroidism can adversely modify and alter the kidney structure and physiological function resulting in the renal failure.

THYROID HORMONES

Tetraidothyronine (T4) and Triidothyronine (T3) are the hormones produced by thyroid glands, beside a healthy thyroid, iodine is an essential element for the biosynthesis of these hormones. Thyroglobuline is an macro protein within the thyroid containing about 5000 amino acids with 150-200 tyrosyle residues (Mansourian *et al*., 2007, 2011). Thyroid hormones are biosynthesized through iodination of tyrosyl residues to produce monoidothyrosyle (MIT) and diidotyrosyle (DIT). Following coupling process of one MIT and DIT, in one hand and two DIT, T3 and T4 are synthesized respectively. Thyroid stimulating hormone (TSH) which is biosynthesized in pituitary is responsible for every single biochemical process within thyroid gland including T4 and T3 production (Samuels *et al*., 1990; Adriaanse *et al*., 1993; Mansourian *et al*., 2010a). These hormone are play key role in basic metabolic rate and whole metabolism in general (Shahmohammdi *et al*., 2008; Mansourian *et al*., 2008; Mansourian *et al*., 2010b; Mansourian and Ahmadi, 2010; Mansourian, 2010d; Mansourian, 2011c).

The biosynthesis of T4 and T3 occur within thyroid gland and thyroid stimulating hormone (TSH) which is released by pituitary is the sole hormone for initiating the T4 and T3 production. The biosynthesis of thyroid hormone is controlled and regulated according to the body requirement by hypothalamus-pituitary axis.

Failure to that result in thyroid disorders including hypothyroidism, a condition which is discussed below (Larsen, 1982; Wiersinga, 2004; Evered *et al*., 1973; Martino *et al*., 2000; Tunbridge *et al*., 1977a; Ford and Carter, 1990; Vanderpump *et al*., 1995; Bigos *et al*., 1978; Evered *et al*., 1973; Mansourian, 2010e; Mansourian, 2011a, b).

HYPOTHYROIDISM

Hypothyroidism is a thyroid disorder accompanied by low serum T4 and T3 or T4 mainly as result of negative feed-back inhibition mentioned above. As result TSH is biosynthesized in larger amount exceeding its higher range of normal value, which is a key biochemical marker for clinical and laboratory assessment of hypothyroidism (Larsen, 1982; Wiersinga, 2004; Evered *et al*., 1973; Martino *et al*., 2000; Tunbridge *et al*., 1977b; Katz and Lindheimer, 1977; Ford and Carter, 1990; Vanderpump *et al*., 1995; Bigos *et al*., 1978; Nilsson *et al*., 1976; Parle *et al*., 1992; Bonger *et al*., 1993; Samuels *et al*., 1990; Adriaanse *et al*., 1993).

The extra TSH concentration is due to metabolic requirement of T4 and T3 which is done by the extra amount of TSH (Hall and Scanlon, 1979; Ord, 1978; Evered *et al*., 1973; Watanakunakorn *et al*., 1965; Gull, 1874).

Although the compensatory thyroid hormone produced in this way but in expenses of thyroid enlargement which is occurs by the extra amount of TSH. This later physiological function can be continued and eventually leading to hypothyroidism, with subsequent catastrophic scenario including renal dysfunction. Clinically the laboratory measurement of TSH, T4 and T3 are the key indices in evaluating thyroid status. Overt hypothyroidism defined on condition of elevated TSH and the reduction of either T4 and T3 or both, but in sub-clinical type of hypothyroidism which only serum level TSH is elevated and can be presented without the overt clinical manifestation of thyroid disorder (Nilsson *et al*., 1976; Parle *et al*., 1992; Bonger *et al*., 1993; Samuels *et al*., 1990; Adriaanse *et al*., 1993; Mansourian, 2010d; Mansourian *et al*., 2010a).

On condition of undiagnosed or misdiagnosed of the thyroid disorder the status of hypothyroidism reach to the level which many normal metabolic pathways are disrupted and a clinical condition namely known as myxedema is manifested.

Kidney disorder is among one of the adverse effect of myxedema with life treating condition, due to hyponathremia cardiovascular and cerebral disorders (Diekman *et al*., 2011; Asmah *et al*., 1997; Hauger-Klene *et al*., 1977; Wiersinga, 2012; Pearson, 2012; Shin *et al*., 2012; Ponsoye *et al*., 2012; Vissenberg *et al*., 2012; Rhee *et al*., 2012; Mansourian, 2012a, b;

Larsen, 1982; Samuels *et al*., 1990; Parle *et al*., 1991; Zulewski *et al*., 1997; Oliveira *et al*., 2001; Persani *et al*., 2000; Mansourian *et al*., 2008).

KIDNEY FUNCTION

Blood filtration is the key responsibilities of kidney and glomerular filtration rate is term given to the rate of fluid refined by the kidney. Glomerular filtration rate is definition which is given to this later biochemical function of kidney and any alteration from a its normal value is an indicative of kidney diseases (Caravaca *et al*., 2002; Kreisman and Hennessey, 1999; Prowle *et al*., 2012). Serum creatinine concentration and its clearance from blood circulation by kidney is applied to assess the Glomerular Filtration Rate (GFR) which correspond to the amount of blood filtered by kidney (Schiffl and Lang, 2012; Kacso *et al*., 1999; Fricker *et al*., 2003; Caravaca *et al*., 2002). Glomerular Filtration Rate (GFR) is valuable index for the state of kidney function and the severity occurred to the renal function. Blood urea is also other biochemical test which elaborates the statues of renal function tests and it is usually measured simultaneously with serum filtrate properly (Prowle *et al*., 2012; Schiffl and Lang, 2012; Acker *et al*., 2002).

Other paramedical radiological, imaging techniques also can be helpful aids besides hematology study of suspected patients on condition of untreated kidney the anatomical, histological and laboratory index of either biochemical or hematological are all affected seriously. Renal function in acute kidney failure is accompanied with low urine and electrolyte disruption (Richter-Rodier *et al*., 2012). Chronic renal failure results from varieties of kidney abnormalities which might not be corrected properly duly, the chronic renal failure may be occurred as result of non-kidney diseases such a hypothyroidism (Prowle *et al*., 2012).

In renal dysfunction the affected person kidney is not able to behave normally among such a disabilities insufficient blood refinery which is known namely as glomerular filtration. On such condition the body waste substances are not removed properly through urine process and they will be remained within human body and blood circulation. If condition remains undiagnosed it will be accompanied by other metabolic diseases including thyroid hormone physiological and biochemical disorders (Diekman *et al*., 2001; Baajafer *et al*., 1999; Kreisman and Hennessey, 1999; Diekman *et al*., 2001).

INTERRELATED METABOLISM OF THYROID AND KIDNEY

There are well documented study on the interrelated metabolism between thyroid and kidney. Thyroid gland and the hormones produced by thyroid are vital for the growth of kidney. Thyroid hormone are not required for the development of kidney, but water and electrolyte balance and regulation are occur through the physiological function of thyroid hormones on kidney (Feinstein *et al*., 1982; Kaptein *et al*., 1982, 1984; Kaptein, 1986; Satav and Katyare, 1982).

Also, thyroid hormones affect on the kidney eventually dictate the growth of kidney and play key role in water and electrolyte metabolism of renal function but the kidney as well is critical for the thyroid hormones metabolism (Shin *et al*., 2012; Ponsoye *et al*., 2012; Rhee *et al*., 2012; Hataya *et al*., 2012; Katz *et al*., 1975).

It seems eventually kidney is involved in key pathways of the T4 and T3 metabolism and any condition with eventual renal dysfunction may lead to thyroid disorder and this abnormality can be manifested through thyroid hormones production and metabolism. Thyroid hormone excretion by the kidney can be considered as in how the kidney affect on thyroid hormones with eventual interfering with thyroid gland metabolism and it is believed that kidney deviation from its normal function, eventually adversely affect thyroid gland and lead to thyroid malfunction (Katz *et al*., 1975; Kaptein *et al*., 1988).

Thyroid disorders adversely influence the kidney structure and function. (Braunlich, 1984; Kaptein *et al*., 1982; Li Bok *et al*., 1982; Vargas *et al*., 2006). Water and electrolyte balance of various tissues of human body is partly regulated by the T4 and T3 and as far as the metabolism of thyroid hormones themselves are attenuated by renal function and interestingly the kidney is considered to be one of the vital tissues for thyroid hormone as well. The latter metabolic pathways clearly indicate how importantly thyroid and kidney are interrelated and any alteration of thyroid gland lead to the change of thyroid hormones level modify the renal function and any disorder in renal function can retard the normal pathway of thyroid hormone. In either of previous cases human metabolism adversely affected and it will be accompanied by serious adverse effects resulting into various metabolic disorders (Katz *et al*., 1975; Capasso *et al*., 1999; Den Hollander *et al*., 2005; Kaptein, 1986).

In direct pin pointing to the role of hypothyroidism it is well established that, reduction of thyroid hormone

which is due to the ultimate effect of hypothyroidism eventually lead do disruption of human body water homeostasis, which is the direct effect of lowering glomerular filtration capacity which occur due to hypothyroidism (Liu *et al*., 1990; Emmanouel *et al*., 1974). Hypothyroidism have a direct effect on the status of electrolyte metabolism within the kidney, in such way that Na^+/K^+ ATPase pump activity is decreased leading to the reduction of Na^+ -reabsorption. There are studies indicating that thyroid hormones reduction also can have direct affect on the lowering renine biosynthesis in kidney. Renine is an enzyme catalyzing the production of angiotnsin-I from angiotensinogen which itself is released from liver into blood circulation. Angiotnsin-II in lung is produced from angiotensin-I catalyzed by angiotensin converting enzyme. Angiotensin-II is the main factor in stimulating adrenal cortex to produce aldestron,,the key hormone in the reabsorption of Na+ from the kidney (Vaamonde *et al*., 1975; Segarra *et al*., 2006; Asmah *et al*., 1997). The hypothyroidism also associated with reduction in the calcium reabsorption. Thyroid hormone reduction also is adversely interfere with potassium metabolism within the kidney proximal tubules (Li Bok *et al*., 1982; Katz and Lindheimer, 1973; Capasso *et al*., 1985; Holmes and Discala, 1970; Michael *et al*., 1972; Lin and Tang, 1977; Vaamonde *et al*., 1975; McCaffrey and Quamme, 1984; Asmah *et al*., 1997). T4 and T3 play and important roles in the renal function, structure and hypothyroidism eventually show its adverse effect on kidney by interrupting its normal physiological function. Elevation of blood creatinine concentration, which happen following kidney disorder is among the key laboratory findings in renal disorder.

Glomerular filtration rate is also adversely modified (Mahjoub *et al*., 1991; Malyszko *et al*., 2006; Marchant *et al*., 1993; Kaptein *et al*., 1991; Yegin *et al*., 1997). Water and electrolyte imbalances are also among other modified kidney physiological changes which subsequently causing to reduce the excretion of water from the kidney. The latter renal abnormalities may eventually return to the normal and routine pathway on condition of healthy thyroid function. Overt hypothyroidism is responsible for kidney disorder but there are some studies indicating that even sub-clinical hypothyroidism can also interfere with renal function test. The elevation of creatinine concentration, which is key laboratory test in the diagnosing of kidney disorders can be accompanied with sub-clinical hypothyroidism. (Montenegro *et al*., 1996; Kreisman and Hennessey, 1999; Acker *et al*., 2002; Verhelst *et al*., 1997).

HOW THYROID HORMONES MANIPULATE KIDNEY GROWTH

The mechanism behind thyroid hormones action relay on the penetration of hormone receptor complex within nucleus of target cells and by doing that the particular gene is activated and the biosynthesis of related protein is initiated. This later phenomenon is applied to kidney as well, therefore T4 and T3 are the biological activator of kidney growth and in case of hypothyroidism this physiological function is retarded and kidney weight begin to shrink (Kumar *et al*., 2009; Baum *et al*., 1998; Ikeda *et al*., 2001; Katz *et al*., 1975). There are extensive reports indicating renal dysfunction in hypothyroidism even during fetal and early infancy. Various key proteins which are responsible for the translocation process are physiologically active due to the biochemical potentiality of thyroid hormones of T4 and particularly T3 which exhibit higher intensity which owe to its higher affinity to hormone receptor on target tissue.

Following thyroid hormones binding to the receptor the particular gene is activated on deoxyribonucleic acid and protein biosynthesis is begun to happen. Thyroid hormone receptor seems to play a key role and any modification on T4 and T3 receptors directly manipulate the entire hormone process in target tissue including kidney. Thyroid hormones receptor biochemical structures extensively studied due to its vital role in the regulation of gene expression and even future gene therapy which is on agenda in medical circle (Baxter *et al*., 2001; Mansourian, 2011a,b; Glass, 1994; Ribeiro *et al*., 1998; Apriletti *et al*., 1998; Nagy *et al*., 1997; Mangelsdorf *et al*., 1995; Baxter *et al*., 2001; Dawson and Markovich, 2002).

KIDNEY VASCULAR MODIFICATION DUE TO HYPOTHYROIDISM

Cardiovascular abnormality is the ultimate consequence of hypothyroidism and the heart output is reduced consequently (Waring *et al*., 2012; Mansourian, 2012a; Katz *et al*., 1975). The cardiovascular disorders of hypothyroidism is mainly occur due to bradycardia, lower ventricular capacity and myocardium contraction (Mansourian, 2012a, b; Crowley *et al*., 1977; Wieshammer *et al*., 1989; Diekman *et al*., 2001; Waring *et al*., 2012). Endocrine factors related to changes in total peripheral vascular resistance after treatment of thyrotoxic and hypothyroid patients.

Hypothyroidism is key factor for higher vascular resistance which is the consequence of vascular

contractility. Hypothyroidism may be the factor in which the kidney can properly response to other stimulator hormone such as adrenaline and noradrenaline. This latest observation might be due to the reduced reaction of catecholamine receptors due to hypothyroidism. This later presentation of catecholamine receptor ultimately lead to lower rennin production from kidney in one hand and also decreased production of angiotensinogen from the liver a result of hypothyroidism modify the normal physiological pathways of aldestron biosynthesis due to lack of angiotensin-II which is required for aldestron production within adrenal cortex (Takiguchi *et al*., 1988; Vanhoutte, 1989; Gunasekera and Kuriyama, 1990; Ruiz *et al*., 1987).

HYPOTHYROIDISM ADVERSELY ALTER GLOMERULAR AND TUBULAR FUNCTIONS

Thyroid hormone suppression negatively affect the glomerular filtration rate, but the effect on tubular mechanism is not as hard as on glomerular function (Capasso *et al*., 1999; Karamikas *et al*., 2004; Den Hollander *et al*., 2005; Gillum *et al*., 1987; Suher *et al*., 2005; Ota *et al*., 1994; Holmes and Discala, 1970; Michael *et al*., 1972; Cadnapaphornchai *et al*., 2003; Vargas *et al*., 1991). It seems following thyroid hormone treatments the renal function return to normal. The reduction of glomerular filtration rate following hypothyroidism occur mainly due to disorders in circulating volume, renine-angiotensinogen-aldestron-system with subsequent reduction in kidney perfusion. This later kidney abnormality happen as result of thyroid hormone deficiency with subsequent retardation in kidney growth and glomerular filtration rate (Gillum *et al*., 1987; Suher *et al*., 2005; Asmah *et al*., 1997; Acker *et al*., 2002). The deficiency in sodium and water reabsorption can also cause filtrate overload in kidney and contributing to renal dysfunctions. On the other hand after hypothyroid prolongation it seems concentrate urine is negatively manipulated which partly related to altered kidney water and electrolytes. it is also reported that mild form of hypothyroidism may not have as sever effect which can have on glomerular function, but the increase of some biochemical metabolite such as creatinine during hypothyroidism is due to hypothyroidism and not due other metabolic disorders. It seems proteinuria and particularly albuminuria is due to transcapillar leaking of blood proteins and it seems proteinuria in hypothyroid patient is started well before the reduction in glomerular filtration rate disruption (Ota *et al*., 1994; Holmes and Discala, 1970; Michael *et al*., 1972; Cadnapaphornchai *et al*., 2003; Vargas *et al*., 1991; Gillum *et al*., 1987; Suher *et al*., 2005; Ikeda *et al*., 2001; Katz *et al*., 1975).

THYROID BEHAVIOR DURING RENAL ABNORMALITIES

It is well documented that the kidney also can have influences on the way thyroid function, in health and disease. The kidney is responsible for metabolism of thyroid hormones through the degradation and excretion of thyroid hormones by renal function. Clearly as kidney function altered, it will have a direct effect on the latter process of hormone metabolism by the kidney leading to a disruption and abnormalities of thyroid hormone and consequently thyroid function adversely altered. Therefore in case of kidney diseases thyroid disorder may be encountered negatively but this process is not straight forward strategy and thyroid abnormalities mainly occur, when chronic renal diseases are present (Lo *et al*., 2005; Chonchol *et al*., 2008). The clinical manifestation of hypothyroidism is commonly seen among patients suffering from kidney diseases. The explanation behind thyroid disorder in renal failure lay on the fact that the iodide which is the main element in T4 and T3 biosynthesis is cleared off by the kidney but in kidney diseases, the iodide filtration rate is reduced and remain elevated in blood circulation. The high concentration of iodide in blood circulation eventually stored within thyroid gland the sole organ for iodide absorption.

The overload iodide concentration in thyroid gland can inhibit thyroid hormone biosynthesis eventually leading to hypothyroidism due the wolff chaikof effect (Kaptein, 1996). It seems most of thyroid hormone and T3 particularly reduced during chronic renal failure, resulting in hypothyroidism due the wolff chaikof effect originating from reduced clearance of iodide due to kidney failure. (Carrero *et al*., 2007; Enia *et al*., 2007; Mansourian, 2010d; Mansourian, 2011d).

There are also other studies indicating thyroid hormone assessments and T3 in particular can help to evaluate in how kidney function. Other studies indicate that suppressed thyroid hormone concentration particularly tridothyronine (T3) may eventually lead to heart diseases, independent of kidney diseases (Mansourian, 2012a, b; Waring *et al*., 2012).

Thyroid hormones and triidothyronine (T3) in particular is required for the well being of kidney function and thyroid disorder is reported to be seen among patients with kidney diseases.

The production of triidothyronine (T3) from thyroxine (T4) occure due to the diidonase, the enzyme responsible for the conversion of thyroxine into triidothyronine in peripheral tissues and T3 supression caused by reduced activity of diidonase partly due to kidney disorder (Tauchmanova *et al*., 2006; Carrero *et al*., 2007; Zoccali *et al*., 2006; Enia *et al*., 2007; Zoccali *et al*., 2005).

CONCLUSION

There are extensive studies indicating that kidney and thyroid function are interrelated through many metabolic pathways and the two vital organs are biochemically interactive by various metabolic pathways and any harm to either of them eventually will lead to the malfunction of the other organ. Thyroid hormones play an important and vital role in kidney growth and development, biochem-physiological functions of nephron the kidney structural unit. Thyroid hormones affect kidney, hemodynamic, blood circulation and renal glomerular filtration rate. Thyroid hormones influence tubular function, various transport system, electrolyte balance and related physiological functions occur by the kidney. Thyroid hormones influence renal function and growth as early as embryonic life. Thyroid hormones reduction which is occurred during hypothyroidism adversely affect kidney functions as whole. Hypothyroidism reduce renal blood flow mainly as result of vasoconstriction. Hypothyroidism adversely affect tubular function and transport system, but this side-effect is not as severe as it happen on glomerular filtration rate. Although the adverse effects of thyroid hormones on kidney is a direct consequence of T4 and particularly T3 on the renal function but the cardiovascular disorders occur due to hypothyroidism might also play a crucial step towards kidney malfunction during hypothyroidism. Kidney diseases in the main time can also adversely manipulate thyroid hormone metabolism. Extensive studies have emphasized on the role of kidney disorders on the thyroid function behavior. The role of various stage of thyroid malfunction on the kidney metabolic abnormalities and the renal function is also a topic of various studies. On the base such findings clinically it is a wise strategy to check the thyroid function in patient with kidney disease and also the renal function test should carried out when the patient suffering from thyroid abnormalities to avoid possible misdiagnosis.

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