Correlation between Oxidative Stress and Chronic Kidney Disease in Thyroid Disorders

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ABSTRACT

In recent years chronic Kidney Disease (CKD) has emerged as a prevalent and serious threat. The traditional risk factors are no longer able to explain the reason behind increased number of CKD. Thyroid hormones have many direct and indirect effects on renal development, renal hemodynamics, Glomerular Filtration Rate (GFR), and sodium and water homeostasis. Both hyperthyroidism and hypothyroidism are associated with clinically important alterations in kidney function. Oxidative stress is very common in CKD patients and is considered to be an important pathogenic mechanism. Both thyroid disorders lead to oxidative stress. Hyperthyroidism causes increased oxygen consumption in mitochondria and leads to increased Reactive oxygen species (ROS). Hypothyroidism leads to increased triglycerides, Low Density Lipoproteins (LDL) and cholesterol and decrease in High Density Lipoproteins (HDL) in the body that results in enhanced LDL oxidation leading to oxidative stress. This review describes the effect of thyroid disorders on oxidative stress and kidney function, the molecular pathways that are altered and the relationship between oxidative stress and kidney dysfunction in Thyroid Disorders. Literature was searched for articles using different search engines with keywords like thyroid, triiodothyronine, tetraiodothyronine, thyroxin, hypothyroidism, hyperthyroidism, thyroid disorders, and renal function, glomerular filtration rate, glomerulonephritis, chronic kidney disease, oxidative stress, and renal carcinoma. The most relevant and current articles were selected. After a thorough analysis of the data available, the present article was compiled. The older references were consulted to include the earlier developments in this area.

Key-words: Thyroid Disorders, Hyperthyroidism, Hypothyroidism, Oxidative Stress, Free Radicals, Reactive Oxygen Species, Chronic Kidney Disease, CKD

INTRODUCTION

According to a recent study the prevalence of Chronic Kidney Disease (CKD) in India was observed to be 17.2 % out of which seven percent were with only stage one.[1] Thyroid and kidney play important roles in each other's function. Thyroid dysfunction affects renal physiology and development by various direct and indirect mechanisms. Hyperthyroidism and Hypothyroidism both are associated with increased oxidative stress.[2] There are various mechanisms responsible for the progression of kidney damage and thyroid disorders induced oxidative stress is one of them. This review focuses on the important and clinically relevant interactions between thyroid function and renal function, which are essential from the perspective of patient management

MATERIALS AND METHODS

Literature was searched for articles using different search engines with keywords like thyroid, triiodothyronine, tetraiodothyronine, thyroxin, hypothyroidism, hyperthyroidism, thyroid disorders, and renal function, glomerular filtration rate, glomerulonephritis, chronic kidney disease, oxidative stress, and renal carcinoma. The most relevant and current articles were selected. After a thorough analysis of the data available, the present article was compiled. The older references were consulted to include the earlier developments in this area.

INTERACTION BETWEEN THYROID AND KIDNEY

There is a special interaction of thyroid and kidneys. Thyroid dysfunction can alter Renal Blood Flow (RBF), Glomerular Filtration Rate (GFR), electrolyte homeostasis, tubular function and kidney structure; on the other hand, kidney performs a key role in the metabolism, degradation and excretion of thyroid hormone and its metabolites. Kidney disease may predispose to alterations in regulation of the hypothalamic–pituitary–thyroid axis, as well as changes in thyroid hormone uptake and action. Clinical conditions such as chronic metabolic acidosis, chronic malnutrition and fasting up to certain extent may affect the synthesis of the T_3 from T_4 in CKD or it may be due to a low peripheral conversion of T_3 from T_4 due to high concentration of cytokines.

THYROID HORMONES AND THEIR DISORDERS

Thyroid gland is one of the most important glands of human body as it affects most of the physiological functions in the body. Thyroid produces two hormones Tri-iodothyronine (T_3) and Tetra-iodothyronine (T_4) or Thyroxine. The synthesis and secretion of thyroid hormones [i.e. tri-iodothyronine

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(T_3) and Thyroxin(T_4)] are stimulated by Thyroid Stimulating Hormone(TSH) which is released from the pituitary gland, which is further regulated by Thyrotropin-Releasing Hormone (TRH) from the Hypothalamus.

TRH and TSH are regulated by feedback inhibition from circulating T4. These hormones regulate basal metabolism, oxidative metabolism, development, protein synthesis as well as many other endocrine glands. Any disorder of the thyroid gland resulting in imbalance of thyroid hormones exerts negative effects on the functioning of various organs of the body. Hypothyroidism and Hyperthyroidism are the common thyroid disorders in which thyroid hormones secretion is decreased and increased respectively. In a cross sectional, multicenter, epidemiological study conducted in eight major cities of India on 5360 adults, the prevalence of Subclinical Hypothyroidism, Hypothyroidism, Subclinical Hyperthyroidism, and Hyperthyroidism was 8.02%, 10.95%, 1.27%, and 0.67% respectively.[3]

OXIDATIVE STRESS

Oxidative stress may be defined as a condition when production of oxidants or Reactive Oxygen Species (ROS) exceeds local anti-oxidant capacity. ROS are generated by the oxidative phosphorylation in the cell. ROS are highly reactive molecules because they contain unpaired electron. ROS comprise partially reduced forms of oxygen such as H_2O_2, hydroxyl radicals (OH^o) and super oxide anions(O_2^-), nitric oxide (NO) and lipid peroxides.

ROS are very strong oxidizing agents which may damage cell structures like cell membranes, cellular proteins, lipids and nucleic acids. As these molecules are generated by the cells normally also, only their presence cannot explain oxidative stress but when antioxidant defence system fails to cope up with these, these imbalance between ROS and antioxidant system create oxidative stress.

OXIDATIVE STRESS IN TYROID DISORDERS

Some studies suggest that the hyper metabolic state of hyperthyroidism is associated with increased ROS production[4] while the hypo metabolic state of hypothyroidism leads to reduced ROS production.[5] Indeed both hyperthyroidism and hypothyroidism are associated with enhanced oxidative stress involving enzymatic and non-enzymatic antioxidants.

Thyroid hormones have great impact on energy metabolism. Mitochondria, the powerhouse of cellular life are the primary target for oxidative stress induced tissue damage due to thyroid hormones. T_3 increases O_2 consumption which leads to enhanced reactive oxygen species and reactive nitrogen species generation in the target tissues, which results in increased consumption of cellular antioxidants thus inducing oxidative stress.

Thyroid hormones affect the expression and/or activity of many ion channels and transporters. In some cases, this is due to direct binding of thyroid hormone to the promoter region of a transporter gene. Thyroid hormones can work as oxidants and produce DNA-damage, probably through the phenolic group, similar to that of steroidal estrogens.[6] In experimental studies, T_3 induced hyperthyroidism was found to be associated with altered lipid peroxidation indices, including elevated levels of TBARS and hydroperoxides.[7]

Hypothyroidism also results in oxidative stress. In hypothyroidism, the level of triglycerides is increased, due to decreased activity of lipoprotein lipase in adipose tissue.[8] T_3 induces LDL receptor gene expression that helps in LDL clearance in liver, but in hypothyroidism number of LDL receptors is decreased in liver and due to that LDL clearance is delayed resulting in increased level of LDL and ultimately causing hypercholesterolemia.

In hypothyroidism, Total HDL levels are also decreased due to the decreased activity of Cholesterol Ester Transfer Protein (CETP) and hepatic lipase.[9] All these changes in lipid metabolism result in enhanced LDL oxidation reflected in the increased levels of lipid peroxidation markers such as MDA.[10] It has been shown by many studies that levels of MDA and NO are increased in hypothyroidism.[11] MDA levels are elevated even in subclinical Hypothyroidism.[12]

THYROID DISORDERS, OXIDATIVE STRESS: EFFECTS ON KIDNEY FUNCTION

Thyroid disorders affect the functioning of kidney by various means. RBF and GFR both are increased in hyperthyroidism. Thyroid hormones can regulate the number of cardiac beta-adrenergic receptors. The increased number of receptors may be responsible for the enhanced catecholamines sensitivity of beta- adrenergic coupled cardiac responses in hyperthyroid patients. The level of thyroid hormones affects the intrinsic contractile state of cardiac muscles and in addition modifies the responsiveness of cardiac muscles to inotropic agents.[13] The increase in RBF is due to increased cardiac output by the positive chronotropic, inotropic effects and reduced systemic vascular resistance. Alongwith that there is reduced renal vasoconstrictor endothelin. All these factors result in increased RBF.

The activation of Renin-angiotensin-aldosterone-system (RAAS) by thyroid hormone, alongwith increased RBF, results in increased GFR. The GFR increases by about 18-25% in hyperthyroid patients.[14] T_3 hormone increase, in hyperthyroidism, results in the increased tubular mass, renal mass and tubular re-absorptive capacity.[15] Increase of Urinary-*N*-acetyl-b- D-glucosaminidase (NAG) in hyperthyroidism shows disruption of glomerular basement membrane due to hyper filtration, hypertrophy and hyperplasia.[16]

The effects of hypothyroidism are quite opposite on kidneys as compared to hyperthyroidism. The RBF is decreased due decreased cardiac output by the negative chronortropic and inotropic effects.[17] In hypothyroidism there is intrarenal vasoconstriction, reduced renal response to vasodialators and increased peripheral vascular resistance. Along with that there is decreased angiotensin II and impaired RAAS activity in hypothyroidism which results in reduced GFR.

Cystatin C (CysC) is a small, basic protein that works as a physiologic inhibitor of cysteine proteinases. CysC is considered to be produced at a constant rate by most nucleated cells. The production of CysC is not influenced by inflam-

Hyperthyroidism	Hypothyroidism
Increased Renal mass	Decreased Renal mass
Increased Tubular mass	Decreased Tubular mass
Increased Vasodilators	Decreased Vasodilators
Decreased Vasoconstrictors	Increased vasoconstrictors
Increased RAAS Activity	Decreased RAAS Activity
Increased Metabolism	Decreased Metabolism
Increased Tubular reabsorptive capacity	Decreased Tubular reabsorptive capacity
Increased GFR	Decreased GFR
Increased RBF	Decreased RBF
Increased oxidative stress	Increased oxidative stress

Table-1: Effect of thyroid Disorders on renal physiology and function

Oxidative stress markers	Hyperthyroidism	Hypothyroidism
MDA	Increased	Increased
Nitric Oxide	Decreased	Increased
SOD	Decreased	Decreased
Glutathione Peroxidase	Decreased	Decreased
Vitamin A	Decreased	Decreased
Vitamin C	Decreased	Decreased
Vitamin E	Decreased	Decreased

Table-2: Effect Of Hyperthyroidism and Hypothyroidism On Oxidative Stress

Tests	Effect
Creatinine	Increase
Urea	Increase
Uric acid	Increase
Serum Albumin	Decrease
Total Protein	Decrease
Urinary protein	Increase

Table-3: Effect of oxidative stress on kidney functions

matory states.[18] CysC is freely filtered at the glomerulus and practically completely reabsorbed and catabolized by tubular cells. Compared to serum creatinine, CysC has a lower inter-individual variability and is not correlated to lean tissue mass, gender, and age.[19]

CysC has been proved to be a reliable marker of GFR in healthy adults and children as well as in patients with renal disorders of neoplastic, rheumatologic, hepatic, and nephrologic origin.[20] Studies show that serum cystatin C levels generally trend in the opposite direction to those of creatinine[21]; that is, cystatin C is commonly elevated in hyperthyroid patients and decreased in hypothyroid patients. This pattern of results has been shown in a wide range of causes and severity of thyroid diseases[22] although the exact mechanism is not known but it is hypothesized to be a direct effect of thyroid hormone on cystatin C production.

Along with all these and many other effects both hyperthyroidism and hypothyroidism cause oxidative stress which further deteriorate the negative effects of these thyroid disorders.

Oxidative stress is associated with a variety of renal diseases such as glomerulonephritis, acute or progressive renal failure or tubulointerstitial nephritis.[23,24] As ROS affect Cell cycle regulation that may cause tubular cell hypertrophy.[25] Oxidative stress is also proved to encourage apoptosis[26], a reason behind the functional tissue loss in CKD. Nuclear factor κ-B, a family of rapid acting nuclear transcription factors, regulate many genes involved in inflammation, immunity, apoptosis, cell multiplication are activated by ROS. Due to all this, these transcription factors start signaling pathways involved in renal fibrosis.[27]

Angiotensin II is strong vasoconstrictor and sodium retaining hormone and it is very important for the regulation of sodium transport in Kidney and Blood pressure. Oxidative stress can modulate Angiotensin II type 1 receptor (AT_1R) expression.[28] Thus during oxidative stress, up-regulation of AT_1R can result in sodium retention and leads to development of hypertension. It has been shown that AT_1R is responsible for Na^+ retaining effects of Angiotensin II in the Kidney.[29]

ROS promote the formation of oxidized amino acids and thus can directly modulate the function of Proteins. It has been shown in studies that Advanced Glycosylation End products occur in β2- microglobulin deposits of long term hemodialysis patients, suggesting that oxidative stress promotes amyloidosis due to protein denaturation.[30]

CONCLUSION

Thyroid disorders and CKD, both appear to be as noticeable medical conditions in India. As these diseases are becoming quite ubiquitous, it is necessary to analyze all the factors associating both of them either physiological or pathological.

Both thyroid disorders (hypothyroidism or hyperthyroidism) affect kidney functions through various factors. It has been confirmed by many studies that oxidative stress is a credible cause of kidney dysfunction. The analysis *vide supra* advocate ROS might be one of the major causes of kidney dysfunction in thyroid disorders and this should be verified experimentally.

Any alterations in the thyroid status may cause subtle changes in kidney tissue leading to oxidative tissue injury and thyroid hormone replacement therapy alone might not be sufficient in bringing back the tissue parameters to normal levels. The role of supportive antioxidant therapy to minimize tissue damage and accompanying symptoms in thyroid disorders is the question to be answered by thorough research.

The use of antioxidants targeted to specific pathways that are altered in thyroid disorders might prove beneficial, but for this different antioxidants will be needed as a multidrug therapy to target oxidant modifying pathways.

Progressive approaches such as target based antioxidant treatment and gene therapy using viral vectors to modulate the expression of antioxidant genes appear to be a promising strategy to counter oxidative stress induced tissue damage.

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