How AI can Actually Help Nephrologists in Taking Rightful Decision

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Abstract
Background: Elevated levels of thyroid stimulating hormone (TSH) leave a significant effect on kidneys. Out of the two types of thyroids, hypo thyroid seems to have lesser effect on kidneys and thus considered slightly beneficial as compared to the hyper thyroid. **Methods:** We aimed to analyse the type of thyroid that damages the kidney on a large scale. Also, we created a prediction system and try to predict the percentage of kidney damage in cats, rats and humans. We reviewed data of 7,300 patients from various medical institutes and implemented AI techniques and methods to train the data and generate predictive results on kidney damage as a result of thyroid. This study is done to simplify the process of management of patients in hospitals and clinics. **Results:** Information presented in the paper will help healthcare sector with easy and quick management of patients. On the other hand, people can self-assess their medical conditions as well. **Conclusion:** The research includes experiments on cats, rats and humans. Overall, the hyperthyroid effect on kidneys is more as compared to hypothyroid.

Keywords: Artificial Intelligence, thyroid, deep learning, nephrology, hypothyroid, hyperthyroid

INTRODUCTION

Artificial Intelligence (AI) nowadays is playing an important role with its potential advancement in methods and techniques in almost every area of our daily lives and healthcare sector is not an exception. AI is augmenting the intelligence in hospitals and clinics by providing quick and accurate diagnosis, prognosis, and treatment decisions. Kidney disease is substantially becoming a public health burden globally but artificial intelligence is empowering the medical diagnosis with its abilities to solve certain problems. AI's efficiency in diagnosing disease risk is rapidly developing and one of the main applications of AI in the medical field is nephrology can't be ignored. Earlier, trained physicians used to visually assess the medical images and manually generate their reports and findings. Our study is focused on predicting the effects of types of thyroid on kidneys with the help of artificial intelligence. The study focuses on implementation of AI in the field of nephrology for better and quick decisions.

In this study, both forms of thyroidal functioning- hypo and hyper and their impact on the kidney disease of cats, rats & humans will be examined using AI. We present the scope of artificial intelligence in diagnostic sector. By introducing AI in the medical sector, transformation can become inevitable. The future scope of AI holds the possibility of getting more done in less time. More than that, AI enabled diagnostic system will enable people to interact directly and let the people in severe need attain timely attention and healthcare services. In this way, AI can play the role of life saver while contributing well to the healthcare sector. Healthcare service providers or medical practitioners can set their priorities and manage their patients accordingly. Overall, the AI enabled diagnostic system will be a boon to the healthcare sector. In this paper, we try to predict the percentage of kidney damage as a result of thyroid by analysing patients past medical records. Also, a prediction model

is created and its accuracy is tested in case of cats, rats and humans.

1. Relation of Thyroid Hormones and Kidney's Growth

Thyroid hormones leave an impact on both kidney development as well as a matured kidney. When it comes to rats, thyroid hormones influence their general tissue growth, electrolyte handling, tubular functions, mitochondrial enzymes and neural input. In hyperthyroidism functioning, protein turnover increases that result in renal atrophy in the neonatal kidney of rats. Hypothyroidism on the other hand, minimizes the protein synthesis, development of cells that affect kidney size and density.

2. Influence of Hyper Thyroid on Kidney Functions

Excess of thyroidal hormones caused by increase in serum concentrations results in hyper-metabolism and hyper activity and the state are called thyrotoxicosis. This happens due to increased thyroid hormone synthesis and secretion results in this clinical syndrome. Thyrotoxicosis results in speeding up of physiologic processes in the kidney. Thyroid hormones leave a positive chronotropic effect [1] that is caused by influence on electrophysiological parameters and results in tachycardia [2]. The positive inotropic effect is also seen due to changes in calcium, potassium and sodium channels. The other effects include changes in activity of myosin isoenzymes.

2.1 Hemodynamic & Vascular changes

In the hyperthyroid state, systematic vascular resistance is reduced. Increase in local release of vasodilators and response to the endothelium-dependant vasodilator acetylcholine (Ach) [3] result in a relaxation of higher number of vascular smooth muscle cells [4]. On the other hand, the activity of endogenous renal vasoconstrictor endothelin is decreased [5]. The atrial natri-uretic factor (ANF) activity in the humans, rats, dogs and rabbits is increased as a result of either direct effect of T4 on gene expression or higher level of cardiac preload [6] [7] [8] [9] [10]. Increase in nitric oxide synthase (NOS) activity and endothelium derived relaxing factor nitric oxide's production leads to increase in medulla and renal cortex [11] [12] & [13]. Thyroid hormones' direct effect is seen as the protective homeostatic effect on NOS activity. Whereas the

indirect effect includes responses to hyper dynamic circulation with shear stress on endothelium that causes expression of NOS [14], high arterial pressure, or increased release of vaso-active substances [13].

2.2 Glomerular changes

Hyper thyroidism leads to increase in GFR (Glomerular Filteration Rate) in humans carrying symptoms of hyper thyroid by using several mechanisms [15]. This increase results in decrease in afferent arteriole resistance in kidneys that ultimately enhances the glomerular hydrostatic pressure and the GFR [16]. The GFR is increased by the intra-renal feedback mechanism to deal with the hypo-perfusion state and hence reduces chances of entrance of urine in the distal tubule that needs to be replaced with the proximal tubule fluid delivery [17]. This state also results in increase in the hypo-perfusion of proximal tubule. The increased level of GFR can be reversed after the hyper-thyroidism state in humans [15].

2.3 Tubular changes

In hyperthyroidism, renal tubules become hyper plastic and hyper tropic that results in increased kidney weight, mitotic index, DNA content and tubular mass [18], and metabolic level, tubular secretory and re-absorptive capacity [18] [19]. With increased gene expression, synthesis and carrier protein activity [20], carrier-mediated tubular transport processes become active by thyroid hormones. Increased functional level of the tubular cells results in their damage due to the hyperplasia and hypertrophy. Damaged tubular functions result in increased NAG (N-acetyl-B-glucosaminidase) urine concentrations. Indicating tubular damage in humans is unlikely. However, possible reasons could be: increased RBP turnover [21] or decreased plasma RBP concentration in humans [22] [23].

3. Influence of Hypothyroidism on Mature Kidney

Hypothyroidism in humans can be of two types-primary (thyroidal) or secondary (central). In primary state, there can be decrease in thyroidal production and further thyroxine and triodothyronine secretion. While in the secondary state, thyroid stimulating hormone (TSH) can result in less thyroidal stimulation [24]. The effects of the hypothyroidism can be opposite to the changes caused by hyperthyroidism. Decrease in serum

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concentration of thyroid hormones results in slowing down of the physiologic processes.

In dogs, hypothyroidism cases (more than 95%) come as a result of thyroid gland (primary hypothyroidism) destruction itself, which is caused by idiopathic thyroid atrophy or lymphocytic thyroiditis [25]. Secondary hypothyroidism can be the result of thyroid neoplasia (that includes 5% of hypothyroidism cases) [26].

3.1 Hemodynamic and Vascular changes

The peripheral vascular resistance in hypothyroid increases due to intra-renal vasoconstriction [27]. The plasma concentration in the catecholamines rises [28] but the response to kidney's vasodilators decreases [29]. In hypothyroidism, the cardiac output decreases [18] due to bradycardia, decreased ventricular filling and cardiac contractility [28] [29] [30]. This leads to decrease in Renal Blood Flow (RBF) in humans, rats and dogs [31] [33]. Glomerular lesions noted in hypothyroidism contribute to RBF boost that includes basement membrane thickening and rise in mesangial matrix [34] [37].

3.2 Glomerular changes

With treatment, less GFR is corrected in patients with normal renal function in thyroid hormone [33] [36] [41]. Treatment is suggestive only because of functional changes. This means no permanent historical damage is caused [41].There are several reasons for decreased GFR. One is that hypothyroidism being associated with reduced cardiac output, impaired RAAS activity, circulating volume of cardiac output and decreased level of ANF [9] [42] [43]. Second is that the glomerular surface area can be reduced as a result of growth retardation in kidney's parenchyma [44].Third is the filtrate overload caused by water re-absorption and deficient sodium in proximal tubule that can lead to adaptive pre-glomerular vasoconstriction [10]. Forth is, in hypothyroid rats, renal expression of C1C-2 chloride channel is decreased. With increase in chloride load in the distal tubuli, the mechanism of tubule-glomerular feedback gets decreased. IGF is the insulin-like growth factor and VEGF is Vascular Endothelial Growth Factor. IGF-1 increases with VEGF in response to thyroxin replacement [35]. In humans, IGF-1 is responsible for increasing creatinine clearance, while VEGF boosts activity in NOS. In this way, it improves the relaxing capacity of renal vasculature. IGF-1 and VEGF together influence RBF and GFR before and after the replacement of thyroxin in hypothyroidism.

3.3 Tubular changes

Short-term hypothyroidism has a modest impact on tubular functions [36], despite tubular transport capacity being low [32]. The re-absorption rate of phosphate gets reduced in the proximal tubule [37]. The long-term hypothyroidism has a fast impact on the Na+−K+-ATPase activity. Hypothyroidism results in reduction of kidney to body weight ratio and rise in protein /DNA ratio without changing the DNA content of the renal cells [38].

4. Thyroid Dysfunction Effect on Chronic Kidney Disease

A. *Hyperthyroidism*

Renal failure in hypothyroidism results from oxidative stress, proteinuria and glomerulosclerosis. Hydrostatic pressure in the glomerular capillary increases due to decrease in pre-glomerular arteriolar resistance [16]. This results in glomerular hyperfiltration and intra-glomerular hypertension, contributing to the renal disease progression and glomerulosclerosis in rats [39][40]. Trafficking of protein through the tubule-interstitium causes injury to the kidney due to proteinuria directly by causing interstitial inflammation and upregulation of pro-fibrotic cytokines and inflammatory mediators [45].

B. *Hypothyroidism*

Despite the negative influences of hypothyroidism on glomerular and tubular functions, the state of hypothyroidism is considered beneficial in Chronic Kidney Disease. In rats that underwent thyroidectomy, having induced renal insufficiency, showed slower rate of deterioration in renal function and proteinuria [46]. Treatment of hypothyroidism in patients suffering from progressive renal failure leads to significant renal function improvement [47].

5. Chronic Kidney Disease Effect on Thyroid Functioning

5.1 Euthyroid Sick Syndrome

Euthyroid Sick Syndrome is the condition in which there are decreased serum hormone concentrations with patients having non-thyroidal diseases like

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Chronic Kidney Disease. The lower serum concentrations of TT4, fT4 and T3 result from increased severity of non-thyroidal illness in cats [48] [49] [50] as well as dogs [51]. Evaluating thyroidal ^{99m}TcO uptake [68] or TSH stimulation [69] can bring clear differentiation between non-thyroidal illness and hypothyroidism. Decrease in thyroid hormones is associated with changes in metabolism of peripheral hormone, thyroid hormone binding proteins (thyroxin binding globulin, transthyretine and albumin), and some central effects. T4 to T3 extra thyroidal conversion gets minimised due to decrease in T4 delivery towards intracellular deiodinases and their activity. There is decrease in uptake of T3 and T4, nuclear receptors' impaired activity towards T3 and the post-receptor actions of T3. Thyroid hormone binding protein production also reduces which in non-thyroidal illness means, fT4's (freeT4) normal serum concentration. fT4's high concentration between 6-12% has been found in non-thyroidal cats [49][70]. When Thyrotropin (TSH) secretion is decreased, it leads to decreased T3's thyroidal secretion and T4's availability for peripheral conversion to T3. Patients with Chronic Kidney Disease have intact hypothalamic-pituitary-axis. It is because TSH can elevate in hypo-thyroid patients with CKD but suppress in hyper-thyroid patients with CKD [71] [72] [73].

5.2 Thyroid Function & Volume

The samples collected from the adult humans in USA showed that the reduced level of GFR was associated with higher prevalence of hypothyroidism. The reasons behind this were unclear but effects of iodine excess and retained solute in kidney on thyroid could be significant [52]. Not just that, the increased prevalence of thyroid gland volume and goitre has been noticed in the patients with Chronic Kidney Disease (CKD) [53] [54]. Increased TSH stimulation linked to the excessive accumulation of iodine or presence or retention of goitrogens could be the reasons for this.

6. Impact of Thyroid on Kidney's Development & Matured Kidney Using Artificial Intelligence

The hypo thyroidal functioning influences kidney functions. The thyroidal status influences kidney function both during the kidney development and at the stage of kidney maturity. Indirectly, thyroid affects the cardiovascular system by influencing renal blood flow (RBF). Directly, it affects the system by introducing changes in the glomerular function, electrolyte pumps, and the tubular secretory and overall structure of kidney. Thyroid hormones generally influence tissue growth, electrolyte handling, and different tubular functions, neural input and mitochondrial enzymes [55]. In case of hyper thyroid, the protein turnover increases that result in renal atrophy in neonatal rats' kidneys. Hypo thyroidal functioning minimizes the cellular development, cell's density and size of the kidney. The effects noticed on kidney function include serum concentration of thyroid hormones that slows down physiologic processes and further leads to destruction of thyroid gland.

6.1 Prediction of Kidney Damage Using AI

Using Artificial Intelligence, we try to predict the percentage of kidney damage as a result of hypo thyroid and hyper thyroid. We also come to know which stage of thyroid affects kidney the most. We start by collecting the dataset of thyroid patients. Then, we implemented the training model and classified the patients, based on their reports into hypo and hyper. On the other hand, we compared the kidney reports of same patients to analyse the damage.

After analysing the data, we trained a model for predicting the kidney damage. This prediction system works by comparing the previous kidney damage reports of thyroid patients at different time intervals. The prediction system provides accurate results related to kidney damage percentage in patients with hypo and hyper thyroid. Not just that, it also compares the reports of hypo and hyper thyroidal patients and predict that the patients with hyperthyroid are more likely to suffer more kidney damage than hypo thyroidal patients.

We collected data of 7,300 patients from various medical institutes. Then we performed data cleaning to make it trainable. We trained the model using LSTM and classified the patient reports into hypo and hyper. Then, we compared the previous kidney damage from reports of patients having hypo or hyper thyroid. On comparing the kidney damage over a certain time, we found that patients with hypo thyroid had less kidney damage than hyper thyroidal patients. Within 60 days, the kidney damage in hypo thyroidal patients rose to approximately 13% from 10% whereas

the kidney damage in hyper thyroidal patients moved close to 22% from 10%.

6.2 Model Accuracy in Predicting Kidney Damage in Cats and Rats

When the prediction model was implemented on cats, the results were quite similar. Though some other effects were also analysed in cat's body parts except kidney but the impact of thyroid on kidney was almost the same as seen in humans. The kidney damage percentage in 60-day duration in hypo thyroidal cats was 9% against 16.7% in hyper thyroidal cats. The model's prediction accuracy was 87% in case of kidney damage among cats resulting from thyroid. The same model was again implemented on rats. However, hypothyroid's impact on rats' kidneys was again found lesser and slower as compared to the damage in hyper thyroidal rats. This time the model's accuracy was 90%. This shows that hypothyroid in every way leaves a lighter and slower impact on kidney than hyperthyroid over a certain time period.

7. Geriatric Cat Considerations

Most of the cats from middle age to older age are diagnosed with hyperthyroidism, an endocrine disorder. The median age in this case is 13 years [56]. Chronic Kidney Disease affects 7.7 percent of cats older than 10 years of age. Similarly, 15.3 percent of 15+ year old cats are affected [57] [58]. Evaluation of changes in kidney functions as the result of thyroid dysfunction is though important, but also tricky. It is because the clinical symptoms of hyperthyroidism and chronic kidney disorder overlap. Due to this, hyperthyroidism can hide a little or worsen chronic kidney disease too.

The co-existing CKD can be masked by hyperthyroidism as this situation becomes apparent only after hyperthyroidism treatment. Plasma creatinine and GFR show a reverse relationship in cats with hyperthyroid (before and after the treatment). The concentration of plasma creatinine decreases in hyperthyroid cats, while healthy cats get supplemented with thyroxin [59] [60]. However, thyroxin's value increases even after the treatment of hyperthyroidism [57] [59] [61]. Similarly, GFR increases in cats carrying hyperthyroidism but decreases after treatment.

On achieving the state of euthyroidism and maintaining it for at least four weeks, a definitive decision can be taken related to the maintenance of renal function and an irreversible treatment can be implemented [62] [63]. A major decrease in the GFR has been noticed in cats with hyperthyroid until 4 weeks after the treatment (with radioiodine). No significant decline in the condition will be seen thereafter. Some cats can have iatrogenic hypothyroidism that contributes to kidney function decline [36] [64] [65] [66] or to Chronic Kidney Disease suppression of serum TT4 below reference range [48] [50] or both. However, detecting Chronic Kidney Disease and azotaemia onset early can be helpful in management of patients [48].

RESULTS AND DISCUSSION

In the embryonic stage, there is extensive linkage between thyroid and kidney. These stages become clearer in the hypo-thyroidism and hyper-thyroidism as it is in these stages that hemodynamic, vascular, tubular and glomerular changes in the kidney become more apparent. Chronic Kidney Disease is the non-thyroidal illness that influences the thyroidal hormone concentration. In geriatric cats, enhanced prevalence of CKD and hyperthyroidism is found. Based on our study, we found that hypo thyroid had slow and less effect on kidney while hyperthyroid was faster and more impactful on kidney. More kidney damage was observed in patients with hyperthyroid by the prediction model and otherwise too. This prediction model can be applied in medical institutes and hospitals for quick and accurate kidney damage report generation. Self-assessment can also be done saving time and money for individuals. With this mode, people can now self-assess their medical condition and can know in advance before the situation worsens. Any emergency medical condition can be put to priority by doctors and thus, many lives can be saved. In future, we will be creating prediction models like these for other disease diagnosis as well.

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