REVIEW OF LITERATURE
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Thyroid gland dysfunctions are known to man since time immemorable. They were known to man probably as early as the beginning of human civilization. Goitre finds a mention in ATHARVADA written in 1600 B.C. as Galgand. Different types of goiters & their possible remedies find a mention in it. The term goitre however, is of Latin origin, meaning gutter. SUSHRUTA in 5th century BC has given detailed description of galgand. He says a case of goitre is attended with difficulty, respiration, softening of whole body, weakness, a low relish for food & loss of voice.

Parrys 1825 gave the classical description of onset of thyrotoxicosis in young women, followed by description by Graves 1835 & Basedow 1840. Therapeutic value of iodine was first noted by Coindet 1820. Kendall isolated thyroxin in 1916. The fact that renal failure leads to retention of toxic products were known early, when Piorry & Heritier coined the term uraemia in 1848. This term at that time implied Presence of urine in blood. Thus we see from the start of civilization, man has been aware of the different functioning organs of the body, the diseases caused by their improper functioning & have been working constantly to get victory over diseases.

Reports of defective iodine metabolism in CRF were reported as early as in 1964 by Wayne et al, who showed excess iodine in circulation
due to uraemia. Oddie et al 1970 considered deficient iodine in chronic hemodialysis patient as a cause of goitre as iodine is removed during dialysis.

Koutras et al 1972 reports results similar to earlier study by Wayne et al 1964 to the extent that, even when on hemodialysis there was increased iodine levels in CRF patients suggesting iodine excess as a cause uraemic goitre contrary to the report by Oddie et al.

Ramirez et al. 1973 studied the existence of goitre in patients of renal failure on chronic hemodialysis, of the 53 patients 31 had clinically apparent goitre, besides this, they noted low iodine uptake in the study. Serum T4 levels were low more so in the clinically evident goitre cases, serum T3 and TSH were shown to the normal, so were T3 resin uptake & thyroxine binding globulin Capacity. The definite cause of goitre in these patients could not be identified and various possibilities were given, the most probable cause is accumulation of goitrogenous substances in uremia because goitre was detected in patients of CRF even before dialysis was commenced, this seemed practical as normal kidneys are able to excrete these substances whereas renal failure causes their accumulation. These substances are either poorly dialyzable or that they have already initiated the process so as to cause the goiter. Decreased iodine concentration do not seem to be a possibility as there were low values of iodine uptake and serum thyrotropin levels were normal though
extraneous supplementation of TRH raised the serum thyrotropin level. Histologically 6 of the patients who have undergone thyroid biopsy 3 showed normal structure gland, one showed colloidal nodule and another had evidence of focal thyroditis however none showed thyroid antibodies or immune deposit ruling out chronic thyroditis as explanation of decreased serum T4, T3 and free T4 values. T4 levels were high in the study by Baily et al [1967] but low serum T3 was reported by Lim et al [1975] in another study.

To study the acute effects of dialysis Kalk et al. [1980] measured thyroid hormone levels Both before and after a single dialysis in 57 patients. They saw significant elevation of T3 and T4 and free thyroxins index but no significant change of TSH levels. Long term Regular hemodialysis revealed no significant rise of free or total thyroid hormone on subsequent dialysis. They rather showed lower levels of thyroxine to the extent that Goitre may have developed. There was blunting of the pituitary to lower serum thyroid hormone levels inspite of giving exogenous thyroid releasing hormones.

In Ramirez et al 1976, the percentage of goitre noted was 32% apart from goiter, no other feature of hypothyroidism was seen. It was seen thyroid hormone levels showed a rising trend till three month of dialysis but one year of continuing dialysis lead to decrease levels, possibilities of decreased values are Hemodilution, increased faecal loss
of thyroxine or direct intrathyroidal defect in hormone genesis or hormone secretion.

Mooradian et al 1983 concluded that there is altered iodine trapping in CRF patient.

Thyroid function test in chronic renal failure were further analysed by sennesael et al [1985]. Thyroxine and tri-iodothyroine were low up to the hypothyroid range, thyrotropin, free thyroxine free tri-iodothyroinine were found to be normal. This study further analyzed iodine metabolism in chronic renal failure. This was done to find Possible relationship between intra thyroidal iodine pool and thyroidal dysfunction.

In clinically euthyroid persons on maintenance hemodialysis for a minimum period of 6 months, this study however, could not derive any such relationship. In conclusion they stated that the measurement of free thyroxine or free tri-iodothyronine was much useful than free thyroxine index or free triiodothyronine index. The indices take in to account the binding capacity of the hormones to their carrier protein. Since thyroid hormone binding capacity of the serum proteins are decreased and hormones can be displaced from their binding site by toxic substances in uremia results can be misleading. But free hormone levels are not shown to change significantly in chronic renal failure. Similar studies regarding the iodine storage function of thyroid gland were conducted earlier by
Ramirez [1976] and Silverberg [1973] and they could not find any definite relationship as mentioned above.

Richard et al, [1985] revealed a unique case of hyperthyroidism while studying the thyroid function test in patients on regular hemodialysis. They described for the first time the interaction between hemodialysis and thyrotoxic heart disease, paroxysmal atrial fibrillation and severe hypotension, all of which interfered with hemodialysis. Correction of this state allowed resumption of hemodialysis.

As in early study by Ramirez [1976] enlargement of thyroid gland was seen this time ultrasonic technique by Hegidius et al [1985]. Thyroid gland volume was found to be increased in uremic patients than in controls. Clinically however, no goiter was visible. Here again the patients were kept on maintenance hemodialysis.

Bermudz et al 1974 reported decreased serum T3 but normal serum T4 & thyrotropin in patient of urinary sepsis. Gemma et al showed slightly lower values of T3 in diabetic nephropathy as with other nonthyroidal illness. Along with it, circulating inhibitor of extra thyroidal conversion of T4 in liver of kidney disease patients.

Hegiduis and his co-workers also confirmed free thyroxine as a better parameter than free thyroxine index to detect any altered thyroid state. Further development in this field was done when a comparative study of thyroid function was done on patients of hemodialysis and
chronic ambulatory peritoneal dialysis and healthy control by Pagliacci et al [1987]. Significant reduction in total thyroxine; total tri-iodothyronine; reverse iodothyronine and free thyroxine was noted. Thyrotropin and free tri-iodothyronine was found in normal range in both hemodialysis and chronic ambulatory peritoneal dialysis. Free thyroxine levels were low but were not so low as to reach below normal range. A difference noted between patients on hemodialysis or chronic ambulatory peritoneal dialysis was that there was significant lowering of thyroid binding globulin and albumin in the latter group. ‘Low T4 syndrome’ was found to exist in both the groups. The cause in each group however, was different. In Chronic ambulatory peritoneal dialysis patient group, cause was the reduced serum binding of thyroid hormone, whereas in hemodialysis the cause was Probably thyroxin binding inhibitors or structural abnormalities of thyroid Binding proteins. In the former group heavy protein loss leading to thyroid dysfunction was reported by Robey et al 1989.

Intrinsic defect of gland was suggested by Hegedus et al [1987] as was done earlier Carter et al. Decreased levels of colloidal glycoprotein of the thyroid gland in uremia support this fact further. Decreased thyroglobulin levels correspond to decreasing levels on subsequent dialysis.
Similarly Dzhavad et al [1987] also showed decreased thyroxine concentration and weakening of thyroid function in CRF apart from other endocrinological abnormalities.

Isolated studies on females with CRF was conducted by Rudolf et al 1988. Basal thyrotropin & thyrotropin releasing hormone [TRH] stimulated levels were measured & deviation from normal was found in 7 out of 11 patients. The pituitary thyroid axis was further studied by Hardy et al 1988. Serum thyroid horomones were significantly low & in hypothyroid range in most of the patient on dialysis than that of control. Serum thyrotropin was raised but did not correspond to the decreased serum thyroid levels. This suggested that there was impaired response of Pitutary to decreased thyroxine levels. Possibly chronic illness evoke a Smaller than normal increase in thyrotropin, in response to decreased Thyroid hormone levels.

Sakuri et al 1988 took pre & post dialysis samples of patient on hemodialysis and measured various parameters of thyroid gland function. Sakurai et al studied serum total &free thyroxine, and total & free triiodothyronine. The thyroid hormone indices, the ratio between thyroxine & thyroxine binding globulin and thyroid hormones were negatively correlated with serum creatininc levels. The ratio between thyroxine & TBG were lower & showed improvement after hemodialysis indicating hemodilution. This also indicated decreased affinity of TBG to
thyroxine as a factor responsible for low Thyroxine, supporting the study by Paglicacci et al 1987, who had also showed that thyrotropin levels remained higher before & after dialysis, while triiodothyronine remained low before & after dialysis. The study concluded the presence of circulating thyroid hormone binding inhibitors [THBI]. The studies are similar to those of Chopra et al 1983.

Gemma et al 1988 while studying for circulating inhibitors in CRF discovered an inhibitor of extrathyroidal conversion [IEC] of thyroxine to triiodothyronine in the casuation of low triiodothyronine in patient of nonthyroidal illness including CRF. Low tri-iodothyronine levels were also noted by Hosimoto et al 1988 but Thyrotropin levels were normal or elevated.

O’sullivan et al 1989 did thyroid & pitutary function study in a small group of patients. They found decreased serum total & free thyroxine levels they also found lowered thyrotropin in response to TRH, in their study dialysis did not have much effect.

Dijiurica et al. [1989] showed like in other studies that thyroid gland function to maintain the euthyroid range and dialysis increases both thyroxine and triiodothyronine slightly but concentration still remain in the euthyroid range. The findings were similar to those by Kalk et al [1985]. Bartalena et al [1990] again demonstrated decreased total, free thyroxine and tri-iodothyronine levels in serum of chronic renal failure
patients undergoing dialysis. Despite the decreased levels, there is no supranormal rise of thyrotropin as that in primary hypothyroidism. They suggested low tri-iodothyronine values may be due to increased clearance by falling kidney as also proposed by Dijuroca et al [1989]. Bartalena and co-workers also noticed the failure of nocturnal surge of thyropin to be significant in C.R.F. patients than in normal controls. The mean morning values were normal in both groups. The study showed impaired TSH secretion in CRF, while base line measurements in the morning may not reveal decreased pituitary response and this fact explains the subclinical hypothyroid state.

Daminov et al 1990 measured the thyroid function tests in children with congenitally abnormal differentiation of renal tissues. 44 children with different varieties of renal dysembryogenesis were examined. Children with acquired renal pathology made up a reference group. Children with congenital nephropathies manifested a higher incidence of delayed growth. These patients showed laboratory signs of both primary and secondary hypothyroidism.

Mehta et al 1991 suggested patients of CRF on conservative treatment showed significant decreased in total T3, Total T4 and free T3 as compared to normal. Whereas patient of CRF on regular dialysis showed less decrease in total T3, Total T4, free T3 and TSH as compared to normal.
Joseph et al 1993 they concluded that serum T3 and serum T4 were significantly lower and increase in TSH, most of the thyroid functions returns to normal after hemodialysis and renal transplantation.

Kayima et al 1992 studied thyroid hormone profile in patients with CRF on conservative management and regular hemodialysis, they concluded T4 and T3 were low in patients compared with controls, TSH was higher in patients than in controls. They reported no significant differences in all parameters between the patients on conservative management and those on hemodialysis.

Kohli and Mahajan et al 1993 concluded S. T4 and S. T3 levels were decreased relatively more comparative to T4 level.

Hochstettrner et al 1994 found low T. T3 low T T4 and free T4 in patient of CRF undergoing hemodialysis S. TSH was normal.

Lukinac L et al 1996 did study of chronic hemodialysis on thyroid function in end stage renal disease. They found that decrease level of thyroid hormone and TBG in ESRD. TSH did not change significantly during chronic hemodialysis, TBG increases after hemodialysis.

Lim VS et al 2001 concluded that CRF after thyroid function in multiple ways including low circulating thyroid hormone concentration, altered peripheral hormone metabolism, disturbed binding to carrier protein, possible decrease in tissue thyroid hormone content and increase iodine store in thyroid gland.
**Thyroid hormones in other non-thyroidal illness:**

First detailed study of this parameter was reported by Oppenheimer et al (1963) which showed decrease in serum thyroxine binding albumin, thyroxine and decreased protein bound iodine. For last two and a half decades, various methods to measure thyroid hormone levels have enabled the detection of various alterations. These can be classified into four categories (Brenner, 1986).

**Low T3 syndrome:**

Characteristically occurring with low T3 but normal serum T4 attributed mainly to decreased peripheral conversion of T4 to T3. These changes are non-specific occurring in liver disease, malignant disease, kidney and heart failure. Non-specificity confines not to systemic illness, but also to conditions of caloric deprivation, after major surgery and after drug administration. Clinically they may be euthyroid, except for prolonged achillies reflex in some patients reported by Carter et al (1974). Bermudz et al (1975) measured serum T3 and TSH levels in clinically euthyroid patients and found these to be low.

**Low T3 and Low T4 syndrome:**

Oppenheimer (1968) reporter that patients falling in the end stages of severe illness or terminal stages are known to have decreased levels of both low T3 and T4, thus low T4 levels are associated with graver prognosis than low T3 alone. Serum thyroid stimulating hormone was at
normal or higher range of normal, while response to TRH was normal. Low levels are attributed to decreased serum binding of hormone, demonstrated by presence of thyroid binding inhibitor proteins, as reported by Oppeheimer et al (1982) and Chopra et al (1983).

**High T₄ Syndrome:**

This is seen in excess iodine intake or acute illness and in certain chronic illnesses, like biliary cirrhosis, ulcerative colitis (Carter et al, 1974). Increased concentration of thyroid binding globulin is the probable cause of this high T₄ levels, but as in the other syndromes mentioned above, T₃ levels are lower, because peripheral conversion of T₄ to T₃ is affected in all systemic illnesses.

Borst et al (1977) reported elevated T4 Gavin et al (1979) reported 15 patients with severe acute systemic illnesses with increased thyroxin and freethyroxine index. Recovery phase had decreased T₄ levels. Thyroid functions in other non-thyroid illness like liver disease or chronic obstructive pulmonary disease or malignancy were different than chronic renal failure, because they do not have goiter, they are clinically euthyroid, they have moderate lowering of serum thyroxine and not severe T₄ lowering.

**Thyroid hormones and adaptations to illness:**

In the above few paragraphs it is noteworthy that systemic illness affect thyroid hormone and severity is again related to alterations in
various types of hormones. Clinically, however the patients usually remain euthyroid. Though physical examination is useful in young patients, in older patients apathetic hypothyroidism intervenes. Normal values or decrease in serum T3 should not itself exclude the diagnosis of hyperthyroidism (Thibaldi, 1985). Therefore these altered levels may be an adaptive change of body mechanism to maintain homeostasis in the altered metabolic state of non-thyroidal illness including CRF. The impact of decreased serum thyroid hormone levels was evaluated by Gardner et al (1979) who suggested that the decreased serum T3 level of fasting patients is associated with reduced muscle protein break down and therefore may be considered an important adaptation to decreased caloric ingestion. Similarly Bacci et al (1982) revealed augmenting levels of TSH in sick patients during their recovery phase. This facilitates more rapid restoration of normal serum T4 and T3 after requirement for adaptation is over.

Chopra et al studied that high concentration of cortisol may inhibit the action of thyroid stimulating hormone on the thyroid gland which is supported by Joseph (1985). Other causes of reduced TSH as revealed by Morely (1981) may dopamine, growth hormone, opiate peptides, besides cortisol’ all of which are secrete in response to stress, severe illness may also reduce capability of hypothalamic to secrete thyrotropin releasing hormone (TRH).
Dopamine suppresses T4 production was also confirmed by Kaptein (1982). He revealed that dopamine probably inhibits TSH release. From the above data we have seen T3 and T4 levels are low corresponding to severity of systemic illness, still patients do not show any overt signs or symptoms of hypothyroidism.

Various methods are used to measure the free thyroxine in acute illness as well as chronic illnesses including patients of chronic renal failure on hemodialysis. Several commercial kits were used and free thyroxine and free thyroxine index were measured. But significant proportion of patients in each groups showed subnormal values of free thyroxine (Chopra et al 1983). In another study while free T4 levels were found increased as reported by Joseph (1985), it was seen that free thyroxine levels were normal when measured by equilibrium dialysis (Chopra, 1979).

Decreased T3 levels can be explained by decreased peripheral conversion of T4 to T5, the same defect which causes increased reversed T3 levels, the inert metabolic of T4, but one finds it more difficult to explain the decreased T4 levels. Suspicion of secondary or tertiary hypothyroidism is raised because thyrotropin concentrations are not elevated to the range seen primary thyroid failure, suggested by Nicoloff (1972). Alternatively this reduction in total serum T4 concentration could be due to an acquired defect. Here T4 binding to serum carrier protein is
reduced possibly similar to congenital absence of thyroid hormone binding globulin. T4 turn over rates as supported by shorter serum half life of T4 of severely ill patients reported by Bellabarba et al (1968) may be responsible for low T4, Kaptein et al (1981) confirmed this by increased metabolic clearance rate of T4 in critical illness. Increased T4 clearance secondary to an increase in free thyroxine fraction was also suggested by them. Increased T3 clearance was also noted. Moreover, the decreased excretion rate of T4 from intravascular space suggests an impaired extravascular binding of T4, probably due to circulating inhibitors of protein binding (Chopra et al 1979). Consistent to above findings, reverse T3 metabolic clearance decreases.

Nishikawa M et al (1993) reported that plasma free T4 (FT4) concentrations could be increased during hemodialysis in patients with chronic renal failure (CRF) because an increase in non-esterified fatty acids (NEFA) could interfere with the binding of T4 to thyroxine binding globulin. FT4 actually increases during hemodialysis due to the actual increase in NEFA, although the marked increase in FT4 during hemodialysis as measured by equilibrium dialysis is an overestimation due to the invitro generation of NEFA. Okabayashi T et al (1996) reported that free thyroxine (FT4) is often low in patients with CRF with low serum concentrations of tri-iodothyronine (T3). FT4 values were reported as being with in the healthy reference range.
Lukinac L et al (1996) reported that the levels of all thyroid hormones were found to be decreased, especially some hormones such as FT3 (87%), T3 (93%) and FT4/FT3 (90%) TSH did not change significantly. TBG level from decreased values (37%) returned to the normal range after hemodialysis.

Hochsteter LA et al (1994) reported serum thyroid stimulating hormone was normal, and the thyroid stimulating hormone response to thyrotropin releasing hormone stimulation was in the low normal range. Serum prolactin was elevated to more than twice the normal level and the prolactin response to thyrotropin releasing hormone was also blunted.

Joseph LJ; Desai KB et al (1993) mean serum TSH levels in the patient group of 2.33 μu/ml (0.07-7.3) was significantly higher in comparison to 1.73 μu/ml (0.25-46) in normal subjects (p<0.001). TSH levels showed a gradual rise with corresponding depression in their T3, FT3 and T4 levels were on hemodialysis (HD).

Kaptein EM et al (1996) reported that in patients with CRF elevated basal TSH values, which may transiently increase to greater than 10mU/litre, blunted TSH response to TRH, diminished or absent TSH diurnal rhythm, altered TSH glycosylation, and impaired TSH and TRH clearance rates. In addition, serum total and free T3 and T4 values may be reduced, free T3 levels are elevated while total values are normal. Dialysis therapy minimally affects thyroid hormone metabolism while
zinc and erythropoetin administration may partially reverse thyroid hormone.