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A study to evaluate the effect of l-thyroxin supplementation on serum creatinine and insulin-like growth factor-1 in hypothyroid subjects: A longitudinal study from eastern India

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Abstract
The aim our study is to detect any renal compromise if at all present in hypothyroid state and whether such compromise is correctable by LT4 replacement. Longitudinal, self-controlled study was performed with 60 Drug-naïve (untreated) primary hypothyroid patients aged between 18 to 60 years with normal urinary findings, no recent therapy with cephalosporines (within two weeks) and with a normal creatinine level (upto 1.3mg/dl). Fasting blood samples were taken for Sr. IGF1 & Sr. creatinine. Then the patients were advice to take daily L-thyroxine (1.6 microgram/kg/day) and reviewed at least after 12 weeks and fasting blood samples were taken for Sr. creatinine and Sr. IGF1 provided the patients achieved euthyroid state. Sr. creatinine, IGF1 and eGFR values before and after levothyroxine therapy were compared statistically. Before and after treatment changes were TSH (86.33 ± 51.9 to 2.60 ± 1.34), IGF-1(182.6 ± 129 to 204.2 ± 118.9) Sr. creatinine (0.92 ± 0.23 to 0.77 ± 0.16) and eGFR (88.39 ± 33.82 to 104.8 ± 26.39). A significant negative correlation between change in TSH and change in eGFR with positive correlation between change in IGF1 & change in eGFR were found. We conclude from our study to consider evaluation of thyroid functions in all CKD patients and to treat hypothyroidism with an expectation of improvement of renal function that may delay the progression of the disease to ESRD and a mild renal compromise if found in hypothyroid state should not be unnecessarily investigated before adequate thyroid hormone replacement.

Keywords: renal compromise, hypothyroid, TSH, serum creatinine, EGFR.

Introduction

Renal jeopardy in hypothyroidism as described in standard text book are decreased renal blood flow, decreased GFR, decreased tubular absorption and decreased secretary maxima. But the clinical chemical parameters like Sr. BUN, Sr. Creatinine and Sr. Uric acid of renal compromise remain unaltered in hypothyroidism [1]. In 1996, Jesus Montenegro *et al* published a paper showing subtle decrease in GFR and rise of Sr. Creatinine in significant percentage of hypothyroid patents, those were corrected by thyroid hormone replacement [2]. In 1999, a similar study was published by Kriesman and Hennessey showing reversible elevation of Sr. Creatinine levels in hypothyroid cases. [3] A study (2004) conducted by the Division of Endocrinology and Diabetes in University Hospital of Zurich pointed towards an association between low IGF-1 (also VEGF) and increased creatinine level in hypothyroidism [4] It is known IGF-1 increases GFR in humans. [5] Finally, 2011 a population based study (HUNT study) showed a clear association between decreased eGFR and hypothyroidism but the study did not examine the effect of L-thyroxine replacement.[6] Therefore change in clinical chemical indicators of renal functions in hypothyroid state are not well characterized and potential area for study. The aims our study is to detect any renal compromise if at all present in hypothyroid state and whether such compromise is correctable by LT4 replacement.

Methods

This longitudinal, self-controlled study was performed with 60 Drug-naïve (untreated) primary hypothyroid patients aged between 18 to 60 years with normal urinary findings on R/E, M/E and no H/O recent therapy with cephalosporines (within two weeks), with a normal creatinine level (upto 1.3mg/dl), attending endocrinology OPD of Dept. of Endocrinology & Metabolism IPGME&R, SSKM Hospital, Kolkata during the duration of May 2012 to December 2014. Patient with hypertension, diabetes mellitus/Prediabetes (With FPG≥110mg/dl), abnormal urinary finding on R/E, M/E, Jaundice, any kidney disease and recent therapy with cephalosporins (within 2 weeks) or any nephrotoxic drug were excluded from study. Clinical examination performed were general survey and anthropometry (Ht,wt, pallor, oedema, B.P, BMI, ankle jerk etc.), systemic examination**,** urine for R/E, M/E and fasting plasma glucose. Fasting blood samples were taken for Sr. IGF1 & Sr. creatinine. Then the patients where advice to take daily L-thyroxine (1.6 microgram/kg/day) and reviewed at least after 12 weeks. On second visit after least 8 weeks again fasting blood samples were taken for Sr. creatinine and Sr. IGF1 provided the patients achieved euthyroid state. Sr. creatinine, IGF1 and eGFR values before and after levothyroxine therapy are compared statistically using Wilcoxon matched pair test and correlation of other variables using spearman's rank correlation test.

Result

Data were analyzed using GraphPad Prism for windows (Version 6.01, GraphPad Software, Inc. La Jolla, CA, USA). Results of continuous measurements were expressed as mean ± SD or median (range) & result of categorical measurement was

expressed in terms of frequency & percentage. P <0.05 was considered as statistically significant. Wilocoxon matched pair test was used to find the significance of study parameters before & after treatment. Spearman's rank correlation was used to determine correlations between various study parameters. General characteristics of the study population is given in table 1. Change in TSH, IGF-1, Serum Creatinine and eGFR before and after treatment is given in table 2 & figure 1, table 3 & Figure 2 and table 4 & figure 3 & 4 respectively. Correlations between Age with first visit values of IGF-1, Creatinine (Cr), eGFR, TSH and correlations between mean change in values (before and after treatment) of IGF-1, Creatinine, eGFR, TSH is given in table 5 and 6 respectively.

Table 1: General characteristics of the study population

Parameters	Values
Age (years), median (range)	32 (18-57)
Sex Male, n (%) Female, n (%)	 30 (50) 30 (50)
BMI (Kg/m²)	24.47 ± 5.31

Table 2: Change in TSH

Parameters	Before treatment (n=60)	After treatment (n=60)	P value
TSH	96.33 ± 51.93	3.60 ± 1.34	<0.001

Table 3: Change in IGF-1

Parameters	Before treatment (n=60)	After treatment (n=60)	P value
IGF-1	183.6 ± 129	206.2 ± 118.9	<0.01

Table 4: Change in Serum Creatinine and eGFR

Parameters	Before treatment (n=60)	After treatment (n=60)	P value
Serum creatinine	0.92 ± 0.23	0.77 ± 0.16	<0.001
EGFR	88.39 ± 33.82	104.8 ± 26.39	<0.01

Table 5: Correlations between Age with first visit (drug naive hypothyroid cases) values of IGF-1, Creatinine (Cr), eGFR, TSH

	IGF-1	Cr	eGFR	TSH
Age	-0.281 (P=0.195)	0.315 (P=0.143)	**-0.510 (P=0.013)**	0.087 (P=0.693)

Table 6: Correlations between mean change in values (before and after treatment) of IGF-1, Creatinine, eGFR, TSH

	dIGF-1	dTSH
dCr	-0.367 (P=0.085)	0.483 (P=0.020)
deGFR	0.529 (P=0.009)	-0.553 (P=0.006)

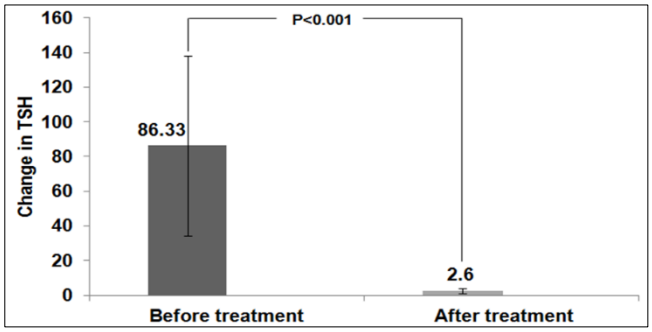

Fig 1: Change in TSH

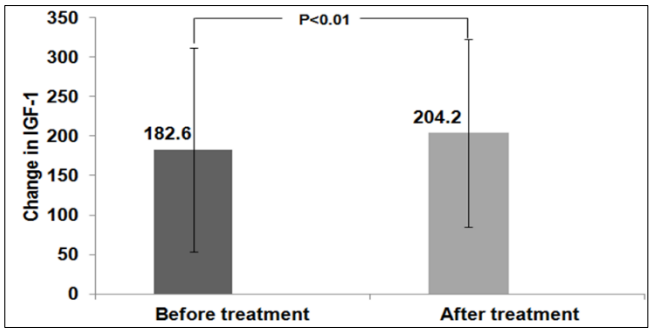

Fig 2: Change in IGF-1

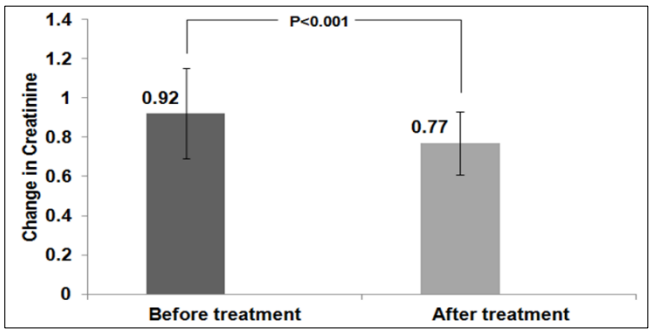

Fig 3: Change in Serum Creatinine

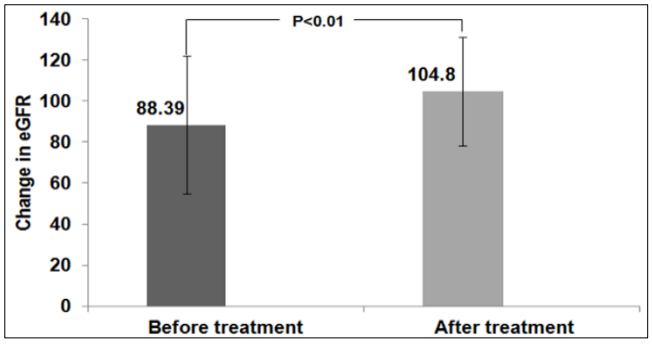

Fig 4: Change in eGFR

Discussion

In our study eGFR is significantly low in drug naïve hypothyroid subjects (mean GFR= 88ml/min) compare to eGFR of the same population after at least 12 weeks of levothyroxine therapy. We found a statistically significant negative correlation of eGFR with age, which is obvious as there is loss of functional nephrons with increasing age. Our study showed a very significant negative correlation between change in TSH and change in eGFR. This indicates lowering of serum TSH from its initial high value to its normal range is clearly associated with betterment of kidney functions. There is also positive correlation between change in IGF 1 & change in eGFR. This indicates a strong probability of IGF 1 mediated increase in GFR and the study of Christoph, Schmidt, *et al* also showed similar results. IGF 1 infusion is known to increase renal plasma flow & GFR by 20-30% and decreases renal vascular resistance in humans and rats[1]. In single nephron micropuncture study IGF 1 infusion decreases both afferent & efferent arteriolar resistance resulting in an increased GFR, probably due to an expansion & relaxation of mesangial cells allowing more surface area available for ultrafiltration. IGF 1 mediates its effects on glomerular hemodynamics via the type 1 IGF receptor & secondarily enhanced NO synthesis that mediates generation of cGMP[2]. Hypothyroidism is associated with a low IGF 1 state and thyroid hormones are known to increase the expression of both IGF1 and type 1 IGF receptors in kidney. The correlation analysis in our study points towards the probability of IGF 1 mediated increase in eGFR after L-thyroxine replacement of the hypothyroid subjects. Our study further confirmed that a mild renal jeopardy in the form of reduced GFR is associated with hypothyroidism which can be reversed by L-thyroxine replacement and most probably the reduced GFR is due to a low IGF1 state commonly observed in hypothyroid patients. [7, 8, 9] Finally, we drive two clinical suggestions from our study. Firstly, to consider evaluation of thyroid functions in all CKD patients and to treat hypothyroidism in CKD patients with an expectation of improvement of renal function that may delay the progression of the disease to ESRD and secondly, a mild renal compromise if found in hypothyroid state should not be unnecessarily investigated before adequate thyroid hormone replacement.

Conclusion

We conclude from our study to consider evaluation of thyroid functions in all CKD patients and to treat hypothyroidism with an expectation of improvement of renal function that may delay the progression of the disease to ESRD and a mild renal compromise if found in hypothyroid state should not be unnecessarily investigated before adequate thyroid hormone replacement.

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