

Original article

Comparative study on HbA1c and eGFR in patient with and without Subclinical hypothyroidism

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ABSTRACT

Background: Diabetic nephropathy is one of the major complications of diabetes and major cause of end-stage renal disease. Diabetic nephropathy increases the risk of death, mainly from cardiovascular causes and is defined by increased urinary albumin excretion in the absence of other renal diseases. Other endocrinal factors like Subclinical hypothyroidism (SCH) which can contribute to cardiovascular and other complications of diabetic nephropathy has not been studied extensively in India. Aim of the study is to compare HbA1c and eGFR in patients with and without SCH.

Methods: In all the selected 218 patients of type 2 diabetes mellitus, renal function was screened by performing serum creatinine by alkaline picrate Jaffe's method and confirmation done by eGFR by using ID-MS traceable MDRD equation. Thyroid function assessed by using ELFA method in VIDAS instrument and these patients divided as comparative groups as depending on their thyroid status i.e. SCH and without SCH.

Results: Significant difference between eGFR, serum creatinine, serum TSH & T4 were observed between two groups (P<0.05).

Conclusion: Diabetic nephropathy is relatively common condition in subjects with subclinical hypothyroidism when compared to subjects with normal thyroid function.

Key words: Diabetes mellitus, SCH, RPG, HbA1c, serum T4, serum TSH, eGFR by MDRD.

Introduction

The interactions between kidney and thyroid functions are known for years. Thyroid hormones are necessary for growth and development of the kidney and for the maintenance of water and electrolyte homeostasis. On the other hand, kidney is involved in the metabolism and elimination of thyroid hormones. From a clinical practice viewpoint, it should be mentioned that both hypothyroidism and hyperthyroidism are accompanied by remarkable alterations in the metabolism of water and electrolyte, as well as in cardiovascular function. The effects of

hypothyroidism on the kidney are usually opposite to the effects of hyperthyroidism.¹ The renal blood flow(RBF) is reduced in hypothyroidism by decreased cardiac output (negative chronotropic and inotropic effects),² increased peripheral vascular resistance,³ intrarenal vasoconstriction,⁴ reduced renal response to vasodilators,⁵ and a reduced expression of renal vasodilators such as vascular endothelial growth factor (VEGF) and insulin like growth factor-1 (IGF-1).⁶ In addition, pathologic changes in the glomerular structure in hypothyroidism, such as glomerular basement

membrane thickening and mesangial matrix expansion, may also contribute to reduced RBF.⁷

Hypothyroidism results in a reversible elevation in serum creatinine due to the reduction in GFR. Hypothyroidism also results in increased glomerular capillary permeability to proteins.⁸ The consequent proteinuria often precedes the reduction in GFR in hypothyroidism.⁹ All these effects generate changes in water and electrolyte kidney management.¹⁰ Moreover, the decline of kidney function is accompanied by changes in the synthesis, secretion, metabolism, and elimination of thyroid hormones. Thyroid dysfunction acquires special characteristics in those patients with advanced kidney disease. The treatment of hypothyroidism helps better control of other associated conditions. The ability to diagnose and treat unsuspected hypothyroidism in these populations may greatly enhance the quality of life. Hence there is need to detect such cases to prevent morbidity and deterioration of quality of life. On the other hand, the different treatments used in the management of patients with kidney and thyroid diseases may be accompanied by changes or adverse events that affect thyroid and kidney function respectively.

Studies done suggest that thyroid disorders are more common in both type 1 and type 2¹¹ than in the general population, highest in type 1 diabetic females and lowest in type 2 diabetic males; most common disorder being subclinical hypothyroidism. Thyroid dysfunction is more common in older patients. Several alterations in thyroid function are found in DM. The most profound changes occur in patients with type 1 diabetes mellitus. Plasma T4 is normal where as plasma T3 is diminished, and plasma level of T3 is elevated in DKA or in patients with severely uncontrolled diabetes. The actual prevalence of diabetes is unknown, as it is an iceberg disease.¹²

Although an increase in incidence and prevalence of both type 1 and type 2 diabetes have occurred globally. Of the two broad classes of DM, type 2 is more prevalent so the present study includes patients with type 2 DM. Thyroid function tests are especially recommended in patients with clinical suspicion and / or unexplained changes in diabetic metabolic control or serum cholesterol and weight gain. The definition of subclinical hypothyroidism is purely a biochemical one, defined as elevated serum thyrotropin (TSH) levels but normal free thyroxine (FT₄) levels.¹³ By definition, subclinical hypothyroidism refers to biochemical evidence of thyroid hormone (FT₄) deficiency in patients who have few or no apparent clinical features of hypothyroidism. There are no universally accepted recommendations for the management of subclinical hypothyroidism, but the most recently published guidelines do not recommend routine treatment when TSH levels are below 10 mU/L. It is important to confirm that any elevation of TSH is sustained over a 3-month period before treatment is given. As long as excessive treatment is avoided, there is no risk in correcting a slightly increased TSH. Moreover, there is a risk that patients will progress to overt hypothyroidism, particularly when the TSH level is elevated and TPO antibodies are present. Treatment is administered by starting with a low dose of levothyroxine (25–50 µg/d) with the goal of normalizing TSH. If thyroxine is not given, thyroid function should be evaluated annually.¹⁴ Study objectives are -

- 1) To estimate the prevalence of nephropathy in Type 2 diabetic patients with subclinical hypothyroidism.
- 2) To estimate the prevalence of nephropathy in Type 2 diabetic patients without subclinical hypothyroidism.
- 3) To compare the nephropathy between the above two groups.

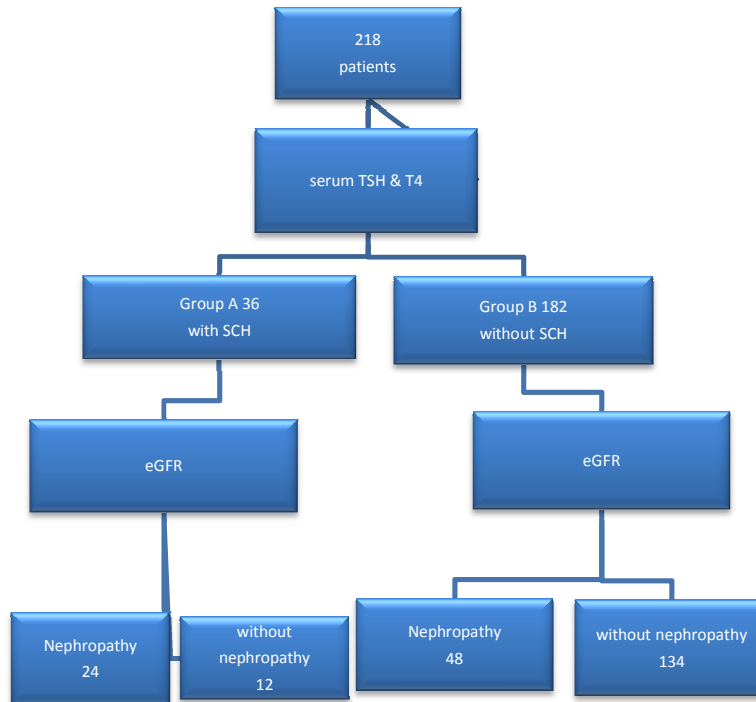
4) To estimate HbA1c and correlate with nephropathy & thyroid status.

MATERIAL AND METHODS

This was a comparative study done in 218 patients conducted at G S L Medical College and hospital at OPD General Medicine, Rajahmundry, Andhra Pradesh. All the study patients were enrolled as per WHO guidelines who had attended GSL Medical College with Type 2 diabetes mellitus after satisfying inclusive and exclusive criteria included in the study. Known type 2 diabetic patients of age

between 30 years to 80 years treated in Hospital. Thyroid function was assessed by immunoassay using ELFA method & these Patients were divided into comparative groups depending on their thyroid status i.e. SCH and without SCH. Renal function was screened by performing serum creatinine by alkaline picrate method and confirmation was done by eGFR using ID-MS traceable MDRD formula^{15,16} $[GFR(mL/min/1.73m^2) = 175 \times \text{serum creatinine [mg/dL]}^{-1.154} \times \text{age [years]}^{-0.203} \times (0.742 \text{ if female}) \times (1.21 \text{ if African American})^{56}$.

STUDY DESIGN



The total study population was 218, out of which 36 subjects(17%) were categorized as group A [with SCH] and 182 (83%)were categorized as group B [normal thyroid function], after all the subjects underwent detailed examination of their thyroid profile (TSH and Free T4).Anthropometric and hemodynamic details were obtained from medical records of all the study subjects. Thyroid

function test was done by immunoassay and TSH value of 5 - 10mIU/L with normal(60-120 nmol/L) Free T4 was considered as having subclinical hypothyroidism.

Plasma samples were used for the estimation of HbA1c by immunoturbidimetric method and Serum Creatinine by Jaffe’s method. Blood samples were taken in the morning after 12 hours overnight fast

for TSH and free T4 and were done following the standard enzymatic procedures.

STATISTICAL ANALYSIS

A statistical package software system 21.0 for windows (SPSS) and Microsoft Excel 2007 were used for statistical analysis. Data were expressed as mean ± SD or proportions. Statistical analyses included the unpaired *t* test (for continuous measures). All known potential confounders (age, gender, HbA1c, serum TSH and serum T4) were entered in the univariable model to ensure giving an unbiased estimate for the relation between diabetic nephropathy and subclinical hypothyroidism & without subclinical hypothyroidism. A *P* value of <0.05 was considered to be statistically significant.

RESULTS

Of the 218 type 2 diabetic patients, analysis done between two groups showed,36 having subclinical hypothyroidism in GROUP A(total no of patients with Nephropathy – 24 and without nephropathy- 12) where male and female ratio is 25:11 (mean age: 51.94±12.06) and 182 in GROUP B with

normal thyroid (with nephropathy- 48 and without nephropathy or normal kidney function -134) where male and female ratio is 124:58(mean age: 52.05±13) . The eGFR [mL/min/1.73m²]in group A (mean: 57.33±28.74) and in group B(85.89±30.13), serum creatinine[>1.2 mg/dl]in group A(mean : 1.456±0.532) and in group B(mean : 1.018±0.495), serum TSH[0.25-5 µU/ml] in group A(mean : 6.7758±1.3693) and in group B(mean : 2.5574±0.8433) , serum T4 [60-120 nmol/L] in group A(mean : 94.2739±14.29) and in group B(mean : 99.3730±13.22) (table 1), showed statistical significance. All other variables did not show significance. Prevalence was found more in male, 68%(17 out of 25) patients with SCH(table 2). Overall prevalence of nephropathy with both Groups combined was 33% (72) and was statistically significant(table 3). Among Group A [Diabetic and subclinical hypothyroidism subjects] 67%(24) and in GROUP B[Diabetic and without subclinical hypothyroidism subjects] 26%(48) had Nephropathy.

TABLE 1-Number of study subjects in each Group, M:F ratio & RPG , HbA1c, serCreatinine and ser TSH & ser T4 of both groups.

variables	GROUP A 36(SCH) no [%]	GROUP B 182 (Without SCH) No [%]	P VALUE
M:F	25:11	124:58	
eGFR [mL/min/1.73m ²]	57.33±28.74	85.89±30.13	0.0001
AGE [years]	51.94±12.06	52.05±13	0.9624

RPG	293.11±63.14	279.37±57.22	0.1972
HbA1c [>6.5]	7.544±0.879	7.738±0.839	0.2109
CREATININE [>1.2 mg/dl]	1.456±0.532	1.018±0.495	0.0001
Ser TSH [0.25-5 µU/ml]	6.7758±1.3693	2.5574±0.8433	0.0001
Ser T4 [60-120 nmol/L]	94.2739±14.29	99.3730±13.22	0.0382

TABLE 2.1. Prevalence of nephropathy when compared between males of both groups and females of both groups. 2. Comparison between males and females of identical group.

	GROUP A SCH		GROUP B Without SCH	
	TOTAL no	Nephropathy no[%]	TOTAL no	Nephropathy no[%]
MALES	25	17 [68%]	124	36 [29%]
FEMALES	11	7 [63.6%]	48	12 [25%]
P VALUE	0.79		0.596	

TABLE 3. Overall prevalence of Nephropathy in study population

Study population no	Nephropathy no[%]	Normal kidney function no [%]
218	72 [33%]	146 [67%]

TABLE 4. Prevalence of Nephropathy in Group A and Group B.

Variables	GROUP A no[%]	GROUP B no[%]	P VALUE
Nephropathy	24 [67%]	48 [26%]	0.0001

DISCUSSION

There are minimal number of studies regarding subclinical hypothyroidism in patients with diabetic nephropathy or normal kidney function which were lacking in comparative studies in both conditions. A recent review has observed that SCH was prevalent in 4–8% of the general population in western countries, and in women who were >60 years of age it was prevalent in up to 15–18% .¹⁷ SCH is recognized as a risk factor for atherosclerotic cardiovascular disease (CVD), hyperlipidemia, low-grade inflammation and hypercoagulability .^{18,19,20} As ESRD and SCH are independent risk factors for CVD mortality, it is possible that patients suffering from both disease entities may have a higher CVD risk. Endocrinal factors like Subclinical hypothyroidism (SCH) which can contribute to cardiovascular ^{21,22,23,24} and other complications of Diabetic nephropathy has not been studied extensively in India. Aim of the study was to find out , prevalence of nephropathy in Type 2 diabetic patients with and without subclinical hypothyroidism.

Earlier cross-sectional analysis showed subclinical hypothyroidism was associated with a greater prevalence of diabetic nephropathy. Some studies reported that thyroid abnormality like goiter in ESRD patients. Few studies, in addition thyroid hormone level abnormalities like low T3 syndrome in patients requiring chronic dialysis as independent predictor of all cause and cardiovascular mortality. Previous studies showed subclinical hypothyroidism was independently associated with albuminuria in people with type 2 diabetes. In this study it was found that there was increased prevalence of Sub-clinical hypothyroidism with 17% in people with eGFR and not with albuminuria , when compared with normal kidney function group which was 67% showing prevalence between diabetic nephropathy and subclinical hypothyroidism.

Subclinical primary hypothyroidism, a relatively common condition among persons with CKD do not require chronic dialysis. A marked decline in kidney function is accompanied by changes in the synthesis, secretion, metabolism, and elimination of thyroid hormones. Earlier studies showed sub-

clinical hypothyroidism was found to be high in diabetic nephropathy patients, of which Low GFR is of statistical significance .

Formal measurements of GFR are time-consuming and expensive, and thus impractical for routine care. A formula predicting GFR was derived from 1070 patients and validated in a further 528 patients being followed in the Modification of Diet in Renal Disease (MDRD) study,²⁵ who had GFR measured by renal iothalamate clearance.²⁶The MDRD formula is a better estimate of GFR than those derived from 24hrs urinary creatinine clearance or the Cockcroft-Gault formula.²⁷ Formula-based estimates of GFR are now commonly referred to as eGFR (estimated GFR), to differentiate them from formally measured GFR. The MDRD formula requires age, gender, race, serum creatinine, serum urea and serum albumin. All of these parameters (except race) are readily available to the clinical chemistry laboratory, whenever serum creatinine is requested. This is a major advantage over the Cockcroft-Gault

formula which requires weight, which is rarely available to the laboratory.

Although numerous contributing factors have been hypothesized, including altered Iodine metabolism, the Wolff-Chaikoff effect or increase in total-body inorganic iodide can block thyroid hormone generation and hence may explain the higher frequency of goiter and hypothyroidism in CKD patients²⁸. Further, chronic metabolic acidosis may cause hypothyroidism in these patients. The possible mechanisms were demonstrated by Brungger et al.²⁹ in their experimental model. They showed that metabolic acidosis significantly decreased serum T₃ and T₄ levels, with a corresponding increase in serum TSH levels thereby resulting in hypothyroidism. Decreased peripheral sensitivity to hormones and autoimmune thyroiditis, the exact underlying mechanisms

linking advanced diabetic kidney disease and primary thyroid dysfunction remain unclear. Conversely, in clinically overt primary hypothyroidism (myxedema), the most significant manifestation of changes in renal function is hyponatremia, which results from an impairment in renal diluting capacity leading to water retention. Moreover, clinically overt hypothyroidism may also cause renal hemodynamic alterations produced by a decreased cardiac output, which lead to a progressive decline in GFR. The pathogenesis of thyroid axis abnormalities in uremia is incompletely understood, and its clinical significance remains unclear. The kidney plays a role on the regulation of metabolism and elimination of TSH and is an important target organ for TSH actions . The decrease in the activity of TSH is accompanied by an inability to excrete an oral water overload. This effect is not due to an incomplete suppression of vasopressin production, or a decrease in the reabsorptive ability in the dilutor segment of the kidney tubule, but rather to a reduction in the glomerular filtration rate . TSH have a hold upon tubular transport of sodium (Na⁺), via their actions on the sodium- potassium adenosine triphosphate pump (Na⁺/K⁺ ATPase) and on the potassium permeability in the membrane of proximal tubules .

A screening program for thyroid dysfunction including 318 patients in which 191 were women with Type2 DM at Segovia in Spain³⁰ showed subclinical hypothyroidism in 34 patients (10.7%) when compared to the screening done in Spain, in type 2 diabetes individuals, the percentage of subclinical hypothyroidism in our study was more ,in Group A or Group B, even though male population was dominant in our study, but in the above study they could not identify any diabetes-related clinical parameter with predictive value on the presence of thyroid dysfunction.

Study in Taiwan³¹ showed in 588 Type 2 diabetic subjects subclinical hypothyroidism was associated with greater prevalence of diabetic nephropathy and did not show a high prevalence of diabetic retinopathy, but our study showed, in patients with diabetic nephropathy there was more prevalence of subclinical hypothyroidism than diabetic nephropathy alone. The increasing prevalence of chronic kidney disease underscores the need for further efforts to understand the metabolic consequences of uremia and address questions such as the impact of thyroid hormone therapy. Studies in db/db Mice showed, T3 prevented progressive kidney damage and remodelling by improving insulin signalling. We need further research to explore the causal relationship between subclinical primary hypothyroidism, diabetic nephropathy and associated complications.

LIMITATIONS

First thing, as it is comparative study, analysis is limited in its ability to establish causal or temporal

relationship between subclinical primary hypothyroidism and Diabetic nephropathy. Second, thyroidal and nonthyroidal causes of subclinical primary hypothyroidism were not identified and diagnosis of diabetic nephropathy was not based on 24hr urine collection test, the gold standard.

CONCLUSIONS

Diabetic nephropathy is relatively common condition in subjects with subclinical hypothyroidism when compared to subjects with normal thyroid function. Hence there is need to look into the regular screening of kidney function in subclinical hypothyroid patients with type 2 DM. There is need for further research to explore the causal relationship between subclinical primary hypothyroidism, Diabetic nephropathy and associated complications by interventional and prospective studies to establish underlying cause for this association and also to make interventional strategies for the same.

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