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Analysis of Insulin Resistance in Newly Detected and Thyroxine Supplemented Cases of Subclinical Hypothyroidism with Special Reference to Geriatric Population

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Abstract

***Context*:** Thyroid hormone causes significant changes on the regulation of glucose homeostasis including IR [Insulin resistance]. There are no remarkable studies researching IR in geriatric and nongeriatric patients of Subclinical Hypothyroidism [SCH] and the changes observed with thyroxine treatment.

***Aims*:** To analyse Insulin resistance in newly detected SCH and Thyroxine supplemented cases of SCH and its comparison in elderly.

***Settings and Design*:** It was an observational cross-sectional hospital-based study.

***Methods and Material*:** It involved 120 SCH patients aged more than 18 years. Group A comprised 60 cases of newly diagnosed SCH cases and Group B was 60 SCH patients on thyroxine treatment for at least 3 months. For both the groups FBS, Fasting Insulin levels and HOMA IR [Homeostatic model assessment -estimated Insulin resistance] was calculated.

***Statistical analysis used*:** Inferential statistics was done using Mann Whitney U test and Pearson product moment correlation tests.

***Results*:** Group A consisted of 17 geriatric patients and group B had 19. Females made up 71% in group A and 83% in group B in both age groups. Comparison of Fasting Insulin levels and HOMA IR between A and B groups showed a significant difference (at 0.01 level). The duration of treatment had inverse correlation with HOMA IR with p=0.007 in non-geriatric population but not in geriatric population.

***Conclusions*:** Insulin resistance is present substantially in patients with newly detected SCH and decreases after administration of thyroxine in both geriatric and nongeriatric population.

Keywords: BMI; Fasting Insulin levels; Geriatric; HOMA IR; Non-geriatric; Subclinical hypothyroidism;

Key Message: Insulin resistance in Subclinical hypothyroidism-a major contributing factor of metabolic syndrome can be reduced by thyroxine treatment. Nevertheless, caution has to be exercised while treating SCH especially in elderly who havenon-specific and non-uniform cut offs.

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Introduction

Subclinical hypothyroidism is clinically referred to as a condition when TSH is raised with T3 and T4 being normal. Prevalence of subclinical hypothyroidism is 6-8% in women and 3% in men.[1] Thyroid hormones have significant influence on all major organ systems and appropriate levels are important for optimal function. The alterations in serum insulin levels, counter regulatory hormones as well as the glucose absorbed by intestine and produced by liver is regulated by thyroid hormone.

The levels of glucose uptake in peripheral tissue are also affected by thyroid hormones which in turn determines the Insulin resistance and it is one of the major causes for complications occurring in patients with Type II Diabetes mellitus especially cardiovascular.[1] There are many causes and clinical conditions associated with Insulin and thyroid resistance. Thyroid dysfunction is one of the them. There is sufficient literature about insulin resistance in hyperthyroid patients, however there are relatively fewer studies in humans dealing with subclinical hypothyroidism and insulin resistance.[2]

There is consensus beyond doubt to treat frank hypothyroidism due to its varied detrimental clinical effects but there is always a dilemma to treat subclinical hypothyroidism as there are reports which claim about 62% of TSH levels between 4 and 10 mIU/L normalising without intervention within five years[20] Many a times patients of subclinical hypothyroidism are treated when the clinician feels the symptoms and signs of the patient are due to low thyroid levels even when the lab values of T3 and T4 are not low and it is only the TSH which is raised. Most patients of subclinical hypothyroidism are treated in special circumstances like infertility menstrual irregularities and in severe dyslipidaemia but insulin resistance is not one of the entities which is considered for routine treatment. When it comes to treating elderly patients for subclinical hypothyroidism it is important to consider multiple factors like age dependent TSH increase and comorbidities. When treatment is necessary, a tailored therapy should be chosen, considering poly-pharmacy and frailty which is most common among the geriatric patients. In the elderly who are above 80 years of age, the upper limit of TSH of the 95% interval of confidence is around 6.0 mIU/L and this value of TSH raises reaching 8.0 mIU/L in over people who are aged more than 90 years[3]Although careful identification of individuals with persistent SCH who could benefit from levothyroxine treatment is necessary, current evidence suggests that individuals with TSH levels greater than 10 mIU/L who test positive for antithyroid antibodies or are symptomatic may benefit from levothyroxine treatment to reduce the risk of progression to overt hypothyroidism, decrease the risk of adverse cardiovascular events, and improve their quality of life. After treatment is initiated, careful monitoring is essential.[4] Despite the fact that insulin resistance is considered to be a major event in the face of cardiovascular illness there are no studies which consider treating patients of subclinical hypothyroidism based on the same. Our study intends to analyse if subclinical hypothyroid patients have notable insulin resistance and whether it is significantly different from patients of SCH who are already receiving thyroxine supplement. Additionally, this study is also undertaken to especially evaluate if there are any additional and comparable differences in insulin resistance when geriatric population is considered.

Materials and Methods

This was a cross sectional study involving 120 subjects divided in to two groups A and B each comprising of 60 participants. Group A was inclusive of newly detected SCH, Group B consisted of patients of SCH who are on treatment with thyroxine for at least 3 months. Both groups were inclusive of geriatric participants aged more than 60 years in a significant proportion. This study was undertaken in patients attending JSS Hospital, Mysore, India for a period of one and half years.

Inclusion criteria

- Age more than 18 years
- Patients who are newly diagnosed to have subclinical hypothyroidism i.e. (normal T3 and T4 values and TSH more than normal levels[5]
- Patients of Subclinical Hypothyroidism on treatment (Thyroxine) for at least for 3 months.

Exclusion criteria

- Hypothyroid patients
- Patients with Diabetes Mellitus.
- Hypertension.
- Known cases of Chronic diseases (chronic kidney diseases, liver diseases, heart diseases)
- Pregnancy or Post partum period or women on oral contraceptives.
- Previous thyroid surgeries.
- Known cases of polycystic ovarian syndrome.
- Patients on Hypolipidemic, Antiepileptic Drugs.

Methodology

All patients for the study were selected as per inclusion and exclusion criteria. Demographic data of the patients were obtained. Patient's past medical history and records were reviewed for evidence of

frank hypothyroid status and overt DM, or any history suggestive of menstrual irregularities for women. Patient drug history was reviewed to identify any drugs that alter thyroid function. BMI was calculated from patients' height and weight. Patients were subjected to investigations FBS, PPBS, fasting insulin levels. Insulin resistance was calculated by HOMA-IR formula.[HOMA-IR = [glucose (nmol/L) x insulin (μU/mL)/22.5], using fasting values]

Statistical Analysis

Summary statistics was done by measuring mean, standard deviation and proportion. Inferential statistics done using Mann Whitney U test and Pearson product moment correlation tests. Statistical package for social sciences (IBM SPSS version 26) was used for statistical analyses. Statistical significance was set at conventional 5% threshold(alpha=0.05)

Results

Age wise distribution

We had varied age distribution among patients in both group A and group B. Elderly made up 30 % of patients in group A and 28% in group B.

The mean age among non-geriatric group A was 38 years and in geriatric age group was 62 years similarly it was 33 and 65 years in group B.

Table 1: Mann Whitney U Z and p values comparing fasting serum insulin and HOMA IR values between group A and group B subjects [inclusive of geriatric and non geriatric]

	Fasting Serum Insulin			Homo IR value		
	U value	Z value	p value	U value	Z value	p value
Geriatric	7	4.99	0.001	6	5.02	0.001
Non geriatric	76.5	7.12	0.001	41.5	7.48	0.001

Sex distribution:

In the group A participants of newly detected subclinical hypothyroid patients the number of men in the non geriatric age group was 17% and in elderly it was 26%. In group B patients, who were non-geriatric, men comprised of 44 % and in geriatric age group it was 28%. Similarly, percentage of women in group A geriatric was 74% and group B geriatric 72%. Among non geriatric participants females were 83% in group A and 56% in group B Table 2.

Table 2: Pearson's corelation of HOMA IR and duration of treatment in geriatric adults.

		Duration of treatment	HOMA IR
Duration of treatment	Pearsons correlation	1	0.84
	Sig [2 tailed]		0.466
	N	18	18
HOMA IR	Pearsons correlation	0.184	1
	Sig [2 tailed]	0.466	
	N	18	18

BMI:

The mean BMI of geriatric patients in group A and group B was 22.93 and 22.79. The mean calculated BMI among non-geriatric patients was 23.21 and 23.04 respectively.

FBS

The mean FBS of non-geriatric population in group A was 101.49mg/dl. And that in group B was 96 mg/dl whereas in the geriatric group the mean FBS was 102mg/dl in group A and 99mg/dl in group B respectively.

Fasting insulin levels:

In the non-geriatric population, among the group A cases the mean fasting insulin level was 12.43 with SD 3.81 and in the group B, mean was 5.11 with SD 2.57. The geriatric population showed similar pattern where in Group A non-geriatric population the mean fasting insulin level was 12.8 with SD 5.85 and group B geriatric population it was 4.3 with SD 2.27. In both geriatric and non-geriatric population, the mean insulin level was significantly lower in the group B than the group A.

HOMO IR:

HOMA IR was calculated for both groups using fasting sugars and insulin values and the results were compared in the Mann Whitney U test. It revealed a significant difference in the Homo IR levels of the two groups in both geriatric and non-geriatric population. Mann Whitney U value, z value and p values are given in the Table 1.

Fig 1 is comparison of HOMA IR between Group A and B geriatric patients and Fig 2 is comparison of HOMA IR between Group A and B non-geriatric patients.

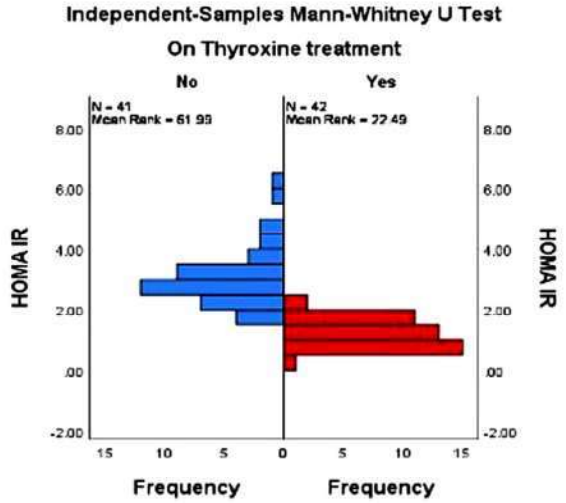

Fig. 1: Comparison of HOMA IR between group A and Group B Geriatric patients.

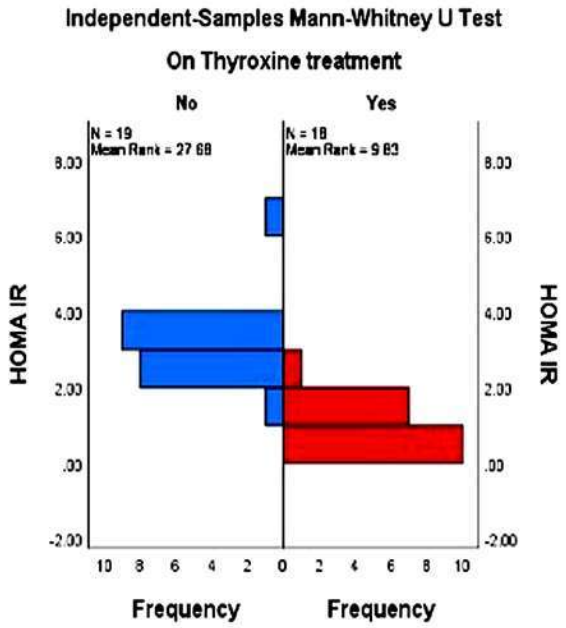

Fig.2: Comparison of HOMA IR between group A and Group B Non-Geriatric patients.

HOMO IR and duration of treatment

Group B patients were divided in to two cohorts [< 2 years of treatment and >2 years of treatment] to corelate the duration of treatment and HOMA IR in the geriatric and non-geriatric population. In the adult, non-geriatric population 24 out of 42 patients were receiving treatment for more than 2 years and among elderly there were 10 out of 18 who were receiving treatment for a duration longer than 2 years. Pearson product moment correlation revealed no significant association between duration of treatment and Homo IR level in geriatric group [Table 2] whereas there was a significant negative correlation between duration of treatment and Homo IR level in the non-geriatric population (r= 4.01; p=0.007) [Table 3]

Table 3: Pearson's corelation of HOMA IR and duration of treatment in non geriatric adults.

		Duration of treatment	Homa IR
Duration of treatment	Pearsons corelation	1	0.408
	Sig [2 tailed]		0.007
	N	42	42
HOMA IR	Pearsons corelation	0.408	1
	Sig [2 tailed]	0.007	
	N	42	42

Discussion

Subclinical hypothyroidism is a challenging disease for both patients and doctors because of its non-uniformity in treatment protocols. It is more common in women and among elderly females it becomes even more commoner. Canaris GJ found that 10% of men and 16% of women in the age group of 65-74 years had TSH levels that were increased above the upper limit of the reference range, while 16% of men and 21% of women age 75 and older had increased TSH levels.[7]

The number of geriatric patients in our study were less than non-geriatric patients because of the fact that many elderlies with subclinical hypothyroidism also had diabetes or on certain drugs or known conditions of insulin resistance who had to be excluded from the study. It is accounted from a cross-sectional study of patients with type 1 or 2 diabetes conducted in Brazil, 12% of patients with T2D also had subclinical hypothyroidism.[18]

Women outnumbered men in all the age groups of SCH which is comparable to most of the subclinical hypothyroidism studies done world-wide. This difference was very well accentuated in our study as well. We also found more elderly women in group B than group A. This may be due to the fact the female elderly with SCH had more somatic symptoms prompting physicians to start early treatment. It has been suggested by some studies that subclinical hypothyroidism may lower the threshold for the occurrence of depression and

may be a risk indicator for depression. This also adds on to the fact that subclinical hypothyroid patients have significant alterations in memory mood, anxiety and somatic symptoms. And it is also suggested people with major depression may not respond to their treatment if their subclinical hypothyroidism is not corrected.

The correlation of FBS among the group A and group B patients did not show any significance in our study although some of the literature available showcase that the FBS values do tend to increase in patients as TSH was increased.[19] The mean TSH value among our newly diagnosed group A patients was 8.2[non geriatric] and 7.6[geriatric].

Unlike the FBS, the fasting insulin levels in both the groups showed remarkable variations. There was striking correlation across treated and non-treated group of both geriatric and non-geriatric population when the fasting insulin levels were compared. The fasting insulin levels were considerably elevated in newly diagnosed group A patients than group B patients. In a study done by Shyam Rameshwar Adhau et al titled as Insulin resistance in sub clinical hypothyroidism showed that TSH levels were positively related to fasting insulin levels in patients with SCH.[1]

Subsequently when the HOMA IR was calculated using the FBS and fasting insulin levels, we found that HOMA IR was significantly raised in newly detected subclinical hypothyroidism patients than subjects who were already on treatment. There are literature emphasizing the presence of insulin resistance in subclinical hypothyroidism in addition to the occurrences of insulin resistance in hypothyroid patients.[8]

Some of the other studies like the one done by Dessein et all observed Subclinical hypothyroidism was encountered as a cause of insulin resistance and its related dyslipidaemia in patients with rheumatoid arthritis.[9]

Similarly in a study done by Sapna V et al titled as Insulin Resistance in Subclinical Hypothyroidism showed that IR levels were significantly increased in SCH when compared with euthyroid.[2] Supporting this were seen in studies done by Rahimtaj B et al and Al Sayed A et al [6 10] Another study done by Garduño-Garcia et al. reported a relationship between insulin and HOMA-IR levels with raised TSH in subclinical hypothyroid elderly, but there was no difference in the prevalence of the MetS[metabolic syndrome] between euthyroid and subclinical hypothyroid individuals.[11] The cause for this increase in insulin resistance in subclinical hypothyroidism has been very well explained in a study done by Eirini Maratou et al. which showed that insulin resistance was increased in patients with hypothyroidism or subclinical hypothyroidism due to decreased translocation of GLUT4 glucose transporters on the plasma membrane.[12]

The acceptance of increased insulin resistance in subclinical hypothyroid patients has not been universal. There are literature contradicting these findings. Brenta et al.[13] did not find significant differences in insulin sensitivity or lipid profile before and after thyroxine replacement in subclinical hypothyroidism. Supporting the same a very recent study by Roxana Adriana stoica et al.[14] who found that there was no association between the thyroid function tests (TSH, fT4) and IR indices in adult Romanian women. This was a case control study with one year retrospective follow up.

Studies which consider only elderly with subclinical hypothyroidism dealing with insulin resistance are very few. Particular mention about this is done in Health ABC study[15] which suggests, that in elderly; even within the normal range of thyroid hormones, there may be a higher prevalence of metabolic abnormalities as TSH levels increase. In our study we observed that insulin resistance in elderly with newly detected subclinical hypothyroidism [group A] was remarkably higher than group B patients. This is a finding very similar in non-geriatric patients also. Thus, our results showed beyond doubt that increased insulin resistance was an important finding in patients of newly detected subclinical hypothyroidism with striking reduction in IR in patients who were already on treatment with thyroxine with normalised TSH. However, this decrease in insulin resistance in patients who are on thyroxine treatment translating to decrease in cardiovascular morbidity requires further follow up of the patients for a longer period of time.

We further wanted to analyse if duration of treatment had any impact on the degree of insulin resistance among the treated cases.

It was been observed in many studies that thyroid functional parameters improved more rapidly in patients when there were given the full dose rather than lower doses but there was no difference in the time it took for hypothyroid symptoms to resolve, although the initial assessment of symptoms was considered only after 12 weeks.[16]

There is no literature pertaining to the duration of treatment for the follow up on the HOMA IR parameters when a patient is being treated for

subclinical hypothyroidism.

Since we did not know the initial degree of IR in group B participants prior to the start of treatment we compared the HOMA IR between patients of less than 2 years of treatment and patients who have been on treatment for a longer period of time. This was also compared across the geriatric population.

It was found that decrease in HOMA IR corelated significantly with duration of treatment in the non-geriatric population but we did not find the same corelation when we compared it among the geriatric population. This finding can be useful when considering treatment in patients of subclinical hypothyroidism.

Conclusion

The study supports that insulin resistance is present in patients of subclinical hypothyroidism across all age groups. The severity of insulin resistance is significantly higher in newly detected cases of subclinical hypothyroidism than in thyroxine treated patients of subclinical hypothyroidism. Additionally, we also found that the duration of treatment with thyroxine corelated with IR among non-geriatric population but not in the geriatric population. Thus, the decision to treat subclinical hypothyroidism for the reason of insulin resistance especially in elderly should be carefully weighed against the adverse effects of over treating the same. Elderly SCH patients have to be followed up for a longer period of time to build a consensus for treatment.

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