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*RESEARCH ARTICLE*

# "EFFECTS OF LEVOTHYROXINE REPLACEMENT THERAPY ON INSULIN SENSITIVITY IN SUBJECTS WITH OVERT HYPOTHYROIDISM."

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## *Abstract*

**Objective:-** To assess fasting plasma glucose, fasting serum insulin and, insulin resistance by oxford HOMA calculator before and after levothyroxine replacement in patients with overt hypothyroidism.

**Material and method:-** We recruited newly diagnosed overt hypothyroid patients who were prescribed 100 µgm levothyroxine and became euthyroid at 6 week and remained eutyhyroid at 3 month. These 64 patients were studied for fasting plasma glucose, fasting serum insulin and insulin resistance (HOMA-IR) by oxford HOMA calculator before and at 3 months after levothyroxine treatment.

**Results:-** Before levothyroxine replacement there was significant($p < 0.001$) positive correlation between TSH & fasting serum insulin(r value + 0.638), TSH and fasting plasma glucose (r value + 0.506), TSH & HOMA-IR (r value+ 0.656) but these correlations were not significant (p value>0.05) after replacement. Significant decrement was noted (p value <0.001) in fasting serum insulin(3.73 + 6.32 ), fasting plasma glucose (8.06 + 10.91 ) and HOMA-IR(0.49 + 0.78) after levothyroxine replacement

**Conclusion:-** In our study overt hypothyroidism was associated with impaired insulin sensitivity which is proportional to thyroid dysfunction and improved with levothyroxine treatment.



## Introduction:-

The prevalence of hypothyroidism in adult population is approximately 5-10% of woman and 0.5-2% men, the annual incidence rate of autoimmune hypothyroidism is up to 4 per 1000 woman and 1 per 1000 men[1]. The prevalence of thyroid disease in patients with diabetes is significantly higher than general population[2]. The term 'thyroid diabetes' was coined in the early literature to depict the influence of thyroid hormone levels on glucose metabolism and for nearly a century, many publications focused on the relationship between diabetes and thyroid disease[3].

Evidence for a relationship between T4 and T3 and glucose metabolism appeared over 100 years ago when the influence of thyroid hormone excess in the deterioration of glucose metabolism was first noticed. Since then, it has been known that hyperthyroidism is associated with insulin resistance[4,5]. More recently, hypothyroidism has also been linked to decreased insulin sensitivity. The explanation to this apparent paradox may lie in the differential

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effects of thyroid hormones at the liver and peripheral tissues level[6]. While thyroid hormones oppose the action of insulin by stimulating hepatic gluconeogenesis and glycogenolysis[7,8], on the otherhand it acts synergistically with insulin[9,10] by up-regulating the expression of genes such as GLUT-4 and phosphoglycerate kinase, involved in glucose transport and glycolysis respectively, in facilitating glucose disposal and utilisation in peripheral tissues.

Compared to the number of reports about insulin resistance in hyperthyroid patients, there are relatively fewer studies in humans dealing with the effects of hypothyroidism on glucose metabolism. Eirini Maratou[15] et al in 2009; Irina kowalska[12]et al in 2011 and Indian study B M Singh[11] et al., 2010; demonstrated insulin resistance in hypothyroidism.

## Materials and Methods:-

We conducted a hospital based prospective interventional type study in department of medicine, SMS Hospital, Jaipur, Rajasthan. We studied 64 newly diagnosed overt hypothyroid (TSH>5μIU/ml, $FT_4$<0.89ng/dl and $FT_3$ <1.8pg/ml) patients for insulin sensitivity before and after levothyroxine supplement. Patients included in study were aged between 20-40 yrs, normal hepatic and renal function, not taking any medication known to affect glucose metabolism and became euthyroid after 100 μgm levothyroxine for 6 week and remained euthyroid at 3 months. Excluded were those with age < 20 yrs or > 40 yrs, hepatic and renal dysfunction, seriously ill, polycystic ovarian disease, diabetes mellitus, past history of diabetes mellitus (gestational diabetes mellitus),patient with chronic diseases, pregnancy, menopause and who required levothyroxine dose other than 100 μgm for becoming euthyroid.

On first visit we studied insulin sensitivity by fasting plasma glucose and fasting serum insulin in subjects who were prescribed 100 μgm levothyroxine. After 6 week of 100 μgm levothyroxine, thyroid profile was repeated and those who became euthyroid continued 100 μgm levothyroxine replacement and reviewed at 3 months. After 3 months of 100 μgm levothyroxine replacement those who were euthyroid re-evaluated for insulin sensitivity.

Thyroid profile (TSH, FT3 and FT4) and insulin levels were estimated by using electrochemiluminescence immuno assay using commercially available kits. Plasma glucose was measured with glucose oxidase technique on automated autoanalyser. Normal range for TSH was (0.4-4.0) μIU/ml, FT3 was (1.8-4.2 pg/ml) and that for FT4 was (0.89-1.76) ng/dl. The normal range for fasting insulin was 6-27 μIU/ml. Data were analyzed by using students paired "T" test, coefficient of correlation and Chi-square test.

**Homeostatic model assessment (HOMA):-**

HOMA has been widely employed in clinical research to assess insulin sensitivity. Rather than using fasting insulin or a G/I ratio, the product of the fasting values of glucose (expressed as mg/dL) and insulin (expressed as μIU/ml ) is divided by a constant. HOMA-IR = [I.sub.0] x [G.sub.0]/405. The constant 405 should be replaced by 22.5 if glucose is expressed in S.I. units. We calculated Insulin resistance by using homeostasis model assessment (HOMA-IR) by Oxford HOMA calculator (http://www.dtu.ox.ac.uk/ homa/index.html) using the fasting glucose and fasting insulin values. Unlike fasting Insulin and the G/I ratio, the HOMA calculation compensates for fasting hyperglycemia[13]. Also keep in mind that HOMA and fasting insulin values increase in the insulin-resistant patient while the G/I ratio decreases. The HOMA value correlates well with clamp techniques and has been frequently used to assess changes in insulin sensitivity after treatment[14]

## Observations and Results:-

In our study females were disproportionately larger in number (78.13%) as compared to males (21.87%) and around 61% of patients were in age group 30 to 39 years (table no.1). There was significant decrease in mean TSH (42.73 $\pm$ 15.99 to 2.53 $\pm$ 1.21) and significant increase in Mean FT4 (0.53 $\pm$ 0.17 to 1.34 $\pm$ 0.25) as well as Mean FT3 (1.32 $\pm$ 0.26 to 3.64 $\pm$ 0.97) after levothyroxine replacement (p-value <0.001)**.** Significant decrement in mean fasting insulin 10.37 $\pm$ 6.73 to 6.64 $\pm$ 3.89 and mean fasting plasma glucose 84.76 $\pm$ 9.30 to 76.70 $\pm$ 7.23 as well as mean HOMA-IR 1.32 $\pm$ 0.83 to 0.83 $\pm$ 0.47 after 3 months of levothyroxine replacement (p-value<0.001) as shown in table no.2.

There was significant positive correlation between TSH and Fasting Insulin; TSH and fasting plasma glucose; TSH and HOMA-IR before levothyroxine replacement (r-values +0.638, +0.506 and +0.656 respectively with p-value <0.001) but nonsignificant correlation after levothyroxine replacement (r-values +0.296, +0.162 and +0.285 respectively with p-value >0.05) as shown in table no.3. There was significant negative correlation between T4 and fasting insulin; T4 and HOMA-IR before thyroxine replacement (r-value -0.419, -0.427 respectively with p-value

<0.001) but nonsignificant correlation after thyroxine replacement (r-value -0.198, -0.184 respectively with p-value >0.05). There was nonsignificant correlation between T4 and fasting plasma glucose before and after thyroxine replacement (r-value -0.238 and +0.001, p-value >0.05) as shown in table no.4.

**Table 1:-** Distribution of patients according to age & sex.

| Age group (In Yrs) | Sex | | | | Total | |
|---|---|---|---|---|---|---|
| | Male | | Female | | | |
| | No. | % | No. | % | No. | % |
| 20-29 | 3 | 4.69 | 17 | 26.56 | 20 | 31.25 |
| 30-39 | 10 | 15.62 | 29 | 45.31 | 39 | 60.94 |
| 40-49 | 1 | 1.56 | 4 | 6.25 | 5 | 7.81 |
| Total | 14 | 21.87 | 50 | 78.13 | 64 | 100.00 |

Mean age ± SD (Male)= 32.35 ± 4.20 Mean age ± SD (Female)= 32.32 ± 5.61

Above table shows that in this study females were disproportionately larger in number (78.13%) as compared to males (21.87%) and around 61% of patients were in age group 30 to 39 years.

**Table 2:-** change in parameters before and after levothyroxine replacement.

| | Mean ± SD | | Mean Change ± SD | P-value | Significance |
|---|---|---|---|---|---|
| | Basal | After 3 month | | | |
| TSH | 42.73 ± 15.99 | 2.53 ± 1.21 | 40.20 ± 15.23 | < .001 | HS |
| FT4 | 0.53 ± 0.17 | 1.34 ± 0.25 | 0.81 ± 0.23 | < .001 | HS |
| FT3 | 1.32 + 0.26 | 3.64 + 0.97 | 2.32 + 0.98 | < .001 | HS |
| F. Insulin | 10.37 ± 6.73 | 6.64 ± 3.89 | 3.73 ± 6.32 | < .001 | HS |
| FPG | 84.76 ± 9.30 | 76.70 ± 7.23 | 8.06 ± 10.91 | < .001 | HS |
| HOMA-IR | 1.32 ± 0.83 | 0.83 ± 0.47 | 0.49 ± 0.78 | < .001 | HS |

Above table shows that there is significant decrease in TSH but significant increase in FT4, FT3, F. Insulin, FPG, HOMA-IR after levothyroxine replacement

**Table 3:-** Correlation between TSH and F. Insulin, FPG, HOMA-IR.

| | Before | | | After | | |
|---|---|---|---|---|---|---|
| Correlation between | r-value | P-value | Significance | r-value | P-value | Significance |
| TSH & F.Insulin | + 0.638 | < .001 | Sig | + 0.296 | > .05 | NS |
| TSH & FPG | + 0.506 | < .001 | Sig | + 0.162 | > .05 | NS |
| TSH & HOMA-IR | + 0.656 | < .001 | Sig | + 0.285 | > .05 | NS |

Correlation between TSH and Fasting Insulin; TSH and fasting plasma glucose; TSH and HOMA-IR is significant and positive before but not significant after levothyroxine replacement

**Table 4:-** Correlation between T4 and F. Insulin, FPG, HOMA-IR.

| | | | | After | | |
|---|---|---|---|---|---|---|
| Correlation between | r-value | P-value | Significance | r-value | P-value | Significance |
| T4 & Insulin | - 0.419 | < .001 | Sig | - 0.198 | > .05 | NS |
| T4 & FPG | - 0.238 | > .05 | NS | + 0.001 | > .05 | NS |
| T4 & HOMA-IR | - 0.427 | < .001 | Sig | - 0.184 | > .05 | NS |

There was significant negative correlation between T4 and fasting insulin; T4 and HOMA-IR before but nonsignificant after levothyroxine replacement. On the otherhand T4 and fasting plasma glucose have nonsignificant correlation before and after thyroxine replacement.

## Discussion:-

The prevalence of thyroid disease in patients with diabetes is significantly higher than general population[2]. Compared to the number of reports about insulin resistance in hyperthyroid patients, there are relatively fewer studies in humans dealing with the effects of hypothyroidism on glucose metabolism. B.M Singh[11] et al in 2010 found that fasting insulin level was significantly higher in hypothyroid (10.56±4.02) compared to controls (5.66±2.9).TSH levels were positively correlated with insulin level (fasting) in patients with hypothyroidism ($r=0.927$, $P<0.01$). They also noticed that mean HOMA-IR was higher in Overt hypothyroidism (3.9±1.32) versus subclinical hypothyroidism (1.7±.58) as well as in both overt and subclinical as compared to controls (0.57±.15). TSH levels were positively correlated with HOMA IR in patients with hypothyroidism ($r=0.835$, $P<0.01$). Eirini Maratou[15] et al found that overt hypothyroid and subclinical hypothyroid having higher plasma insulin than the euthyroid ($P<0.05$). They also found that Homeostasis model assessment index was increased in overt hypothyroid (1.97 $\pm$0.22) and subclinical hypothyroid (1.99 $\pm$0.13) versus euthyroid (1.27 $\pm$0.16, $P<0.05$) suggesting insulin resistance. These results are similar to our study. Irina kowalska[12]et al in 2011 also reported improvement in insulin sensitivity ($p=0.012$) in subclinical hypothyroid patient after levothyroxine replacement by using different technique for measuring insulin sensitivity( hyperinsulinemic euglycemic clamp technique). He also observed a decrease in fasting plasma glucose ($P = 0.019$) after levothyroxine treatment. These results are similar to our study.

## Conclusions:-

Our study concluded that overt hypothyroidism is associated with impaired insulin sensitivity which is proportional to thyroid dysfunction. Appropriate treatment of this entity with levothyroxine will not only improve thyroid hormone levels but also improve insulin sensitivity.

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