Section: Biochemistry

Original Research Article

LEPTIN - A POTENTIAL BIOMARKER IN TYPE 2 DIABETES MELLITUS (T2DM) PATIENTS WITH HYPOTHYROIDISM

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Received : 05/01/2024
Received in revised form : 15/02/2024
Accepted : 24/02/2024

Keywords:
Leptin, Hypothyroidism, type 2 Diabetes Mellitus.

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DOI: 10.47009/jamp.2024.6.1.279

Source of Support: Nil,
Conflict of Interest: None declared

Int J Acad Med Pharm
2024; 6 (1); 1400-1405

Abstract

Background: Diabetes Mellitus and Thyroid are two major highly spread health problems worldwide. Diabetes Mellitus is a general term for heterogenous disturbances of metabolism, caused either by impaired insulin secretion or insulin action or both. Type 2DM is a common form of DM characterised by hyperglycemia, insulin Resistance as well as improper insulin insufficiency. Hypothyroidism may occur as a result of primary gland failure and is diagnosed as low levels of T3,T4 and elevated levels of TSH (> 10 µ IU/ml).Thyroid hormones are insulin antagonists ,both are involved in cellular metabolism and excess and deficit of anyone can result in functional derangement of other. DM appears to influence thyroid function in two sites: firstly at the level of hypothalamic control of TSH release and secondly at the conversion of T4 to T3 in the peripheral tissue. Leptin is a 167 amino acid, 16-KDa, 4 α- helical Protein, the product of the Ob gene, produced mainly in the adipose tissue and is involved in the neuroendocrine regulation of pituitary function. Together with thyroid hormones, Leptin maintains weight and energy expenditure. **Material and Methods:** It is a Cross-sectional Observational study consisting of 62 subjects with age and sex-matched individuals. They were divided into 2 groups. GROUP 1: T2DM Patients without Hypothyroidism. GROUP 2: T2DM Patients with Hypothyroidism. Serum Leptin was measured by the ENZYMATIC immunoassay method. T3, T4, TSH levels were measured by CLIA. HbA1c% and FBG were measured by autoanalyzer (Roche COBAS 311). **Results:** the serum levels of Leptin in T2DM Patients with Hypothyroidism are 19.6±8.1(ng/ml) which is significantly higher as compared to 14.9 ± 6.4(ng/ml) in T2DM Patients without Hypothyroidism. **Conclusion**: Higher levels of serum Leptin are associated with T2DM Patients with Hypothyroidism, making Leptin a potential biomarker.

INTRODUCTION

Hypothyroidism and diabetes mellitus are the two most common endocrine diseases encountered in clinical practice and they've been shown to affect each other mutually.

Hypothyroidism (also called underactive thyroid, low thyroid or Hypothyreosis) is a disorder of the endocrine system in which the thyroid gland doesn't produce enough thyroid hormones.[1]

Hypothyroidism is the most common thyroid complaint in India with a frequency of 10.95%.[2]

Hypothyroidism is caused by inadequate function of the gland itself (primary hypothyroidism), inadequate stimulation by thyroid- stimulating hormone from the pituitary gland (secondary hypothyroidism), or insufficient release of thyrotropin- releasing hormone from the brain's hypothalamus(tertiary hypothyroidism).[3]

The hypothalamic – pituitary – thyroid axis plays a crucial part in maintaining thyroid hormone levels within normal limits. Production of TSH by the anterior pituitary gland is stimulated in turn by thyrotropin- releasing hormone (TRH), released from the hypothalamus. production of TSH and TRH is dropped by thyroxine by a negative feedback process.

Thyroid hormone is required for the normal functioning of numerous tissues in the body. In healthy individualities, the thyroid gland generally secretes thyroxine (T4), which is converted into triiodothyronine (T3) in other organs by the selenium-dependent enzyme iodothyronine deiodinase.[4] Triiodothyronine binds to the thyroid

ISSN (O): 2687-5365; ISSN (P): 2753-6556

hormone receptor in the nucleus of cells, where it stimulates the turning on of particular genes and the production of specific proteins.[5]Also, the hormone binds to integrin αvβ3 on the cell membrane, thereby stimulating the sodium – hydrogen antiporter and processes such as formation of blood vessels and cell growth.[6] In blood, nearly all thyroid hormones (99.97%) are bound to plasma proteins such as thyroxine- binding globulin; only the free unbound thyroid hormone is biologically active.

Hypothyroidism decreases the basal metabolic rate, oxygen consumption, and lipolysis and it may affect the action of adipose tissue.[7]

Hypothyroidism is characterised by a drop in free triiodothyronine (FT3) and free thyroxine (FT4) levels and an increased level of thyroid stimulating hormone (TSH) which is generally associated with obesity and IR.[8]

Diabetes mellitus (DM) is a group of metabolic conditions characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both. DM has several orders, the main subtypes of DM are Type 1 diabetes mellitus (T1DM) formerly referred to as insulin-dependent diabetes mellitus (IDDM) or juvenile- onset diabetes, generally arises in childhood. Type 2 diabetes, formerly called non-insulin-dependent diabetes mellitus (NIDDM) or adult- onset diabetes, generally occurs after age 40 and becomes more common with increasing age due to poor life style and dietary choices.

Type 2 diabetes mellitus (T2DM) with a frequency of 8.9% becomes the most common endocrine disorder accounting for around 90% of all cases of diabetes.DM is proving to be a global public health burden as this number is anticipated to rise to another 200 million by 2040.[9]. In T2DM, the response to insulin is lowered, and this is defined as insulin resistance. During this state, insulin becomes ineffective but to maintain glucose homeostasis, it is initially countered by an increase in its production resulting in T2DM. Though Insulin resistance generally develops from obesity and aging but it is multifactorial.

T2DM involves a more complex interplay between genetics and lifestyle. Roughly 50 polymorphisms have been described to date to contribute to the threat or protection for T2DM. A genome-wide association study (GWAS) found inheritable loci for transcription factor 7- like 2 gene(TCF7L2), which increases the risk for T2DM.[10,11] Other loci that have arraignments in the development of T2DM are NOTCH2, JAZF1, KCNQ1, and WFS1.[12,13]

Chronic hyperglycemia also causes nonenzymatic glycation of proteins and lipids leading to damage in small blood vessels in the retina, kidney, and peripheral nerves. This damage leads to the classic diabetic complications of diabetic retinopathy, nephropathy, and neuropathy and the preventable issues of blindness, dialysis, and amputation, respectively.[14] Long- term complications include hypoglycemic coma and diabetic ketoacidosis, and this imposes a high burden on the country's health care system and the frugality.[15-17]

white adipose tissue synthesises a Peptide hormone named as Leptin. The leptin gene (LEP or ob) is on chromosome 7q31.3.[18] The mature protein is comprised of 146 amino acids and produced through mRNA-directed protein synthesis.[19] Its structure is like the proinflammatory cytokines found throughout the body, such as interleukin 6 and granulocyte colony-stimulating factor.[20]

Leptin targets the medio basal arcuate nucleus of the hypothalamus, inhibiting appetite.[21]Its deficiency or resistance results in hyperphagia, obesity and diabetes mellitus.[22,23,24] It is also implicated in the aetiopathogenesis of myriads of other diseases such as metabolic syndrome, inflammatory diseases, atherosclerosis and cardiovascular diseases.[25-27] Hormonal and metabolic factors affect leptin inclusive of insulin, steroid, thyroid and estradiol which stimulate, while testosterone inhibits leptin synthesis.[28]

Leptin decrease pre-proinsulin mRNA expression in beta cells thus decrease the synthesis of insulin. It also reduces the release of insulin from human pancreatic beta cells, which leads to the development of type 2 DM.

MATERIALS AND METHODS

Research setting: conducted at VIMSAR, Burla, Sambalpur, in Department of Biochemistry in collaboration with Department of General Medicine.
Period of study: AUG 2022 – SEP 2023
Study design: cross – sectional observational
Study population:
Cases: in and out patient department of medicine
Controls: age and sex matched individuals
Sample size: $\eta = (SD/SE)^2$
Sampling: purposive sampling of cases fitting to our requirements
Selection of cases:
Inclusion criteria: All Patients between the age group of 40 – 65 years with a known history of Diabetes Mellitus and Hypothyroidism were taken into the study.
Exclusion criteria: Patients with kidney failure, Anaemia, liver, cardiovascular diseases and Autoimmune Diseases, and connective tissue disorders, pregnant women with gestational diabetes mellitus (GDM), drug induced hypothyroidism patients, patients who were on anti – diabetic medication were excluded from the study.
Intervention: nil
Methodology
Sample Collection:
venous sampling was carried out in the morning after an overnight fast of 12-14 hours. the blood was drawn into Fluoride tube, EDTA tube, Red top tube (empty tubes)respectively and then centrifuged for 10 min.

ISSN (O): 2687-5365; ISSN (P): 2753-6556

Parameters Estimated

BMI was calculated by dividing the weight in kilograms by square of height in metres. (Kg/(mt)^2).

Serum Leptin levels were analysed by enzyme immunoassay by ELISA (LISA SCAN) by Elab Science Reagent kit in both groups.

T3, T4, TSH levels were analysed by CLIA by Electra Fully Automated CLIA Analyser.

HbA1c, by Particle enhanced immunoturbidimetric test method was measured in autoanalyzer (Roche COBAS 311).

FBG, by GOD-POD method was measured in autoanalyzer (Roche COBAS 311).

Data Analysis

The results were expressed as mean ± SD values.

Data was analysed by recommended SPSS version 26 software.

Chi-Square test was applied, the paired t test was used for nonparametric data.

Correlations between two quantitative variables were assessed using Pearsons coefficient.

All tests were considered two-tailed and a P value less than 0.05 was considered to be statistically significant.

RESULTS

Sixty Two participants were included in our study, out of whom 54% were males and 46 % were females. Age range varies from minimum Forty year to maximum Sixty Five year with a mean age of Forty five yrs. maximum 56 % of study population belonged to age group of Forty to Sixty years. Similarly, 45 % belonged to urban area and 55 % from rural area.

The present study provides a wide view on biochemical features in type 2 Diabetic Mellitus with hypothyroidism patients.

The mean age of type 2 Diabetic Patients who were participated in our study was (48.5± 7.4) years coincides with the fact that type 2 Diabetes mellitus usually develops after age 40 years.

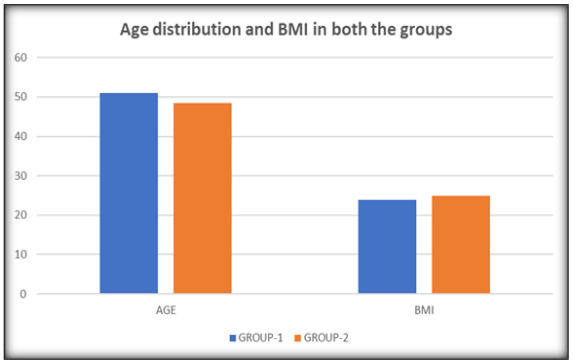

Figure 1:

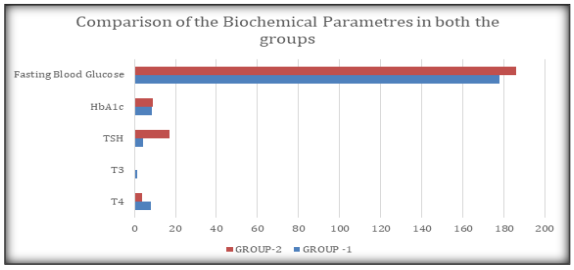

Figure 2: ?

Serum Leptin levels in group 2 is (19.6 ± 8.1) which is higher compared to the (14.9 ± 6.4) in Group-1. P value was 0.01 (the difference was statistically significant. [Table 2]

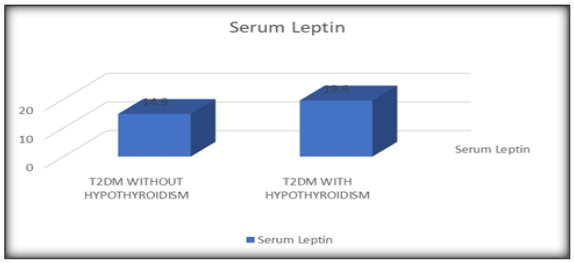

Figure 3: Showing Serum Leptin in both the groups

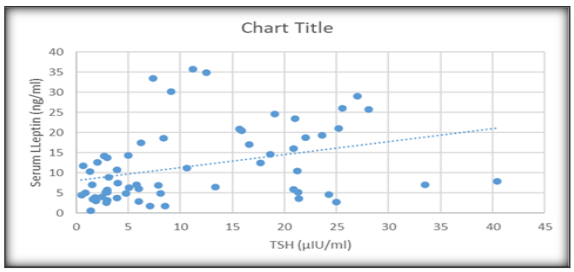

Figure 4: Correlation graph of Serum Leptin levels and TSH at p=0.01 and r=0.5

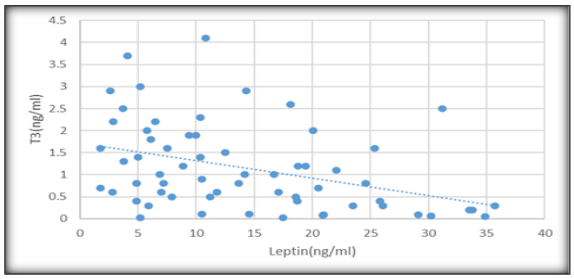

Figure 5: Correlation graph of Serum Leptin and T3 at p =0.01 and r = -0.3

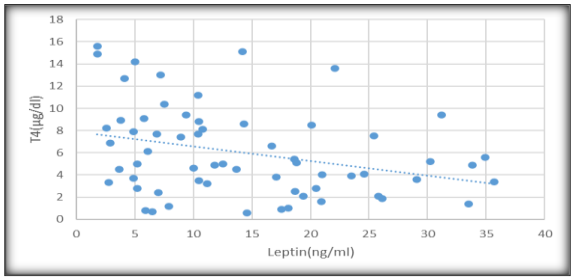

Figure 6: Correlation graph of Serum Leptin and T4 at p= 0.05 and r = -0.4

ISSN (O): 2687-5365; ISSN (P): 2753-6556

Table 1: The age and sex distribution and Anthropometric Parametres in the Study Population

variables	Group -1	Group -2	P- Value
Age	51.05 ± 8.8	48.50 ± 8.6	0.09
Sex (F: M)	12 : 19	17 : 14	
BMI	25.12 ± 2.64	24.96 ± 3.8	0.05

Table 2: Comparison of the biochemical parameters in the study group

	TYPE 2 DM WITHOUT HYPOTHYROIDISM	TYPE 2 DM WITH HYPOTHYROIDISM	P - Value
Fasting Blood Glucose (mg/dl)	178 ± 2.5	186 ± 2.9	0.02
HbA1c	8.4 ± 1.1	9.0 ± 1.6	0.03
TSH (µIU/ml)	4.2 ± 2.4	17.1 ± 5.6	0.01
T_3(ng/ml)	1.6 ± 0.4	0.3 ± 0.1	0.04
T_4(µg/dl)	8.1 ± 2.6	3.6 ± 1.0	0.04

The fasting blood glucose levels (mg/dl) in group 2 is (186 ± 2.9) which is higher compared to (178 ± 2.5) in group 1. p value was 0.02(the difference was statistically significant)
The HbA1c levels in group 2 is (9.0 ± 1.6)which is higher compared to (8.4 ± 1.1) in group 1. P value was 0.03 (the difference was statistically significant)
The TSH levels (µIU/ml) in group 2 is (17.1 ± 5.6) which is higher compared to
(4.2 ±2.4)in group 1. P value was 0.01 (the difference was statistically significant)
T3 (ng/ml) levels in group 2 is (0.3 ± 0.1) which is lower compared to (1.6 ± 0.4) in group 1. p value was 0.04(the difference was statistically significant)
T4 levels (µg/dl) in group 2 is (3.6 ± 1.0) which is lower compared to (8.1 ± 2.6) in group 1.
p value was 0.04 (the difference was statistically significant)

Table 3: the comparison of the Serum Leptin in both the groups

	Group -1	Group -2	P- value
Serum Leptin (ng/ml)	14.9 ± 6.4	19.6 ± 8.1	0.01

DISCUSSION

The possible reason postulated for an association between diabetes mellitus and hypothyroidism could be inheritable, biochemical or of hormonal origin.[29]
Resistance to insulin has an important part in the development of hypothyroidism in cases with type 2 diabetes mellitus.
Factors like old age, obesity, and female sex, hospitalization, and thyroid peroxidase antibody Ab positive all enhance the risk of developing hypothyroidism in type 2 Diabetes. Diabetes impairs thyroid function by changing thyroid- stimulating hormone (TSH) levels and by disturbing the conversion of thyroxine (T4) to triiodothyronine (T3) in peripheral tissues.[30]
Leptin, the adipocyte-secreted hormone, has direct and indirect effects on metabolically active tissues, and regulates several neuroendocrine axis. It takes part in the regulation of energy homeostasis, insulin action and lipid metabolism, and signals primarily on the status of the body energy reserves in fat to brain and other tissues.
Former studies suggested that insulin resistance, hyperglycemia, and leptin influence the level of serum thyroid- stimulating hormone (TSH).[31]
Leptin, through the Janus activating kinase(JAK)- 2 or signal transducer and activator of transcription(STAT)- 3 factor, tends to increase serum TSH levels in numerous diabetic Cases,[32]by modulating the hypothalamic- pituitary- thyroid axis and in turn, TSH increases leptin secretion from adipose tissues.
TSH and leptin altogether play a significant part in the metabolism of hepatic glucose by acting at the mRNA level, resulting in increased expression of glucose-6-phosphate and phosphoenolpyruvate Carboxykinase (PEPCK), which has stimulatory effects on hepatic glucose production.[33,34] Also, TSH increases serum blood glucose levels by diminishing insulin secretion and its synthesis from pancreatic beta cells.[35]
The Type 2 Diabetes Mellitus with Hypothyroidism Participants show higher Leptin levels compared to Type 2 Diabetes Mellitus without Hypothyroidism participants in our research.
Leptin regulates the production of thyrotropin-releasing hormone (TRH) in the hypothalamus and increases the release of TSH from the anterior pituitary.
In our study, we found that Leptin levels showed good correlation with TSH levels but not with T3 and T4 levels.
This may explains the significant positive correlation between leptin and TSH in hypothyroid patients, suggesting the changes in thyroid hormone are directly related to leptin independent of obesity.
Leptin has been shown to be involved in Patho-physiological mechanisms related to diabetes.
Leptin inhibits insulin gene expression and glucose-stimulated insulin secretion, and these actions adapt glucose levels to body fat stores.[36,37] In turn, insulin stimulates both leptin synthesis and secretion, thus establishing an adipose-islet axis.[38]

ISSN (O): 2687-5365; ISSN (P): 2753-6556

Different mediating effects of Leptin on insulin, glucagon and insulin like growth factor could explain why leptin and T2DM are linked. Leptin testing could be beneficial as a predictive diagnostic marker for the development of T2DM, according to recent research.

Evidence suggested that chronic leptin treatment improves insulin- stimulated hepatic and peripheral glucose metabolism in severely insulin – resistant lipodystrophic patients.

CONCLUSION

Primary hypothyroidism is highly prevalent in patients with T2DM, thyroid profile is recommended as a routine test in all patients with T2DM in the initial diagnosis and follow up.

TSH plays a relevant role in regulation of leptin metabolism independent of thyroid hormones. Leptin levels might be utilised in checking and early analysis of thyroid dysfunction.

The results of this study have led to conclusion that leptin may participate in the complex pathogenesis of DM2 associated Hypothyroidism and be a predictor of the development of this disease, making leptin a potential biomarker.

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ISSN (O): 2687-5365; ISSN (P): 2753-6556