Estimation of serum insulin, Homeostasis model assessment-insulin resistance and C-peptide can help identify possible cardiovascular disease risk in thyroid disorder patients

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ABSTRACT

Aim: We aimed at evaluating the cardiovascular disease (CVD) risk of thyroid disorder patients at diagnosis, using the traditional lipid profile, apo-B and apo-A1 in correlation with serum insulin and insulin resistance (IR) and C-peptide. Background: With an ever increasing incidence of CVD in most urban populations, there has been a demand for newer techniques that could help in the early detection of the risk of this disease complex. Materials and Methods: The present study was conducted on 100 healthy controls and 150 hypothyroid and 70 hyperthyroid patients, coming for the first time to our OPDs. The patients were selected on the basis of symptomatology and serum T3, T4, thyroid stimulating hormone (TSH) evaluations. They were then analyzed for body mass index (BMI), blood pressure (BP), serum insulin, homeostasis model assessment-insulin resistance (HOMA-IR), C-peptide, lipid profile and apo-B and -A1. Statistical analysis was done using Student's “t” test and Spearman's coefficient of correlation. Results: The hypothyroid patients presented with high BMI, diastolic hypertension, dyslipidemia, hyperinsulinemia, IR and raised serum C-peptide. There was highly significant correlation of serum insulin, HOMA-IR and C-peptide with lipid fractions and CVD risk ratios, T. chol/HDLc and apo-B/apo-A1, in hypothyroid patients. The hyperthyroid patients presented with systolic hypertension and a significant correlation of T. chol/HDLc with HOMA-IR. Hyperthyroid patients also had hyperinsulinemia, but reduced serum C-peptide levels. Conclusion: We conclude that the estimation of traditional lipid profile along with serum insulin, IR, C-peptide, apo-A1 and apo-B would not only help assess the thyroid status, but can also help in the early evaluation of a possible risk of CVD.

Key words: C-peptide, cardiovascular disease risk ratios, dyslipidemia, homeostasis model assessment-insulin resistance, hypertension

INTRODUCTION

Thyroid disease is quite common in the general population and the disturbances of normal functioning of thyroid occur more frequently in the elderly than in the young.\textsuperscript{[1]} The prevalence of thyroid dysfunction in adults in the general population ranges from 1 to 10% and is even higher in selected groups\textsuperscript{[2-4]}

Thyroid function abnormalities could significantly affect the patient's lipid profile as well as management.\textsuperscript{[5]} Both hypothyroidism and hyperthyroidism are associated with atherogenic lipid profiles. An association between thyroid dysfunction and dyslipidemia was first reported in 1930s.\textsuperscript{[6]} The association of thyroid disorders with an increased risk for coronary heart disease is attributed to impaired metabolism of atherogenic lipids and lipoproteins.

Dyslipidemia associated with the thyroid disorders have for long been associated with increased risk of cardiovascular...
disease (CVD) in these patients. The physicians have been consistently trying to regulate the serum lipid profile in the thyroid disorder patients for reducing the risk of CVD. But thyroid disorders are associated with not just an alteration of the metabolic parameters, i.e. the serum lipids or the sugar levels. It has been shown by various researchers over the years that thyroid hormones considerably influence the plasma levels of hormones like insulin and C-peptide.[7] Insulin and C-peptide are the pancreatic hormones which help stabilize the blood sugar level to normal. Hypothyroidism shows higher plasma insulin levels and the hyperthyroid state has lower plasma insulin.[7] The insulin resistance (IR) syndrome has been observed and reported in both hyper and hypothyroid states. Reaven[8] at the Banting lecture and in 1995[9] explored the role of IR in human diseases. It has been shown in various correlative studies that insulin, IR and C-peptide have a strong association with dyslipidemia in thyroid disorders.[10,11]

Background
With an ever increasing incidence of CVD in most urban populations, there has been a demand for newer techniques that could help in the early detection of the risk of this disease complex. Western Rajasthan is also not an exception. The prevalence of CVDs in the Rajasthani urban and rural populations has been reported in the Jaipur Heart Watch Study – 1, 2 and 3 from 1999 to 2005. There were reportedly more cases of CVD in the urban population than in the rural population, owing to increasing obesity in the urban population. Moreover, with urbanization, there is an escalating problem of stressful lifestyle, compromised nutrition and an increased incidence of thyroid diseases with advancing age. There has been no population study reported in this part of western Rajasthan for the prevalence of thyroid disorders and associated CVDs. However, there have also been an increased number of thyroid disorder patients reporting with CVDs in our outpatient clinics.

Aim
In the present study, we have tried to delineate the biochemical parameters in addition to lipid profile that might be associated with the increased CVD risk in these patients. This may assist the physicians for a more efficient evaluation of the risk of CVD in thyroid disorder patients and its proper management.

Materials and Methods
The present study was a part of Ph. D. research program of 3 years duration at Dr. S. N. Medical College, Jodhpur, in the Department of Biochemistry. The patients were taken from the outpatient thyroid clinics of Department of Medicine, Dr. S. N. Medical College and associated group of hospitals.

Criteria for selection of patients
A total of 320 subjects participated in this study. There were 100 healthy controls (50 each of males and females) with a mean age of 47 ± 12.5 years. Age-matched thyroid disorder patients were enrolled – 150 hypothyroid (73.3% females and 26.6% males) and 70 hyperthyroid (54.3% females and 45.71% males) patients. The thyroid disorder patients were selected on the basis of patients’ complaints and clinical and biochemical [thyroid stimulating hormone (TSH) evaluation] examination.

An informed consent was taken from all the subjects. A performa was prepared and duly filled for each patient, regarding their complaints, family history, anthropometric and biochemical evaluations.

All the patients included in the study who showed symptoms of thyroid disorders and with an abnormal TSH were confirmed as hypo/hyperthyroid by performing complete thyroid profile tests, i.e. T<sub>3</sub> and T<sub>4</sub> also. All the patients were diagnosed as hypo or hyperthyroid for the first time and were not taking any medication for diabetes mellitus or hypertension or hypolipidemic drugs.

Methods
Anthropometric analysis
Weight and height of all the subjects were taken in light clothing and without shoes. The body mass index (BMI) was then calculated using the formula:

\[ \text{BMI} = \frac{\text{Wt. (in kg)}}{\text{Ht.}^2 \text{(in m)}} \]

This gave an idea about the degree of obesity amongst the patients.

Clinical examination of the patients included taking the blood pressure of the patients by auscultatory method.

Biochemical analysis
Fasting venous blood samples were taken (5 ml). Serum was separated after half an hour and evaluated biochemically for the following:
1. serum insulin [enzyme-linked immunosorbent assay (ELISA)],
2. serum C-peptide (ELISA),
3. lipid profile (enzymatically),
4. apo-A<sub>1</sub> (immunoturbidimetrically),
5. apo-B (immunoturbidimetrically) and
6. Homeostasis model assessment-insulin resistance (HOMA-IR) (formula).
All the biochemical tests were done using fully automated analyzer Chemwell of Ark Company. The observations were then subjected to essential statistical evaluations like mean, SD, Student’s t-test (unpaired) to establish statistical significance, and Spearman’s correlation coefficient was used to find out the correlation of various biochemical parameters and blood pressure with anthropometric parameter, BMI. The correlative analysis was carried out to identify the risk of CVD amongst the thyroid disorder patients at an early stage of the disease, which could give the physicians a novel array of tests that may help in choosing the correct modalities of treatment and improving the quality of patient’s life.

RESULTS

The results of the study are presented in Figures 1-7.

**DISCUSSION**

The cardiovascular system is a major target of thyroid hormones, as it is sensitive to both excess and deficiency of the thyroid hormones at the tissue level.\[12,13\] The cardiovascular risk in patients with hypothyroidism results from changes in the cardiovascular function and from accelerated atherosclerosis. For long, physicians have evaluated serum lipids in thyroid disorder patients to assess the thyroid function deterioration in these patients. Alterations in serum cholesterol levels, as observed in the current study, are a frequent finding in such patients (both hypo and hyperthyroid).\[14-18\] Similarly, the levels of serum apoproteins like apo-A\(_1\) and apo-B are altered in thyroid disorders owing to the role of thyroid hormones in rate of synthesis of these apoproteins.\[19\] These apoproteins are elevated in the hypothyroid patients and reduced in the...
hyperthyroid patients\cite{20,21} consistent with our observations [Figure 7]. This alteration in the levels of apo-A\textsubscript{1} has been attributed to the influence of thyroid hormones on the distribution of apo-A\textsubscript{1} and the composition of high-density lipoprotein cholesterol (HDLc).\cite{16} Alterations in serum lipoproteins are the major cause of atherosclerosis, which progresses to CVDs.

Hypertension has been proven beyond doubt to be one of the major independent risk factors for heart disease and stroke. A close association has been reported between hypothryoidism and hypertension,\cite{22,23} in particular, diastolic hypertension, as observed in the current study. Similarly, systolic hypertension has been associated with hyperthyroidism, consistent with our observations [Figure 1b].\cite{24} The systolic hypertension of hyperthyroid and diastolic hypertension of the hypothyroid patients makes these patients prone to CVD.

Study of serum insulin metabolism at various levels of thyroid activity has been of great interest. Hyperinsulinemia has been observed in both hypo and hyperthyroidism as compared to the healthy controls [Figure 3], consistent with the findings of various researchers.\cite{25-30} The hyperinsulinemia of hypothyroid patients in the present study was associated significantly with dyslipidemia characterized by raised total cholesterol,\cite{10} triglycerides and cholesterol-rich lipoproteins, along with a rise of atherogenic apoprotein, apo-B [Figures 6 and 7]. Furthermore, the CVD risk ratios – T. chol/HDLc and apo-B/apo-A\textsubscript{1} – showed a highly significant correlation to serum insulin [Table 1a], i.e. these ratios rose with increase of serum insulin. The hyperthyroid patients, however, were observed to have a nonsignificant, but negative correlation between serum insulin and various lipid fractions [Table 1b].
Thus, the evaluation of serum insulin in the thyroid disorder patients helps to assess the risk of CVD in these patients, as the risk increased with a rise of serum insulin. Persistent hyperinsulinemia leads to a state of IR. IR has been observed in both hypo and hyperthyroidism. However, the present study showed a state of IR in hypothyroidism, but not a significant insulin-resistant state in the hyperthyroid patients as compared to the healthy controls [Figure 4]. The dyslipidemic state of the hypothyroid patients was clearly due to the significant association of HOMA-IR with the lipid fractions and the T. chol/HDLc, apo-B/apo-A\textsubscript{1} ratios [Table 2a]. The hyperthyroid patients reportedly had a significant correlation of HOMA-IR with T. chol/HDLc ratio [Table 2b].

Serum C-peptide evaluations have been done consistently in the thyroid disorder patients to study the insulin kinetics and its effect on carbohydrate metabolism.\textsuperscript{31,32} However, the serum C-peptide evaluation in the present study showed a highly significant association with the lipoprotein fractions

### Table 1a: Correlation of serum insulin with lipid profile, apoproteins and ratios in hypothyroid patients

| Hypothyroid | r   | P          | Statistical significance |
|-------------|-----|------------|-------------------------|
| T. chol     | 0.661 | <0.0001 | HS                      |
| TG          | 0.378 | <0.0001 | HS                      |
| HDLc        | 0.019 | 0.821   | NS                      |
| LDLc        | 0.650 | <0.0001 | HS                      |
| VLDL        | 0.390 | <0.0001 | HS                      |
| Apo-A\textsubscript{1} | 0.16 | 0.155   | NS                      |
| Apo-B       | 0.488 | <0.0001 | HS                      |
| T. chol/HDLc | 0.531 | <0.0001 | HS                      |
| Apo-B/apo-A\textsubscript{1} | 0.288 | <0.0001 | HS                      |

* T. chol – total cholesterol, TG – triglycerides, HDLc – High density lipoprotein, LDLc – Low density lipoprotein, VLDL – Very low density lipoprotein, HS – Highly significant, NS – Non – significant

### Table 2a: Correlation of HOMA-IR with lipid profile, apoproteins and ratios in hypothyroid patients

| Hypothyroid | r   | P          | Statistical significance |
|-------------|-----|------------|-------------------------|
| T. chol     | 0.669 | <0.0001 | HS                      |
| TG          | 0.481 | <0.0001 | HS                      |
| HDLc        | 0.088 | 0.28    | NS                      |
| LDLc        | 0.629 | <0.0001 | HS                      |
| VLDL        | 0.491 | <0.0001 | HS                      |
| Apo-A\textsubscript{1} | 0.165 | 0.429   | NS                      |
| Apo-B       | 0.363 | <0.0001 | HS                      |
| T. chol/HDLc | 0.491 | <0.0001 | HS                      |
| Apo-B/apo-A\textsubscript{1} | 0.171 | 0.035   | S                       |

### Table 1b: Correlation of serum insulin with lipid profile, apoproteins and ratios in hyperthyroid patients

| Hyperthyroid | r   | P          | Statistical significance |
|-------------|-----|------------|-------------------------|
| T. chol     | -0.216 | 0.07 | NS                      |
| TG          | -0.128 | 0.287   | NS                      |
| HDLc        | -0.057 | 0.636   | NS                      |
| LDLc        | -0.202 | 0.091   | NS                      |
| VLDL        | -0.127 | 0.295   | NS                      |
| Apo-A\textsubscript{1} | -0.127 | 0.291   | NS                      |
| Apo-B       | -0.177 | 0.142   | NS                      |
| T. chol/HDLc | -0.089 | 0.460   | NS                      |
| Apo-B/apo-A\textsubscript{1} | -0.021 | 0.862   | NS                      |

### Table 2b: Correlation of HOMA-IR with lipid profile, apoproteins and ratios in hyperthyroid patients

| Hyperthyroid | r   | P          | Statistical significance |
|-------------|-----|------------|-------------------------|
| T. chol     | -0.094 | 0.437 | NS                      |
| TG          | -0.033 | 0.783   | NS                      |
| HDLc        | -0.016 | 0.182   | NS                      |
| LDLc        | -0.100 | 0.405   | NS                      |
| VLDL        | -0.032 | 0.790   | NS                      |
| Apo-A\textsubscript{1} | -0.149 | 0.214   | NS                      |
| Apo-B       | -0.078 | 0.515   | NS                      |
| T. chol/HDLc | 0.819 | <0.0001 | HS                      |
| Apo-B/apo-A\textsubscript{1} | -0.025 | 0.836   | NS                      |

### Table 3a: Correlation of C-peptide with lipid profile, apoproteins and ratios in hypothyroid patients

| Hypothyroid | r   | P          | Statistical significance |
|-------------|-----|------------|-------------------------|
| T. chol     | 0.630 | <0.0001 | HS                      |
| TG          | 0.364 | <0.0001 | HS                      |
| HDLc        | 0.031 | 0.70     | NS                      |
| LDLc        | 0.618 | <0.0001 | HS                      |
| VLDL        | 0.375 | <0.0001 | HS                      |
| Apo-A\textsubscript{1} | 0.116 | 0.156   | NS                      |
| Apo-B       | 0.473 | <0.0001 | HS                      |
| T. chol/HDLc | 0.501 | <0.0001 | HS                      |
| Apo-B/apo-A\textsubscript{1} | 0.275 | 0.0006 | HS                      |

### Table 3b: Correlation of C-peptide with lipid profile, apoproteins and ratios in hyperthyroid patients

| Hyperthyroid | r   | P          | Statistical significance |
|-------------|-----|------------|-------------------------|
| T. chol     | -0.158 | 0.187   | NS                      |
| TG          | -0.135 | 0.261   | NS                      |
| HDLc        | 0.036 | 0.768    | NS                      |
| LDLc        | -0.163 | 0.174   | NS                      |
| VLDL        | -0.135 | 0.262   | NS                      |
| Apo-A\textsubscript{1} | 0.0231 | 0.848   | NS                      |
| Apo-B       | -0.083 | 0.493   | NS                      |
| T. chol/HDLc | -0.167 | 0.163   | NS                      |
| Apo-B/apo-A\textsubscript{1} | -0.078 | 0.517   | NS                      |
in the hypothyroid patients\(^\text{[3]}\) [Table 3a]. Thus, it may be deduced that the raised serum C-peptide levels [Figure 5] indicate a state of dyslipidemia and deteriorated CVD risk ratios. However, no such association has been observed in hyperthyroid patients in the study [Table 3b].

The current study shows the hypothyroid patients to have the triad of metabolic syndrome – raised BMI, hypertension and dyslipidemia – making the patients highly susceptible to CVDs. The hyperthyroid patients show systolic hypertension, IR and a raised T. chol/HDLc ratio, which may be responsible for the CVD risk in these patients.

**CONCLUSION**

We conclude that the estimation of traditional lipid profile along with some additional parameters like serum insulin, IR, C-peptide, apo–A\(_1\), and apo–B would not only help assess the thyroid status, but can also help in the early evaluation of a possible risk of CVD.

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