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ATHEROGENIC INDICATIONS IN THYROIDISIM PATIENTES AND THE RISK OF CARDIOVASCULAR DISEASES

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ABSTRACT

The body's energy metabolism can be significantly affected by thyroid diseases, making them a prime concern for medical professionals. Despite this, traditional lipid profile tests are still commonly used by physicians to diagnose these conditions. The aim of the current study is to assess the efficacy of several atherogenic indices in predicting the risk of cardiovascular disease among patients with thyroid dysfunction, including the atherogenic index of plasma (AIP), Castelli's risk index I and II (CRI-I and II), the atherogenic coefficient (AC), and the cholesterol index (CHOL index).Methods: A100 woman was involved in this study which diagnosed with thyroid dysfunction, and their thyroid hormone levels were used to divide them equally into two groups: Hyperthyroidism patients (n=50) with aged 18-60 years old and Hypothyroidism with patients (n=50) with aged 18-75 years old. Additionally, 30 healthy women between the ages of 18 and 70 were included as a control group. To collect data, demographic and clinical measurements were taken, including body mass index (BMI), age, weight, lipid profile and atherogenic indices such as AIP, CRI-I, CRI-II, AC, and CHOL index. Thyroid hormone levels (TSH, T_3 and T_4, freeT_3, freeT_4) were also recorded for all participants. Results: The calculated atherogenic indices of the patients and controls revealed the presence of significant increase ($P<0.05$) in these indices in both thyroidism patients groups when compared with that of control group. Conclusions: These results suggest that patients with thyroidism are at high risk to cardiovascular diseases and the regular monitor for dyslipidemia is very important in order to start an early treatment and advise them for changing their life style.

Keywords: Hyperthyroidism; Hypothyroidism, Atherogenic Indications, Cardiovascular Diseases.

المؤشرات الاثيروجينية في مرضى الغدة الدرقية ومخاطر امراض القلب والاوعية الدموية

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الخلاصة:

يمكن أن يتأثر استقلاب الطاقة في الجسم بشكل كبير بأمراض الغدة الدرقية، مما يجعلها مصدر قلق رئيسي للمهنيين الطبيين، على الرغم من ذلك، لا تزال اختبارات تحليل الدهون التقليدية شائعة الاستخدام من قبل الأطباء لتشخيص هذه الحالات. الهدف من الدراسة الحالية هو تقييم فعالية العديد من مؤشرات تصلب الشرايين في التنبؤ بخطر الإصابة بأمراض القلب والأوعية الدموية بين المرضى الذين يعانون من اختلال وظيفي في الغدة الدرقية ، بما في ذلك مؤشر تصلب الشرايين للبلازما(AIP) ، ومؤشر مخاطر كاستيلي الأول والثاني(CRI-I) و (CRI- II)ومعامل تصلب الشرايين(AC)، ومؤشر الكوليسترول (CHOL.INDEX. الطريقة: شاركت 100 امرأة في هذه الدراسة التي تم

[*] **The research is taken from a master's thesis by the first researcher.**

تشخيصهم بضعف الغدة الدرقية، واستخدمت مستويات هرمون الغدة الدرقية لديهم لتقسيمهم بالتساوي إلى مجموعتين: فرط نشاط الغدة الدرقية مع المرضى الذين تتراوح أعمارهم بين 18-60 عامًا وقصور الغدة الدرقية لدى المرضى الذين تتراوح أعمارهم بين 18 و 75 عامًا. بالإضافة إلى ذلك، تم تضمين 30 امرأة صحية تتراوح أعمارهن بين 18 و 70 كمجموعة ضابطة. لجمع البيانات، تم أخذ القياسات الديموغرافية والسريرية، بما في ذلك مؤشر كتلة الجسم (BMI) والعمر والوزن وملف الدهون و TG و TC و HDL-C و LDL-C، بالإضافة إلى مؤشرات تصلب الشرايين مثل AIPو -CRI مؤشر I و CRI-II و AC و .CHOL تم أيضًا تسجيل مستويات هرمون الغدة الدرقية TSH و T3 و T4و freeT3 و freeT4 لجميع المشاركين. النتائج: كشفت مؤشرات تصلب الشرايين المحسوبة للمرضى والضوابط عن وجود زيادة معنوية في كل من مجموعتي مرضى الغدة الدرقية بالمقارنة مع مجموعة السيطرة الاستنتاجات : تشير هذه النتائج الى ان مرضى الغدة الدرقية معرضون لخطر كبير للإصابة بأمراض القلب والأوعية الدموية، وأن المراقبة المنتظمة لخلل شحميات الدم مهمة جدًا لبدء العلاج المبكر وتقديم المشورة لهم لتغيير نمط حياتهم.

الكلمات المفتاحية: فرط نشاط الغدة الدرقية ، قصور الغدة الدرقية، مؤشرات تصلب الشرايين، امراض القلب والاوعية الدموية.

INTRODUCTION:

All metabolic processes within the body are influenced by thyroid hormones. Lipid synthesis, mobilization, and breakdown are all impacted as a result. Numerous factors play a role in lipid breakdown, outweighing those of lipid production. Insufficient levels of thyroid hormones are produced in cases of hypothyroidism. Generating more TSH and increasing blood TSH levels, the decrease in T4 and T3 levels causes a biochemical change **(Fotakis *et al.*, 2022)**. Meanwhile, hyperthyroidism boosts heart rate and pulse pressure while also potentially affecting arterial stiffness. For those with metabolic or atherosclerosis conditions, T4 and thyroid mimetics may prove beneficial as they can reduce total blood cholesterol and Low density lipoprotein(LDL)levels. In hypothyroidism, cholesterol synthesis is curtailed due to the stimulation of HMG-CoA reductase by thyroid hormones **(Landazuri *et al.*, 2019).** Several studies reveal that high levels of triglycerides (TG), LDL-C, and total cholesterol (TC) resulting from anomalies in lipid metabolism are associated with overt hypothyroidism. This condition significantly elevates the risk of cardiovascular diseases (CVD) **(Rizos *et al.*, 2011 & Mavromati *et al.*, 2021).** The TC/HDL-C, TG/HDL-C, and LDL-C/HDL-C lipid ratios are more effective in assessing cardiovascular risk than the standard lipid profile. Interestingly, the atherogenic index of plasma (AIP), a logarithmically transformed ratio of TG to HDL-C, is deemed a reliable surrogate marker of sdLDL and an excellent predictor of cardiovascular risk in comparison to traditional lipid parameters. Nevertheless, there is insufficient research on the complicated interplay between thyroidism and lipid ratios, including AIP **(Abid *et al.*, 2021).**

New biomarkers or more precise indices are necessary to improve clinical practices due to correlations found between overt hypothyroidism and high levels of LDL-C, abnormal diastolic blood pressure, low-grade inflammation, and hypercoagulability . For the past two decades, alternative diagnostic methods like atherogenic indices have emerged as useful predictors of CVD risk and treatment effectiveness, especially when conventional lipid profiles appear normal. The study by **(Fernandez-Macias *et al.*, 2019)** focused on several indices such as the atherogenic coefficient AC, Castelli's risk index I and II (CRI-I and CRI-II), and cholesterol index (CHOL INDEX). Among these, AIP emerged as a crucial predictive index with a strong correlation to CVD and potential benefits in preventing CAD. In predicting CVD occurrences in certain regions, numerous studies have analyzed the AIP. As a result, atherogenic indices have become useful for both research and clinical practice and need to be evaluated thoroughly **(Sapunar *et al.*, 2018).**

The objective of this research lies in assessing cardiovascular risk by means of atherogenic indices in patients with thyroidism as an alternative to conventional lipid profiles.

MATERIALS AND METHODS

Subjects

A case-control study involving 100 women with thyrodism, ranging in age from 18 to 75, was conducted with their informed agreement. Likewise, thirty healthy women between the ages of 18 and 70 were chosen for the comparison group. Cases covering the period from October 2021 to the end of January 2022 were gathered from the Al-Imameen Al-Kazimin Medical Center in Baghdad for this research. The exclusion criteria included women who were pregnant, smokers, had diabetes mellitus (T1DM or T2DM), were chronic or hereditary sickness sufferers, or had a family history of the conditions. The study was approved by the scientific and ethical committee.

Anthropometric Measurement

Body mass index (BMI) is determined by measuring standing height with a stadiometer and weighing with a precision balance using the following equation

$$BMI\ (kg/\ m^2) = weight\ (kg)/height^2\ (m)$$

Collection of Blood Samples

Each subject had an overnight fast before 5 mL of venous blood was taken, clotted for 10 min at room temperature, and centrifuged for 10 min at 3000 rpm before analysis. Separated serum was kept at -20°C in Eppendrof tubes.

Determination of Thyroid Hormones and Lipid Profile:

Using equipment from Cobas/Hitachi, Germany, the thyroid profile, which includes triiodothyronine (T3), thyroxine (T4), thyrotropin (TSH), free T3 (fT3), and free T4 (fT4), was measured. According to Mindray's guidelines, the blood lipid profile also includes the following measurements: total cholesterol TC, triglyceride TG, high-density lipoprotein HDL, low-density lipoprotein LDL, and very low-density lipoprotein VLDL.

Determination of Atherogenic Indices

Atherogenic index of plasma:

The molar ratio of TG to HDL-C is represented as the logarithm of the plasma atherogenic index (AIP), a novel lipid ratio.

$$\mathbf{AIP = \log (TGs/HDL\text{-}C)}$$

Castelli's risk indices (I&II)

The Castelli Risk Index, also referred to as the Cardiac Risk Index, is a lipid ratio. CRI-I is the ratio of TC to HDL-C, while CRI-II is the ratio of LDL-C to HDL-C.

$$\mathbf{CRI\text{-}I = TC/HDL\text{-}C}$$

$$\mathbf{CRI\text{-}II = LDL\text{-}C/HDL\text{-}C}$$

Atherogenic coefficient (AC):

The non-HDL cholesterol to HDL cholesterol ratio is known as the atherogenic coefficient. It has been utilized as a diagnostic proxy to forecast the likelihood of cardiovascular events.

$$AC = TC\text{-}HDL\text{-}C / HDL\text{-}C$$

Cholesterol index (CHOL INDEX)

The cholesterol index is a straightforward indicator that more correctly predicts the chance of getting CAD than other indices. When plasma TG is less than 400 mg/dL, it may be estimated from LDL-C and HDL-C.

$$CHOL\ index = LDL\text{-}C - HDL\text{-}C$$

If the TGs concentration is greater than or equal to 400 mg/dL, VLDL-C = TGs / 5 should also be included.

$$CHOL\ index = LDL\text{-}C - HDL\text{-}C + TGs/5$$

STATISTICAL ANALYSIS:

The statistical analysis was carried out using the statistical program SPSS 26, and the significant p value was fixed at 0.05. The parameter variables from both patients and controls were compared using the ANOVA test (unpaired Student's t-test). Findings are shown as the mean and standard deviation (SD) of two nonparametric variables in comparison.

RESULTS AND DISCUSSIOIN:

The differences in clinical features between patients and controls are shown in table 1. Contrary to expectations, age variation had no impact on the BMI level, which was considerably higher in those with hyperthyroidism than in those with hypothyroidism. The observation control group, however, didn't exhibit any discernible differences. The weight value assessed in the hypothyroidism group (77.66 ±11.08) was noticeably greater than both the hyperthyroidism group (68.0±9.11) and the control group (63.96±3.78), which was an eye-catching finding.

Substantial differences in lipid profiles were found between the two patient groups and the control group. It should be noted that individuals with hypothyroidism and hyperthyroidism had higher levels of TC, LDL, and TG ($P< 0.05$). On the other hand, there was no statistically significant difference in the levels of HDL and VLDL ($P>0.05$). Remarkably, there was no discernible difference between the two groups, despite the hypo group having greater levels of lipid profiles than the hyperthyroidism group.

Table (1): Mean ±SD of age, body weight, BMI, and blood lipids in the hypothyroid group, hyperthyroid group, and control group.

Variables	Control (n=30)	Hypothyroidism (n=50)	Hyperthyroidism (n=50)	P-Value
Age(years)	34.32±12.56	39.1±14.01	34.93±12.76	0.320
Weight(Kg)	63.96±3.78	*77.66±11.08[a]	*68.0±9.11[a]	**0.000**
BMI(Kg/m^2)	23.58±1.38	30.37±3.69[a]	31.44±3.25[a]	**0.0284**
TC(mg/dl)	146.86±17.0	*231.93±26.1[a]	*204.20±21.4[a,b]	**0.000**
TG(mg/dl)	92.66±16.55	*123.06±46.77[a]	*120.05±41.43[a]	**0.006**
HDL-C(mg/dl)	53.59±9.10	52.36±10.78	52.82±11.14	0.903
LDL-C(mg/dl)	102.41±14.57	*171.27±8.54[a]	*143.78±8.96[a]	**0.018**
VLDL(mg/dl)	24.35±8.49	25.68±9.16	26.86±5.62	0.484

* The letter in the p value <0.05 indicates whether there is a significant difference between groups. Specifically, the small letter "a" denotes significance when compared to the control group, whereas the letter "b" signifies significance in the comparison of the hypo and hyperthyroidism groups.

Thyroid stimulating hormone was significantly higher in hypothyroidism group (8.45±3.76 µIU/ml) than controls (2.43±0.96 µIU/ml) which were in turn significantly higher than hyperthyroidism group (0.50±0.56 µIU/ml). In contrast, patients in hyperthyroidism group demonstrated higher level of T3, T4 (2.34±1.10 nmol/L, 13.37±2.57 µg/dl than either controls (1.25±0.30 nmol/L, 9.6±1.08 µg/dl or hypothyroidism group (0.37±0.11nmol/L, 3.16±0.99 µg/dl) with significant differences between the three group, as show in Table 2.

Table (2): mean±SD of Thyroid hormone level in hyperthyroidism, hypothyroidism, and control groups.

Variables	Controls (n=30)	Hypothyroidism (n=50)	Hyperthyroidism (n=50)	p- value
TSH µlU/ml	2.43±0.96	*8.45±3.76[a]	*0.50±0.56[a,b]	**0.001**
T3 nmol/L	1.25±0.30	*0.37±0.11 [a]	*2.34±1.10[a,b]	**0.001**
T4 µg/dl	9.6±1.08	*3.16±0.99 [a]	*13.37±2.57[a,b]	**0.001**
FT3 pmol/L	3.48±0.28	*3.01±0.17 [a]	3.96±0.55	**0.001**
FT4 ng/dl	1.24±0.19	1.21±0.82	1.52±1.15	0.285

*P value <0.05. The small letters refer to presence of significance; a: significant when compared with control, b: significant when compared between hypo and hyper.
Table 3 displays the estimated atherogenic indices for the patients and controls. As compared to the control group, both thyroidism patient groups showed a substantial rise in these indices (P <0.05).

Table (3): (Mean ±SD) of atherogenic indices in hypothyroidism, hyperthyroidism, and controls.

Variables	Control (n=30)	Hypothyroidism (n=50)	Hyperthyroidism (n=50)	P-Value
AIP	0.20±0.08	*0.35±0.20[a]	*0.33±0.19[a]	**0.001**
CRI-I	0.93±0.60	*3.89±1.12[a]	*3.35±0.77[a,b]	**0.000**
CRI-II	1.52±0.42	*2.31±0.77[a]	*1.93±0.53[a,b]	**0.000**
AC	1.93±0.60	*2.89±1.12[a]	*2.35±0.77[a,b]	**0.000**
CHOL INDEX	27.71±22.9	*63.80±29.93[a]	*45.71±23.35[a,b]	**0.000**

* p value < 0.05 The little letter denotes the presence of significance between groups; for example, a indicates significance when compared to the control group, while b indicates significance when compared to the hypo- and hyperthyroidism groups.

Thyroid hormones are playing a significant role in cell growth, development and metabolism. Supporting the pathophysiology of various thyroid types is a plethora of studies **(Mancini *et al*., 2016 & Shahid *et al*., 2022).** According to the findings of one study, AIP was considerably greater in both thyroidism groups than in the control group.**(Wu *et al*,. 2021)** has demonstrated the tight relationship between the atherogenic index of plasma and the sdLDL atherogenic fractions of LDL lipoprotein. It has also been demonstrated to be a more accurate predictor of cardiovascular disease (CVD) when compared to individual lipids **(Dobiásová *et al*., 2011).** As a result, it has been determined that AIP is a trustworthy marker for determining cardiovascular risk**.** Our study showed that TC, TG, and LDL were elevated in participants with thyroidism compared to normal control. This corroborates a finding from William Castelli's research from 18 years ago, which demonstrated a positive correlation between lipid markers and CVD, confirmed in subsequent reports, as well as a negative correlation with conditions like COPD **(Delitala *et al*.,2015).** Carotid arteries in young adults demonstrate the ability of CRI-I to reflect the formation of coronary plaques and intima-media thickness. Therefore, clinicians should consider CRI-I and II as valuable tools in predicting or evaluating atherosclerosis and CVD **(Culha *et al*.,2020).**

Patients suffering from obesity were found to have a connection between AIP and Omentin, a main adipokine secreted by visceral fat **(Kadium *et al*., 2023).** Meanwhile, a study on patients with T2DM revealed a promising discovery regarding FBXW7protein - a positive correlation with the atherogenic index that suggests its potential as a gene expression regulator of lipid metabolism, promoting cholesterol synthesis and uptake of LDL **(Mohammed *et al*., 2021).** Additionally, a study conducted to predict the risk of cardiovascular diseases among T2DM patients found a significant link between AIP and lipocalin-2 **(Wadood *et a*l., 2016).** These results suggest that there is potential for exploring various markers in different diseases and their connection with AIP. In comparison to the control group, newly diagnosed and Tamoxifen-treated women had a significant increase (P<0.0001) in atherogenic index, indicating that breast cancer patients may be more vulnerable to CVD. The correlation between lipid metabolism and hypothyroidism has prompted several theories, and thyroid diseases alongside diabetes mellitus are prevalent endocrine disorders. Hypo or hyperthyroidism is more prevalent in people with type 2 diabetes, and thyroid hormones have a significant impact on blood glucose, protein metabolism, and numerous some organs and tissues. Although studies have examined the connection between thyroid disease and atherosclerosis, their findings have

been conflicting, with some demonstrating that overt or subclinical hypo or hyperthyroidism can raise CV risk while others indicating no such effect. Numerous factors, such as different study designs, brief follow-up times, and the inclusion of patients taking thyroid hormone replacement therapy or other medications that affect lipid profiles, may contribute to the controversy surrounding the relationship between thyroidism and carotid atherosclerosis. In addition to limited sample numbers and variable ranges of normal thyroid hormone levels, the variation in approach when it comes to measuring intima media thickness (IMT) and evaluating carotid arteries may create further bias. It's important to keep in mind that changes in thyroid levels over time may lead to a mistaken diagnosis of temporary subclinical thyroid dysfunction and make it more difficult to determine how it affects carotid atherosclerosis. Transient thyroid insufficiency may be disregarded in order to more properly determine how long-term thyroid failure affects carotid atherosclerosis. altogether (Papadopoulou *et al*,.2020).. To aid in predicting the condition of atherogenic patients and further evaluating this disease, atherogenic indices could be a useful tool for thyroidism specialists.

CONCLUSION:

Thyroidism has been connected to ratios and indices such AIP, CRI-I, CRI-II, AC, and CHOL INDEX, which are rarely utilized but may be useful in predicting the incidence of certain CVDs. It seems that people with thyroid disorder have a higher risk of acquiring cardiovascular problems, hence screening for dyslipidemia is essential for starting therapy early and advising lifestyle changes. Using uncomplicated mathematical equations that can be implemented seamlessly by automated analytical appliances without any additional fees, one can effortlessly compute all atherogenic indices.

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