Open Access Research Article

Measurement of Serum Stromelysin-2 Level in Iraqi Patients with Subclinical and Clinical Hypothyroidism

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Abstract:

Background: Hypothyroidism is a medical condition characterized by increased levels of thyroid stimulating hormone and normal or decreased levels of thyroid hormones. This condition may contribute to dyslipidemia, hypertension, atherosclerosis, cognitive impairment, neuromuscular dysfunction and infertility. Several factors that increase the risk of cardiovascular disease, such as metabolic syndrome and dyslipidemia, are related to obesity. Stromelysin-2, also known as matrix metalloproteinase-10, is an enzyme produced by cells that breaks down the extracellular matrix in various tissues, including blood vessels.

Objective: To assess the levels of serum stromelysin-2 in patients with subclinical and clinical hypothyroidism and compare them with healthy controls. Additionally, to determine the relationship between serum stromelysin-2 levels and the anthropometric measures.

Methods: A case control study was conducted with 130 Iraqi individuals divided into three groups. The study aimed to measure serum stromelysin-2 and anthropometric parameters such as body mass index, waist circumference, and waist-to-hip ratio. To differentiate between more than two independent means the ANOVA test was used for blood investigations.

Result: The study found that clinical and subclinical hypothyroid patients had significant higher mean body mass index (P = 0.001), waist circumference (P = 0.001), waist to hip ratio (P = 0.001), and serum stromelysin-2 (P = 0.001) compared to healthy control. Among patients with clinical hypothyroidism group, there were positive correlations between serum stromelysin-2 and body mass index (r = 0.413, p = 0.005), waist circumference (r = 0.406, p = 0.006), and waist to hip ratio (r = 0.367, p = 0.013).

Conclusion: It has been observed that patients suffering from clinical and subclinical hypothyroid patients tend to have a higher body weight, as measured by their body mass index, waist circumference, and waist-to-hip ratio. This may indicate an increased risk of cardiovascular disease. Additionally, such patients have been found to have high levels of stromelysin-2, a protein that is believed to be indicative of early atherosclerosis in blood vessels. This suggests that stromelysin-2 could potentially be used as a marker for predicting cardiovascular disease in hypothyroid patients.

Keywords: Anthropometric measurement**;** Hypothyroidism; Obesity; Stromelysin-2; Subclinical atherosclerosis.

Introduction:

Subclinical hypothyroidism and hypothyroidism are differentiated by elevated levels of thyroid stimulating hormone and either normal or abnormal levels of thyroid hormones (1). Subclinical and/or clinical hypothyroidism are caused by a reduction in the synthesis of thyroid hormones and low thyroid hormones levels in the blood, women are more likely to suffer from this condition (2). Patients with subclinical and clinical hypothyroidism are more likely to develop complications for hypertension, atherosclerosis, cognitive impairment, neuromuscular dysfunction, infertility, in addition to obesity, and dyslipidemia (1). Obesity is the accumulation of excess fat (3). Obesity is linked to an increase in cardiovascular risk elements like type 2 diabetes, dyslipidemia, hypertension, and sleep disturbances (4). Cardiovascular diseases in Iraq are one of the main causes of disease-related deaths, with high rates among young people (5). Myocardial infarction, deep venous thrombosis, and other cardiovascular diseases all have thrombosis as a major risk factor (6). Stromelysin-2 is also called matrix metalloproteinase-10(MMP-10), belong to the family of endopeptidases known as matrix metalloproteinases (7), is an enzyme produced by cells that breaks down the extracellular matrix in various tissues, including blood vessels. Research has shown that stromelysin-2 levels are increased in

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activated macrophages and smooth muscle cells in atherosclerotic lesions (8). It plays a significant role in various cellular processes within atherosclerotic plaques and responsible for their complications, development, and rupture in particular (7). Due to an imbalance between matrix metalloproteinases and their inhibitors, atheroma plaque destabilization and rupture occur (9). Elevated serum MMP-10 levels are associated with increased carotid intima-media thickness CIMT and with the presence of atherosclerotic plaques in asymptomatic subjects and hence, it has been suggested that MMP-10 could be related to plaque progression and instability (10). The aims of this Study were to measure serum stromelysin-2 levels in patients with subclinical and clinical hypothyroidism and compare their levels with those of healthy controls. Also, to estimate the relationship between serum stromelysin-2 levels and the anthropometric measures.

Patients and Methods

One hundred thirty (130) participants (94 female and 36 male) from 23 to 70 years of age, collected from Iraqi individuals who attended Baghdad radiotherapy and nuclear medicine center and private laboratories between October 2022 to January 2023. Every participant gave his agreement after being informed. The present study was given permission by the Ethical Committee of the University of Baghdad College of Medicine. Three groups were classified: group A, which included 45 patients (36 female and 9 male) diagnosed with clinical hypothyroidism; group B, which included 43 patients (33 female and 10 male) diagnosed with subclinical hypothyroidism; and group C, which included 42 euthyroid healthy participants (25 female and 17 male) as controls.

Laboratory tests are then used to confirm the diagnosis of hypothyroidism, including measuring levels of the TSH and the FT4 and FT3. A high TSH level, and low levels of FT4 and FT3, are typically indicative of hypothyroidism. In subclinical hypothyroidism, the FT4 and FT3 hormone levels are usually within normal limits, but TSH levels are elevated.

Patients who have hypothyroidism due to thyroidectomy or radiotherapy, secondary hypothyroidism, diabetes mellitus, chronic renal failure, hypertension, alcoholism, and smoking were excluded from current study.

Biochemical investigation involved serum stromelysin-2 which was measured by ELISA (Elabscience) (11). In addition, anthropometric parameters included (BMI, WC and WHR) were calculated as follows:

1-Body mass index (BMI): Is a tool used to classify people as either underweight, normal weight, or overweight (12), as demonstrated by the following:

"[BMI = weight (kg) / (height (m)) ²]"

Normal range (18.5 – 24.99)

2-Waist circumference (WC): Is calculated using the midpoint between the rib cage lower edge and the iliac crest (13).

Normal range (man <90, female <80)

3-Waist to hip ratio (WHR): Is calculated by dividing waist circumference by hip circumference (14).

Normal range (men is 0.9 and for women is 0.85).

Statistical analysis

The data was analyzed using SPSS-25. The data represented as mean, standard deviation, and ranges. The significance of quantitative data differences was tested using ANOVA for more than two independent means. The diagnostic ability of stromelysin-2 levels was also assessed based on the area under the curve (AUC). In addition, Pearson correlation was utilized to determine the relationship between two quantitative variables, and the *t*-test was used to see how significant the relationship was. A level of *P* value less than 0.05 was considered significant.

Results

The patients and controls of current study were age-matched. However, there is a significant difference in the mean values of BMI (*P* = 0.001), WC (P = 0.001), and WHR (P = 0.001) between groups A (clinical hypothyroid patients), B (subclinical hypothyroid patients), and C (controls), as shown in **Table 1.**

Variable	Study group A Mean ± SD	B Mean ± SD	C Mean ± SD	*P* - Value
Age (Year)	39.11 ± 11.21	41.09 ± 12.32	39.17 ± 10.15	0.650
BMI (Kg/m^2)	30.06 ± 4.62	28.78 ± 5.45	25.06 ± 2.97	0.001
WC (cm)	103.5 ± 10.68	102.8 ± 9.80	88.30 ± 17.06	0.001
W/H Ratio	0.99 ± 0.06	0.99 ± 0.08	0.89 ± 0.16	0.001

*Significant difference between more than two independent means using ANOVA-test at 0.05 level.

In addition, figure1 showed distribution of patients (both clinical and subclinical hypothyroidism) and controls according to stromelysin-2 levels. The higher levels of stromelysin-2 were found in clinical and subclinical hypothyroid patients as compared to control group.

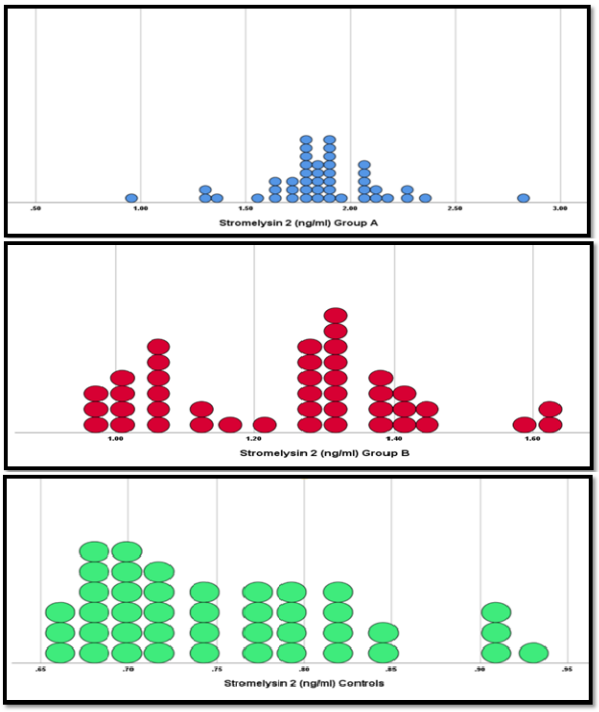
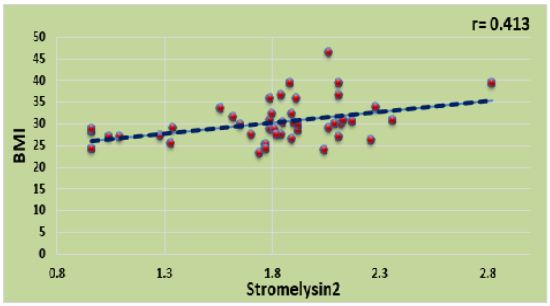
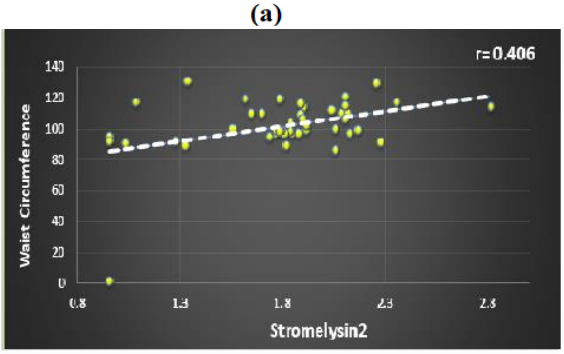


Figure 1: Serum stromelysin-2 levels in the studied groups.

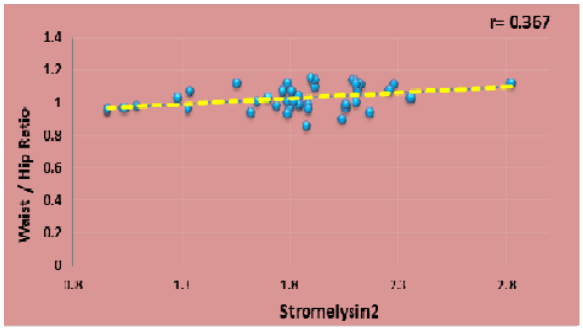
Moreover, the results of the current study showed positive correlation between serum stromelysin-2 levels and BMI (r =0.413, P=0.005), WC (r =0.406, P=0.006) as well as W/H ratio (r = 0.367, P=0.013) as demonstrated in Figure 2A, 2B and 2C, respectively.



(a)



(b)



(c)

Figure 2: Positive correlation between Stromelysin-2 and anthropometric measures in patients with clinical hypothyroidism.

Discussion

Hypothyroidism causes atherosclerosis in many different ways, including dyslipidemias, greater arterial stiffness, obesity, and endothelial dysfunction (15). Most of clinical and subclinical hypothyroid patients suffer from obesity, and obesity is one of the most common factors for atherosclerosis (16). Thyroid hormone tests are frequently requested when investigating the causes of obesity because most cases are due to thyroid hormones**.** Serum TSH levels tend to be higher or slightly higher in obese people, even if FT3 and FT4 are still within the normal range. Many different organs and tissues, such as the liver, brain, heart, pancreas, skeletal muscles, and adipose tissue are controlled by TSH. Appetite, energy balance, thermogenesis, free fatty acid oxidation, basal metabolic rate, and lipid and glucose metabolism are all under their control (17). Weight gain in patients with hypothyroidism is not only associated with excess fat accumulation but also with excess salt and water accumulation. Thyroid hormones help decompose fat by metabolizing stored calories used for energy, so in the case of a decrease in thyroid hormones, it causes a slow metabolism, which results in burning fewer calories and thus causes weight gain (18).

This research showed that patients with clinical and subclinical hypothyroidism had higher BMI, WC, and WHR compared to controls. This is consistent with another study which demonstrated that hypothyroidism correlates with an increased BMI and a greater prevalence of obesity, as well as hypothyroidism causes decreased thermogenesis and metabolic rate (19). Subclinical hypothyroidism, a mild form of thyroid dysfunction, has been linked to significant weight changes and is a risk factor for overweight and obesity, according to clinical evidence (20).

A study by Van and colleagues (2020) showed that there is evidence that obesity is both a risk factor and a risk indicator for coronary artery disease, cardiac arrest, and atrial fibrillation, even in people who don't have any symptoms (21).

Atherosclerotic plaques have been shown to release an enzyme known as stromelysin-2. Individuals who had subclinical atherosclerosis and elevated levels of

stromelysin-2 were found to have coronary calcifications (22).

This study also showed that clinical and subclinical hypothyroid patients had significantly higher stromelysin-2 levels in comparison to the control group. This agreed with Chen study, which showed that stromelysin-2 levels rise in patients with hypothyroidism to predict atherosclerosis (23). Also, high serum levels of stromelysin-2 are associated with increased carotid intima-media thickness (CIMT) increased inflammatory markers, and atherosclerotic plaques (24).

Conclusion

Serum stromelysin-2 is higher in people with clinical and subclinical hypothyroidism; which is considered as a vascular marker that may be useful for predicting the initial stages of atherosclerosis. Also, significant positive correlation was found between Stromelysin-2 and anthropometric measures represented by (BMI, WC and WHR) which showed higher levels in hypothyroid patients and are considered as risk factors for atherosclerosis and CVD.

Authors Declarations:

Conflicts of interest: None.

We hereby confirm that all the Figures and Tables in the manuscript are ours. No real names or personal information were collected, and the patients answers to questions were done and collected anonymously for privacy of data.

Author Contributions:

Study conception & design: (Rand M. Ibrahim). Literature search: (Rand M. Ibrahim). Data acquisition: (Rana A. Hamdi and Satar M. Kadam.). Data analysis & interpretation: (Rand M. Ibrahim). Manuscript preparation: (Rand M. Ibrahim). Manuscript editing & review: (Rana A. Hamdi and Satar M. Kadam).

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قياس مستوى سترروميليسين -2 في الدم لدى المرضى العراقيين الذين يعانون من قصور الغدة الدرقية السريري وتحت الإكلينيكي

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الخلاصة:
الخلفية: قصور الغدة الدرقية هو حالة طبية تتميز بزيادة مستويات هرمون الغدة الدرقية ومستويات طبيعية أو منخفضة من هرمونات الغدة الدرقية. قد تساهم هذه الحالة في دسليبيدميا وارتفاع ضغط الدم وتصلب الشرايين والضعف الإدراكي والخلل العصبي العضلي والعقم. ترتبط العديد من العوامل التي تزيد من خطر الإصابة بأمراض القلب والأوعية الدموية، مثل متلازمة التمثيل الغذائي واضطراب شحوم الدم، بالسمنة. Stromelysin-2، المعروف أيضا باسم المصفوفة ميتالوبروتيناز-10، هو إنزيم تنتجه الخلايا التي تعمل على تحطيم المصفوفة خارج الخلية في الأنسجة المختلفة، بما في ذلك الأوعية الدموية.
الهدف من الدراسة: تقييم مستويات سترروميليسين-2 في الدم لدى المرضى الذين يعانون من قصور الغدة الدرقية تحت الإكلينيكي والسريري ومقارنتها مع الأصحاء. بالإضافة إلى ذلك، لتحديد العلاقة بين مستويات سترروميليسين -2 في الدم والقياسات البشرية.
الطرق: أجريت دراسة الحالات والشواهد على 130 فردا عراقيا مقسمين إلى ثلاث مجموعات. هدفت الدراسة إلى قياس سترروميليسين -2 في الدم والمعلمات الأنثروبومترية مثل مؤشر كتلة الجسم ومحيط الخصر ونسبة الخصر إلى الورك. للتمييز بين أكثر من وسيلتين مستقلتين تم استخدام اختبار ANOVA لفحوصات الدم.
النتيجة: وجدت الدراسة أن مرضى قصور الغدة الدرقية السريري وتحت الإكلينيكي لديهم متوسط مؤشر كتلة الجسم أعلى بكثير (P = 0.001)، ومحيط الخصر (P = 0.001)، ونسبة الخصر إلى الورك (P = 0.001)، ومصل سترروميليسين -2 0.001. (P = 0.001)) مقارنة بالسيطرة الصحية. بين المرضى الذين يعانون من مجموعة قصور الغدة الدرقية السريرية، كانت هناك ارتباطات إيجابية بين مصل سترروميليسين -2 ومؤشر كتلة الجسم (r = 0.413، p = 0.005)، ومحيط الخصر (r = 0.406، p = 0.006)، ونسبة الخصر إلى الورك (0.367. r = 0.006، ع = 0.013).
الخلاصة: لقد لوحظ أن المرضى الذين يعانون من قصور الغدة الدرقية السريري ودون الإكلينيكي يميلون إلى أن يكون لديهم وزن أعلى في الجسم، كما تم قياسه من خلال مؤشر كتلة الجسم، ومحيط الخصر، ونسبة الخصر إلى الورك. قد يشير هذا إلى زيادة خطر الإصابة بأمراض القلب والأوعية الدموية. بالإضافة إلى ذلك، وجد أن هؤلاء المرضى لديهم مستويات عالية من سترروميليسين -2، وهو بروتين يعتقد أنه مؤشر على تصلب الشرايين المبكر في الأوعية الدموية. يشير هذا إلى أنه من الممكن استخدام سترروميليسين-2 كعلامة للتنبؤ بأمراض القلب والأوعية الدموية لدى مرضى قصور الغدة الدرقية.
الكلمات المفتاحية: القياسات البشرية، قصور الغدة الدرقية، السمنة، سترروميليسين-2، تصلب الشرايين تحت الإكلينيكي.

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