ESTIMATIVA DO NÍVEL DE ADROPINA PARA PACIENTES IRAQUIANOS COM DOENÇA CARDÍACA E ATHEROSCLEROSE E OS FATORES QUE AFETAM O SEU NÍVEL

ESTIMATION THE LEVEL OF ADROPIN FOR IRAQI PATIENTS WITH CARDIAC DISEASE AND ATHEROSCLEROSIS AND THE FACTORS AFFECTING ITS LEVEL

تقدير مستوى الأدرابين للمرضى العراقيين المصابين بأمراض القلب وتصلب الشرايين والعوامل المؤثرة على مستواه

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RESUMO

Adropina é um biomarcador de doença cardíaca e aterosclerose. Descoberto em 2008, esse peptídeo está envolvido no controle do metabolismo de carboidratos e ácidos graxos. Um conhecimento detalhado dos mecanismos desses peptídeos e dos fatores que afetam sua liberação pode fornecer um novo diagnóstico e tratamento de distúrbios metabólicos, incluindo doença cardíaca e aterosclerose. Este estudo teve como objetivo estimar o nível de adropina para pacientes iraquianos com doença cardíaca e aterosclerose e os fatores que afetam seu nível, bem como sua relação com as variáveis estudadas. Este estudo foi realizado em 130 adultos, incluindo 90 pacientes com doença cardíaca e aterosclerose e 40 adultos não infectados foram considerados um grupo de controle. Nível sérico de adropina e perfil lipídico (HDL, LDL e TC) foram estimados. Os resultados do estudo mostraram uma diminuição significativa no nível de adropina ($p < 0,0001$) nos seguintes casos: geralmente em todos os pacientes afetados com doença cardíaca e aterosclerose ($4,3 \pm 1,5$ ng/ml) em comparação com indivíduos saudáveis ($10,2 \pm 2,3$ ng/ml); em pacientes obesos ($3,4 \pm 0,7$ ng/ml) em comparação com pacientes não-obesos ($5,2 \pm 1,2$ ng/ml); em pacientes que também apresentam diabetes mellitus tipo 2 ($3,2 \pm 0,8$ ng/ml) e pacientes que também afetam com hipertensão ($4,1 \pm 1,2$ ng/ml) quando comparados com pacientes que não têm outra doença ($5,7 \pm 1,5$ ng). Uma correlação negativa significativa entre o nível de adropina sérica e o nível de IMC ($r = 0,493$; $p = 0,0001$), LDL ($r = -0,628$; $p = 0,0001$) e nível de TC ($r = -0,249$, $p = 0,018$). Uma correlação positiva significativa ($r = 0,395$, $P = 0,0001$) apareceu do nível de adropina com o nível de HDL. Pode-se observar que um nível mais baixo de adropina pode desempenhar um papel vital na fisiopatologia cardíaca e aterosclerose. Além disso, a diminuição do nível de adropina pode ser considerada um fator de risco para esses pacientes. Portanto, a medição e a vigilância das alterações na adropina sérica podem ser consideradas como um novo diagnóstico e avaliação da progressão da doença.

Palavras-chave: Doença cardíaca, aterosclerose, obesidade, diabetes mellitus-2, hipertensão.

ABSTRACT

Adropin is a biomarker for cardiac disease and atherosclerosis. Discovered in 2008, this peptide is involved in controlling the metabolism of carbohydrates and fatty acids. Detailed knowledge of these peptides' mechanisms and the factors that affect their release can provide new diagnostic and treatment of metabolic disorders, including cardiac disease and atherosclerosis. This study aimed to estimate the level of adropin for Iraqi patients with cardiac disease and atherosclerosis and the factors affecting its level and its relationship with the studied variables. This study was conducted on 130 adults, including 90 patients suffering from cardiac disease and atherosclerosis, and 40 uninfected adults were considered a control group. Serum levels of adropin and lipid profile (HDL, LDL, and TC) were estimated. The results of the study showed a significant decrease in the level of adropin ($p < 0.0001$) in the following cases: generally in all patients who affected with cardiac disease and atherosclerosis (4.3 ± 1.5 ng/ml) compared with healthy subjects (10.2 ± 2.3 ng/ml); in obese patients (3.4 ± 0.7 ng/ml) compared to non-obese patients (5.2 ± 1.2 ng/ml); in patients who also affected with diabetes mellitus type 2 (3.2 ± 0.8 ng/ml) and patients who also affected with hypertension (4.1 ± 1.2 ng/ml) when compared with patients who do not have other diseases (5.7 ± 1.5 ng). A negative significant correlation between serum adropin level and BMI ($r = 0.493$; $p = 0.0001$), LDL ($r = -0.628$; $p = 0.0001$) level and TC ($r = -0.249$, $p = 0.018$) level. A positive significant ($r = 0.395$, $P = 0.0001$) appeared correlation of adropin level with HDL level. It was observed

that a lower adropin level could play a vital role in cardiac pathophysiology and atherosclerosis. Also, a decrease in the adropin level can be considered a risk factor for these patients. Therefore, measurement and surveillance of changes in serum adropin can consider as a new diagnosis and assessment of disease progression.

Keywords: Cardiac disease, atherosclerosis, obesity, diabetes mellitus-2, hypertension

الملخص

الأدروبين هو علامة بيولوجية لأمراض القلب وتصلب الشرايين. اكتشف هذا الببتيد في عام 2008، وهو يساهم في التحكم في عملية التمثيل الغذائي للكربوهيدرات والأحماض الدهنية. يمكن أن توفر المعرفة التفصيلية لآليات هذه الببتيدات والعوامل التي تؤثر على إطلاقها تشخيصًا جديدًا وعلاجًا لاضطرابات التمثيل الغذائي، بما في ذلك أمراض القلب وتصلب الشرايين. هدفت هذه الدراسة إلى تقدير مستوى الأدروبين للمرضى العراقيين المصابين بأمراض القلب وتصلب الشرايين والعوامل المؤثرة على مستواه وكذلك علاقته بالمتغيرات المدروسة. أجريت هذه الدراسة على 130 بالغًا، من بينهم 90 مريضًا يعانون من أمراض القلب وتصلب الشرايين، واعتبر 40 بالغًا غير مصاب مجموعة ضابطة. تم تقدير مستوى المصل من الأدروبين والدهون (HDL و LDL و TC). أظهرت نتائج الدراسة انخفاضًا معنويًا في مستوى الأدروبين ($p < 0.0001$) في الحالات التالية: عند كل المرضى المصابين بأمراض القلب وتصلب الشرايين (1.5 ± 4.3 نانوغرام / مل) مقارنة مع الأصحاء (2.3 ± 10.2 نانوغرام / مل)؛ في المرضى الذين يعانون من السمنة المفرطة (0.7 ± 3.4 نانوغرام / مل) مقارنة مع غير المصابين بالسمنة (5.2 ± 1.2 نانوغرام / مل)؛ في المرضى الذين أصيبوا أيضًا بداء السكري 2 (0.8 ± 3.2 نانوغرام / مل) والمرضى الذين أصيبوا أيضًا بارتفاع ضغط الدم (1.2 ± 4.1 نانوغرام / مل) عند مقارنتهم بالمرضى الذين ليس لديهم مرض آخر (1.5 ± 5.7 نانوغرام). ارتباط معنوي سلبي بين مستوى الأدروبين في الدم ومؤشر كتلة الجسم ($r = 0.493$; $p = 0.0001$)، ومستوى LDL ($r = -0.628$; $p = 0.0001$) ومستوى HDL. يمكن ملاحظة أن انخفاض مستوى الأدروبين يمكن أن يلعب دورًا حيويًا في الفيزيولوجيا المرضية للقلب وتصلب الشرايين. أيضًا، يمكن اعتبار انخفاض مستوى الأدروبين عامل خطر لهؤلاء المرضى. لذلك، يمكن اعتبار قياس ومراقبة التغيرات في أدروبين الدم بمثابة تشخيص وتقييم حديثين لتطور المرض.

الكلمات المفتاحية: الأدروبين، مرضى القلب، تصلب الشرايين، السمنة، مرض السكري 2، ارتفاع ضغط الدم.

1. INTRODUCTION:

A major global public health concern is Cardiac disease and atherosclerosis (Ambrosy *et al.*, 2014; Guo, Lip, and Banerjee, 2013; Lüscher, 2015; Sayago-Silva, García-López, and Segovia-Cubero, 2013). Atherosclerosis is the leading cause of the cardiac disease (Li, Xie, Zheng, Yin, and Tang, 2016; Tian *et al.*, 2012). The etiology of atherosclerosis includes multiple metabolic disorders, including obesity, diabetes, and hyperlipidemia (Li *et al.*, 2016; Markelic *et al.*, 2011). In recent years, scientists have identified new regulatory peptides called adropin, which control the metabolism of carbohydrates and fatty acids (Cao *et al.*, 2019; Li *et al.*, 2016). Various research on different fields of medical sciences tends to expose their unique properties. Detailed knowledge of the mechanisms of these peptides and the factors that affect their release can provide new diagnostic and treatment of metabolic disorders, including Cardiac disease and atherosclerosis (Li *et al.*, 2016)

Adropin was discovered in 2008 by Kumar while studying the expressing gene that affects obesity in rat liver (Kumar *et al.*, 2008; Li *et al.*, 2016; Marczyk, Cecerska-Heryć, Jesionowska, and Dołęgowska, 2016). The name adropin is derived from two Latin words, the first "duro" meaning to set fire, and the second word "pinquis"

meaning fat or oil (Marczyk *et al.*, 2016). It is a peptide hormone with a molecular weight of 45-59 kDa (Cao *et al.*, 2019; Chang, Chu, Lin, Hsu, and Chen, 2018; Li *et al.*, 2016; Marczyk *et al.*, 2016). Besides, it is formed by the Enho gene, which is mainly generated in the liver and brain (Chang *et al.*, 2018; Kumar *et al.*, 2008; Li *et al.*, 2016). Adropin is composed of 76 amino acids and is monomeric (Kuloglu and Aydin, 2014; Kumar *et al.*, 2008; Li *et al.*, 2016). The amino acid sequence of adropin is similar in humans, mice, and rats (Kumar *et al.*, 2008; Li *et al.*, 2016; Marczyk *et al.*, 2016): in pig, the amino acid sequence is similar to 98-99% of the amino acid sequence (Li *et al.*, 2016; Wang *et al.*, 2015). Adropin is a membrane-bound protein, the first 9 amino acids from the amino end are expressed within of cytoplasm region (Li *et al.*, 2016), and the 9-30 amino acids are expressed within the cytoplasmic membrane; these amino acids are characterized by being hydrophobic (Li *et al.*, 2016; Marczyk *et al.*, 2016; Wang *et al.*, 2015). The remainder of the amino acids from the carboxylic end of the 30-76 amino acid is outside the cytoplasmic membrane (Li *et al.*, 2016; Wang *et al.*, 2015). Adropin is essential in regulating glucose and fatty acid metabolism and energy balance (Cao *et al.*, 2019; Chang *et al.*, 2018; Kumar *et al.*, 2008; Marczyk *et al.*, 2016). And that obesity affects the level of adropin, where the level

of pathways decreases in obese people (Chang *et al.*, 2018; Marczuk *et al.*, 2016). Also, adropin is a regulator of cardiovascular function as it increases blood flow and has a protective role in protecting endothelial cells (Li *et al.*, 2016; Lovren *et al.*, 2010; Marczuk *et al.*, 2016).

The study aimed (1) to estimate the level of adropin for Iraqi cardiac disease and atherosclerosis patients, (2) the effect of the factor of obesity and other diseases (diabetes mellitus-type 2 (DM-2, and hypertension), age, and sex at the level of adropin and (3) the relationship of adropin with the studied variables such as obesity, affected with other diseases (diabetes-2 or hypertension) age and sex.

2. MATERIALS AND METHODS:

The current study evaluated the adropin hormone level in patients with heart disease and atherosclerosis in Mosul City in 2019 from 5 May to 10 December.

2.1 Patients and Methods

This study was performed with 130 adults, including 90 patients suffering from cardiac disease and atherosclerosis of both sexes (31 females, 59 males, ages ranging from 35 to 65). They were attending Al-Salam Teaching Hospital, Ibn Sina Teaching Hospital, and medical clinics for heart disease and atherosclerosis, which were licensed by the Ministry of Health in Mosul - Iraq. A total of 40 uninfected adults were considered a control group of both sexes (18 females, 22 males aged 35 to 55 years). Besides, the patient group was divided into two groups. The first was non-obese (BMI <30 kg/m²), and the second was obese (BMI > 30 kg/m²). Moreover, the patient group was also divided into three groups. The first of which the patients had no other disease (n = 33, 14 females, 19 males, 35 to 52 years of age); The second patients had diabetes-2 (n = 30, 12 females, 18 males, ages 48-65 years); And the third patients had hypertension (n = 27, 12 females, 15 males, aged 46-65 years). Excluded from the study were people who smoke and pregnant women, and those with other diseases such as kidney disease and cancer. The study protocol was reviewed by the ethics commission at Mosul University and the Nineveh Department of Health, and all subjects were informed written form of informed consent.

2.2 Sample Collection

Informed consent was obtained from all

participants. Five milliliters (5 ml) of venous blood were collected after overnight fasting; the serum obtained was kept under freezing -20°C (Hammodat and Mustafa, 2018) to analyze adropin lipid profile weekly.

2.3 Variables Assay

2.3.1 Serum adropin

It was measured using a commercial ELISA Kit (biosciences), an immunoassay for the quantitative in vitro diagnostic measurement of adropin in plasma, serum, and tissue. All serum samples were diluted 25 folds with diluting the sample. Also, the adropin level was expressed in terms of ng/ml.

2.3.2 Serum lipid profile

Lipid profiles, including high-density lipoprotein (HDL), low-density lipoprotein (LDL), and total cholesterol (TC), were measured by cobas c111 system that automatically calculated the level of each sample (Haritwal, Chourasia, and Ojha, 2015).

2.3.3 Body mass index (BMI)

BMI was estimated by dividing the weight (Kg) on height (m²) (Jacobsson *et al.*, 2009).

2.3. Statistical Analysis

The results were carried out using the statistical program package for social sciences (SPSS), version 25.0. The results were expressed as a mean ± SD (standard deviation). Correlation analysis is expressed by using Pearson's correlation coefficient. That p-value considers significant when it is less than 0.05 of a statistical significance (Beddo and Kreuter, 2004).

3. RESULTS AND DISCUSSION:

Adropin is a hormone peptide that plays an essential role in patients with cardiac disease and atherosclerosis. While research into the effects of adropin is still in the early stages. Nonetheless, our current awareness of the cardiovascular safety of adropin comes mainly from animal studies.

Table 1 shows the average age of patients was 52.7 ±11.1 years, and the average age of healthy people was 50.5 ±14.3 years. Moreover, a significant decrease (p<0.0001) in the level of adropin in cardiac and atherosclerosis patients is 4.3±1.5 ng/ml compared with serum controls

10.2±2.3 ng/ml. These results agree with (Celik *et al.*, 2013; Yu *et al.*, 2014; Zhang *et al.*, 2014). This result can be explained because of adropin is associated with nitric oxide synthase (eNOS). When eNOS level is full down in cardiac disease and atherosclerosis patients, the level of adropin also reduced (Li *et al.*, 2016; Lovren *et al.*, 2010). Kuloglu *et al.* had researched adropin variability and inducible expression of nitric oxide synthase (iNOS) in streptozotocin (STZ)-induced diabetic rats in the renal tissues. With the severity of diabetes, the intensities of adropin and iNOS immunoreactivities increase (Kuloglu and Aydin, 2014).

Patients with cardiac disease have a significant difference in lipid profile level (Table 1), where patients had a lower HDL level (40±8.4 mg/dl patients vs. 54.1 ±14.5 mg/dl control; $p<0.0001$), and higher level of LDL (111.7±34.6mg/dl patients vs. 82.9±25.4 mg/dl control; $p<0.0001$) and TC (195.6 ±57.3mg/dl patients vs. 155.8 ±43.4 mg/dl control; $p<0.0001$). And that's consistent with (Akçilar *et al.*, 2016; Cao *et al.*, 2019; Ghoshal *et al.*, 2018).

Moreover, various factors on the level of adropin, such as obesity, are affected by other diseases (diabetes-2 or hypertension), age, and sex (Table 2 and Figure 1). Serum adropin level significantly decreased ($p<0.0001$) in obese patients (3.4±0.7kg/m²) when compared to non-obese patients (5.4±1.2kg/m²); these results are in concordance with (Butler *et al.*, 2012; Ganesh-Kumar *et al.*, 2012; Sayın, Tokgöz, and Arslan, 2014). Lian *et al.*, 2016 showed that serum adropin level was not affected by obesity (Lian, Wu, Liu, Jiang, and Jiang, 2016). This may be because of adropin has a significant role in the regulation of fatty acid metabolism (Altamimi *et al.*, 2019; Cao *et al.*, 2019; Li *et al.*, 2016; Marczuk *et al.*, 2016).

Additionally, the adropin level decreased significantly ($p<0.0001$) in patients who were also affected with type 2 diabetes mellitus (DM-2) (3.2±0.8 ng/ml) when compared with patients who were non-affected with other diseases (5.7±1.5 ng/ml). These results were in agreement with (Kuloglu and Aydin, 2014). This may be because adropin has a significant role in regulating glucose metabolism (Altamimi *et al.*, 2019; Lin *et al.*, 2014; Marczuk *et al.*, 2016). Gao *et al.* (2015) showed that DM-2 affected adropin levels in mice (Gao *et al.*, 2015). Also, patients affected with hypertension had lower adropin levels (4.1±1.2 ng/ ml; $p<0.0001$) when compared with patients non-affected with other diseases (5.7±1.5 ng/ ml). This result agrees with (Chen, Ouyang, and Zhou, 2015) and may be due to the association of adropin with nitric oxide

synthase (eNOS) (Li *et al.*, 2016; Lovren *et al.*, 2010). Aydin *et al.*, 2015, revealed that adropin level effects on blood pressure by protective endothelial job (Aydin *et al.*, 2016), while Altincik *et al.*, 2015 showed no blood effects pressure on adropin level in obese children (Altincik and Sayın, 2015).

No significant difference was observed for sex ($p=0.7$) and age ($p=0.91$). The serum adropin in males and females was 4.9± 1.3 ng/ml, 4±1.2 ng/ml, respectively. These results are in concordance with (Butler *et al.*, 2012; Sayın *et al.*, 2014). Butler found that males have more adropin levels than females, but without significant differences (Butler *et al.*, 2012). Sex factors do not show a moral effect on the level of adropin. Moreover, serum adropin levels in age groups ≤45 years and ≥46 years, which were 4.7±1.4 ng/ml and 4±1.3 ng/ml respectively, had non-significant differences. These results are in concordance with (Butler *et al.*, 2012).

Table 3 and Figure 2 also showed that the level of serum adropin in patients is associated with a significant negative correlation with obesity ($r=-0.493$ ($p=0.0001$)), which means that obesity has a bad effect on the level of adropin and, therefore, negatively affects patients. These results are in concordance with (Ganesh-Kumar *et al.*, 2012). Besides, the adropin level in patients was associated with a significant positive correlation with HDL level ($r=0.395$, $p=0.0001$). In contrast, it was associated with a meaningful inverse relationship with both LDL ($r=-0.79$, $p=0.0001$) and TC ($r=-0.249$, $p=0.0001$). These results are in concordance with (Ghoshal *et al.*, 2018).

4. CONCLUSION:

Serum adropin levels in patients with cardiac disease and atherosclerosis significantly decreased. Also, adropin levels were affected by patients with obesity, type 2 diabetes mellitus, and hypertension. A lower adropin level could play a vital role in cardiac pathophysiology and atherosclerosis. Also, decreased adropin levels can be considered a risk factor for patients affected by cardiac disease and atherosclerosis, especially for patients affected by DM-2 or hypertension. Therefore, measurement and monitoring changes in serum adropin can be known as new disease diagnosis and progression assessment. Although research into the effects of adropin is still in its early stages, rising evidence has suggested that this hormone peptide plays a protective role in developing cardiovascular

diseases.

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Table 1. Clinical and biochemical characteristics of controls and patients with cardiac disease and atherosclerosis

Variables	Controls, n=40	Patients, n=90	p-value
Age (mean $\pm$ SD) years, (range, years)	50.5 $\pm$ 14.3, (35-55)	52.7 $\pm$ 11.1, (35-65)	0.4 (NS)
Sex (F:M)	18:22	31:59	-
Adropin (ng/ml)	10.2 $\pm$ 2.3	***4.3 $\pm$ 1.5	0.0001
BMI (kg/m ²)	28.7 $\pm$ 4.1	29.61 $\pm$ 3.6	0.41 (NS)
HDL (mg/ dl)	54.1 $\pm$ 14.5	***40 $\pm$ 8.4	0.0001
LDL (mg/dl)	82.9 $\pm$ 25.4	***111.7 $\pm$ 34.6	0.0001
TC mg/dl)	155.8 $\pm$ 43.4	***195.6 $\pm$ 57.3	0.0001
Smoking/ non-smoking	9/14	39/27	--
patients			
Total Patients, n=90	Patients without affected any disease, n=33 (36.4%)	Patients affected with diabetes mellitus, n=30 (33.3%)	Patients affected with hypertension, n=27 (30.3%)
Age (mean $\pm$ SD) years,(range, years)	52.7 $\pm$ 11.1, (35-55)	49.3 $\pm$ 11.1, (49-65)	65.2 $\pm$ 12.4, (48-63)
Sex (F:M)	14:19	12:18	12:15

SD: Stander deviation; M: Male; F: Female; **significant when p–value equal at 0.001; while, ***significant whn p-value equal to 0.0001

Table 2. The effect of obesity, affected by other diseases (diabetes-2, hypertension) age, sex, and smoking on the level of adropin in patients with cardiac disease and atherosclerosis.

Obesity factor						
Adropin (ng/ml)/Obesity	BMI 20-29, 27.4±7.3 (kg/m ²), n= 33			BMI ≥ 30, 35.6±9.2 (kg/m ²), n=57		p-value
	5.2±1.2			***3.4±0.7		0.0001
Patients affected with other disease						
Adropin (ng/ml)/patients affected with other diseases (diabetes mellitus-2 or hypertension)	Diabetes mellitus-2 (DM-2)			Hypertension(HT)		
	Without-DM-2, n=33	With-DM-2, n=30	p-value	Without-HT, n=33	With-HT, n=27	p-value
	5.7±1.5	***3.2± 0.8	0.0001	5.3±1.5	***4.1± 1.2	0.0001
Age factor						
Adropin (ng/ml)/Age	≤ 45 years, n=28			≥ 46 years, n= 62		p-value
	4.7±1.4			4±1.3		0.091
Sex factor						
Adrropin (ng/ml)/Sex	Male, n=59			Female, n=31		p-value
	4.9±1.3			4± 1.2		0.07

SD: Stander deviation; M: Male; F: Female; ng: Nano gram; kg: kilogram; m: miter; ml: milliliter; mg: milligram; dl: Deciliter; n: number; HDL: High density lipoprotein; LDL: Low density lipoprotein; TC: Total cholesterol; BMI: Body mass index; *** significant when the level of p- value equal to 0.0001; **significant when the p-value equal to 0.001; Diabetes mellitus-2 (DM-2); Hypertension(HT); BMI; Body mass index; kg: kilogram; n: number; m: miter.

Table 3. The relationship of adropin level with the studied variables of patients with cardiac disease and atherosclerosis

Variables	Adropin (ng/ml), r =, (p, Pearson correlation), n= 90
BMI (kg/m ²)	** -0.628, (0.0001)
HDL (mg/dl)	** 0.395, (0.0001)
LDL (mg/dl)	** -0.698 (0.0001)
TC (mg/dl)	* -0.249 (0.018)

ng: nano gram; kg: kilogram; m: miter; mg: milligram; dl: Deciliter; n: number; LDL: Low density lipoprotein; HDL: High density lipoprotein; TC: Total cholesterol; BMI: Body mass index; ** correlation is significant when the level of p-value equal to 0.001; * correlation is significant when the level of p-value equal to 0.05.

Figure 1. A comparison of serum adropin levels between healthy controls and patients; the effect of obesity factor and other diseases (diabetes-2, hypertension) age, sex, and smoking on the level of adropin in patients with heart disease and atherosclerosis

Figure 2. The relationship of serum adropin level and the variables studied for patients with cardiac disease and atherosclerosis. ng: Nano gram; ml: milliliter; kg: kilogram; m: meter; mg: milligram; dl: Deciliter; HDL: High density lipoprotein; LDL: Low density lipoprotein; TC: Total cholesterol; BMI: Body mass index.