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Using Chemerin and Inflammation Markers to Predict Coronary Artery Disease in Metabolic Syndrome Patients

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ABSTRACT: The systemic inflammation plays a role in both metabolic syndrome (MetS) and coronary artery disease (CAD). This study was undertaken to determine chemerin's role and inflammation indicators in the emergence of CAD in MetS patients. The study was conducted on 120 subjects (male and female), whose ages (35 to 65)years. The study subjects divided into three groups which are 45 MetS patients with CAD and 40 MetS patients without CAD, and 25 control, who underwent coronary angiography for the evaluation of CAD. The chemerin level, as well as the levels of inflammatory markers such as interleukin-6 (IL-6), high-sensitivity C-reactive protein (hs-CRP), leptin, and tumor necrosis factor-alpha (TNF-α), were measured by enzyme-linked immunosorbent assay (ELIZA). The results show that the concentrations of chemerin, TNF-α, leptin, and Il-6 were significantly elevated in MetS patients with CAD compared with control group. Triglycerides, cholesterol, and LDL-C were significantly increased, while HDL-C was significantly decreased in MetS patients compared with control. The present study show that chemerin is associated with markers of inflammation and predictors such as IL-6, hs-CRP and TNF-alpha, which important risk factors determining CAD in Iraqi subjects with MetS. Adipokines might also be seen as crucial clinical biomarkers and pharmacological targets for lowering the mortality and incidence of CAD in MetS patients.

Keywords: Metabolic syndrome, Chemerin, Coronary Artery Disease, Leptin.

1. INTRODUCTION

Metabolic syndrome is a collection of metabolic abnormalities linked to cardiovascular risk factors, such as abdominal obesity, insulin resistance, high triglyceride levels, low HDL cholesterol levels, hypertension, and glucose intolerance. These abnormalities are associated with endothelial dysfunction and inflammation [1]. Initially, it was thought that genetics and external factors like diet, sedentary lifestyle, and alcohol use were the primary causes of these metabolic abnormalities. Low-grade systemic inflammation is one of the proposed mechanisms connecting MetS to cardiovascular

disease [2, 3]. Follow-up studies on MetS patients with CAD have shown increased risk of cardiovascular morbidity [4, 5]. The connection between CAD and metabolic syndrome lies in systemic inflammation, which involves evaluating pro-inflammatory markers (IL-6 and TNF-a) and adipocytokines (such as adiponectin, leptin, resistin, and chemerin) [6,7]. One possible pathogenic relationship between obesity and cardiovascular diseases is the disruption of adipokine secretion in obese individuals [8].

Among many inflammatory markers, TNF-a is a key cytokine that influences intermediary metabolism [9]. TNF-a treatment in animal models resulted in a serious reduction of insulin sensitivity and glucose tolerance. TNF-a could therefore be used as a therapeutic target for these diseases [10, 11]. The initial step in the development of atherosclerosis is characterized by impaired functioning of the endothelium [5, 12]. This process is triggered by the presence of TNFα, while chemerin, regulates various biological processes such as energy metabolism, the formation of fat cells, and the growth of new blood vessels [13]. There is a positive correlation between chemerin in the body and obesity-related conditions such as body mass index (BMI), and serum triglyceride levels, indicating its potential role in metabolic disorders [5, 11]. Consequently, it may serve as an independent adipocytokine marker of metabolic syndrome (MetS) [1, 7]. Additionally, because there was a positive link between the existence of CAD and chemerin levels, it has been proposed that chemerin levels define the severity of coronary lesions [14]. Aortic and coronary atherosclerosis positively associated with chemerin production in the perivascular tissue [15]. A recent study conducted in Iraq showed that chemerin levels were significantly higher in subjects with MetS compared to controls [16]. This study highlights the potential role of chemerin as a biomarker for the early detection and prediction of the development of coronary artery disease (CAD) in patients with MetS. It also underscores the importance of addressing low-grade inflammation in the management and prevention of cardiovascular disease in the MetS population.

2. MATERALS AND METHODS

2.1. Study design and participant recruitment

The Specimens collection was started from July 2022 till June 2023. The study consisted of 120 subjects (male and female) whose ages ranged from (35 to 61) years, who were divided into three groups, which were 35 control (19 males and 16 females) who had none of the criteria of MetS and no history of obesity, dyslipidemia, diabetes mellitus, and any infection at the time of sampling. 45 MetS patients with CAD (26 males and 19 females) and 40 MetS patients without CAD (23 males and 17 females), MetS patients attending Al Ramadi General Hospital. Who underwent coronary angiography for the evaluation of CAD. According to the National Cholesterol Education Program Adult Treatment Panel III (2002) (NCEP ATP III) recommendations, the metabolic syndrome was recognized [17]. Exclusion criteria included those with a history of recent infection, or other endocrinal. CAD was defined as subjects who had angiographic evidence of stenosis >50% in at least one major coronary artery. After an overnight fasting of 12 hours, venous blood samples were collected in plain tubes without anticoagulants. The serum was assigned to the fasting glucose and lipid profile rapid assay. Serum levels of chemerin, leptin, TNF-a, hsCRP and Il-6 were determined with commercially available ELISAs.

2.2 Blood analysis:

2.2.1. Glucose Levels: measured according to [18] method, which was provided with the kit from linear company/ Spain.

2.2.2. Total cholesterol (TC), Triglycerides (TG), and HDL-C (High density lipoprotein cholesterol): were measured by routine enzymatic colorimetric methods using spectrophotometer [19, 20, 21].

2.2.3. LDL-C (Low density lipoprotein cholesterol): It was calculated according to "Friedewald equation":

LDL-C = Total cholesterol - (HDL-C + TG/5). This equation was used if the serum TG level was less than 400 mg/dL[22].

2.2.4. Chemerin, Leptin, TNF- *α*, Hs-CRP and IL-6 levels were measured according to instructions of ELISA kits provided by the manufacturing company (Elabscience / U.S.A).

2.3 Statistical analysis:

The data are presented as means ± SD. Using one-way ANOVA after inserting data into SPSS version 25, biochemical parameters were examined among MetS patients with CAD, those without CAD, and control individuals. Categorical variables were analyzed by the Chi-square tests. The associations between serum chemerin levels and inflammation parameters were examined using Pearson's correlation test. A P-value < 0.05 was considered statistically significant.

2.4 Ethical Considerations:

Before the sample was obtained, each participant signed a document indicating their informed consent. A local ethics committee for medical and bioethics reviewed and gave its approval to the study protocol and subject information. Ref:91 on June 27, 2022.

3. RESULTS AND DISCUSSION

The results in **(Table 1)** show that no significant differences in age and gender among the three groups. While the BMI mean is higher significantly in MetS patients with CAD and MetS patients without CAD compared with control, but BMI mean showed no significant differences between MetS patients with CAD and those without CAD, at p <0.05.
The results in **(Table 2)** show that there was a significant difference between MetS patients and the control regarding FBS was higher in MetS patients with or without CAD than in the control. Serum triglycerides (TG), serum total cholesterol (TC), and LDL-C were significantly increased in MetS patients without CAD, followed by MetS patients with CAD compared with control. While HDL-C was significantly decreased in MetS patients compared with control. The results in (table 2) indicated that the levels of serum chemerin, TNF-a, leptin, and Il-6 were significantly increase in MetS patients with CAD compared with MetS patients without CAD and controls. While MetS patients without CAD showed higher concentrations of chemerin, TNF, leptin, and Il-6 than did the control group. MetS patients without CAD showed a significantly elevated hs-CRP, compared with control and MetS patients with CAD.
The investigation between chemerin level and other inflammatory indicators in **(Table 3)**. There was a strong positive association found between serum chemerin and TNF-a in IL-6, and hs-CRP in the MetS patients without CAD group at ($p<0.01$) and in the MetS patients with CAD group at ($p<0.05$). Moreover, there was a non-correlation between serum chemerin levels and leptin in both groups.

Table 1: Baseline characteristics of the MetS Patients and Controls.

	Control	MetS patients		P value
		without CAD	With CAD	
N.	35	40	45	
Age	53.22 ± 8.19	56.1 ±3.2	57.3±4.1	NS
Sex (M/F)	19/16	23/17	26/19	NS
BMI	22.11 ± 2.35^{b}	26.32 ± 3.42^{a}	28.12 ± 5.15^{a}	0.03

*(a, b) means significant difference at P ≤0.05. *NS: non-significant differences at P ≤0.05.

Table 2: Shows Biochemical and inflammation Parameters of MetS Patients and Controls.

groups	Control	MetS patients		P-value		
		without CAD	With CAD	P1	P2	P3
N.	35	40	45			
FBS (mg/dL)	76.30 ±4.22^{a}	117.00 ±4.69^{b}	120.2±2.5^{b}	<.05	<.05	NS
TC (mg/dL)	181.65 ±11.20^{a}	229.55± 15.14^{b}	216.3±12.5^{bc}	<.05	<.05	NS
TG (mg/dL)	110.30 ±5.16^{a}	186.00± 4.83^{b}	181.6±5.3^{bc}	<.05	<.05	NS
LDL-C (mg/dL)	106.82 ±12.17^{a}	161.85± 15.52^{b}	155.3±14.1^{bc}	<.05	<.05	NS
HDL-C (mg/dL)	52.75± 3.88^{a}	30.50 2.06^{b}	31.2 ± 0.19^{b}	<.05	<.05	NS
Chemrin (µg/L)	92.27 ± 26.60^{a}	116.52± 34.24^{b}	138.08± 31.30^{c}	<.05	<.05	<.05
TNF-a (pg/L)	2.77± .41^{a}	4.51± 1.06^{b}	6.21±0.51^{c}	<.05	<.05	<.05
Leptin (ng/ml)	4.03± .72^{a}	20.25 ±4.15^{b}	25.6±4.35^{c}	<.05	<.05	<.05
IL-6 (ng/ml)	1.26± .25^{a}	2.03± .42^{b}	3.12±6.3^{c}	<.05	<.05	<.05
Hs-CRP(mg/L)	1.76 ± 0.44^{a}	2.60 ± 0.58^{b}	0.30 ± 0.66^{c}	<.05	<.05	<.05

*(a, b, c) means significant difference at P ≤0.05. *NS: non-significant differences at P ≤0.05.

P1: p value between control and MetS patients without CAD.
P2: p value between control and MetS patients with CAD.
P3: p value between MetS without CAD and those with CAD.

Table 3: Correlation between chemerin and other inflammation Parameters in Mets without CAD and Mets with CAD.

Parameters		Chemrin levels in MetS without CAD	P- Pearson correlation coefficient	Chemrin levels in MetS with CAD	P- Pearson correlation coefficient
TNF-a	**R^2**	0.750[b]	0.01	0.875[a]	0.05
Leptin	**R^2**	-0.116	-	-0.260	-
IL-6	**R^2**	0.526[b]	0.01	0.735[a]	0.05
Hs-CRP	**R^2**	0.382[b]	0.01	0.421[a]	0.05

The results in **(Table 1)** agree with those obtained by Ali and Al Hadidi, [8] and Dong, *et al*.; [23], who indicated that there were no significant differences in age and gender between MetS patients and controls. The results of this study agree with study by Niklowitz *et al*., [24] who found that the mean BMI was significantly higher in MetS patients compared with controls, but this study disagrees with our results when researchers indicated that the mean age (11.6±2). Also, our results agree with results by Lachine *et al*., [25] who found a significant difference between diabetic patients with CAD and control groups regarding BMI.

Regarding gender and age, research studies have shown that there may not be significant differences in the prevalence of MetS between men and women or between different age groups [6, 8]. This could be due to several factors such as lifestyle choices, genetics, and environmental factors that can affect both men and women equally [23]. Therefore, it's crucial to maintain a healthy lifestyle by eating a balanced diet, engaging in regular physical activity, and avoiding smoking, to reduce the risk of developing MetS and related health complications. This suggests that MetS affects both genders and all age groups equally, and highlights the need for early screening and management of MetS in individuals at risk, regardless of age or gender [8, 25]. Despite the fact that women were more likely to be obese and to engage in less physical exercise, an Egyptian investigation found no significant difference in the prevalence of MetS across genders [25]. Age may not be a significant risk factor for MetS, according to a previous Chinese study that reported similar prevalence of MetS condition in all age groups [1]. Research has demonstrated that, even after adjusting for age, sex, and other potential confounders, people with MetS typically have a higher BMI than people without MetS. This is most probable because abdominal obesity, a major factor in MetS, is highly correlated with greater BMI. BMI is frequently used to evaluate an individual's overweight and obesity [8, 23]. Furthermore, a further characteristic of MetS that might result in weight gain and an elevated BMI is insulin resistance. It is crucial to remember that BMI has some limitations and is not a perfect indicator of body fat. For example, it does not account for variations in muscle mass or body composition. However, a higher BMI in MetS patients compared to control is likely due to the presence of metabolic abnormalities that contribute to weight gain and obesity [8, 25].

The results in **(Tables 2 and 3)** are similar to results by Ali and Al Hadidi, [8] who recorded that FBS, TG, Cholesterol, LDL, TNF-a, chemerin, IL6, and leptin were significantly higher in metabolic patients when compared to type 2 diabetes mellitus group and control, and who found that significant positive correlation between chemerin levels and each of IL-6 and TNF-a. Also similar to many studies Lachine *et al*., [25], Kammerer, *et al*., [26], and Zhang *et al*., [27], found the levels of chemerin, TNF-a, leptin, and Il-6 were significantly increased in MetS patients with CAD compared with MetS patients without CAD and controls. Dong and Zhang [1] mentioned that the MetS group showed higher levels of serum CRP and TG, as well as lowered HDL-c levels than did the control. These results are dissimilar with Osman *et al*., [28] who discovered that the metabolic syndrome group had a significantly lower CAD-risk percentage when compared to controls. According to Isomaa *et al*., [29], MetS is increasingly acknowledged as a significant risk factor for general population mortality and cardiovascular disease. For preventative efforts, it's critical to anticipate CAD risk early in people with MetS [25]. For patients with cardiovascular disease, serum biomarkers are crucial tools for prognosis, risk stratification, diagnosis, and making of therapeutic decision [30]. Serum biomarkers that have been linked to MetS and CAD are chemerin, TNF, leptin, and IL-6 which are significantly elevated in patients with MetS and CAD compared to those without CAD and controls, this indicates that there is increased inflammation and metabolic dysregulation in these individuals, which may contribute to the development and progression of CAD in patients with MetS. Therefore, the reason for the elevated levels of these inflammatory markers in MetS patients with CAD is due to the underlying atherosclerosis, which is the underlying cause of CVD. These results emphasize how crucial it is to recognize and keep an eye on these inflammatory markers as possible targets for the management and prevention of CVD in individuals with

MetS [8, 30, 31]. Dyslipidemia, or high serum triglyceride, cholesterol, and LDL-C levels along with low HDL-C levels, is one of the characteristics of MetS. It is unclear exactly why there is an increase in TG, TC, and LDL-C in MetS patients with CAD, as opposed to MetS patients without CAD [8]. Nonetheless, insulin resistance a defining feature of Metabolic Syndrome is thought to be important. Adipose tissue produces more free fatty acids as a result of insulin resistance, which in turn stimulates the liver to create more TG and TC [1]. Additionally, insulin resistance impairs the clearance of TG-rich lipoproteins, leading to an accumulation of TG and LDL-C in the bloodstream [5]. Other factors that may contribute to dyslipidemia in MetS patients include inflammation, oxidative stress by impairing the function of lipoprotein receptors in the liver, and genetic factors. Inflammatory cytokines such as IL-6 and TNF-alpha have been shown to increase the production of TG and LDL-C in the liver [8, 24]. Studies conducted on Iraqi subjects with metabolic syndrome have also indicated a potential link between chemerin levels and the risk of CAD [8]. These findings provide crucial evidence to support chemerin's additive role that of traditional risk factors in the determination of cardiovascular risk and the establishment of primary prevention measures for CAD [1]. Previous research has indicated a substantial correlation between high serum chemerin levels and inflammatory markers such TNF-a, IL-6, and high sensitivity CRP [8]. Raised hs-CRP concentrations in MetS patients may indicate that inflammation plays a role in early atherosclerosis processes because hs-CRP is thought to be a sensitive marker of inflammation [25]. CRP concentrations predict cardiovascular risk associated with both primary and secondary prevention of CAD [1, 30].

In the past, TNFα was identified as the initial adipokine that potentially connects obesity, and inflammation [4]. When present in endothelial cells, TNFα stimulates the activation of genes that promote inflammation, blood coagulation, and cell proliferation [32]. The impairment of endothelial function is the primary step in the development of atherosclerosis [8], and TNFα's role in inducing this state partially explains why obese patients experience a higher incidence of atherosclerosis-related events. In experimental models, inhibiting the signaling pathways triggered by TNFα, which facilitates LDL transcytosis, effectively reduced atherosclerosis [30, 35]. These findings underscore the potential of strategies aimed at modulating the inflammatory actions induced by TNFα as promising therapeutic approaches for treating atherosclerosis [4]. The role of IL-6 in CAD disease is complex. IL-6 can have both pro- and anti-inflammatory effects, depending on the balance between classic and trans-signaling cascades [24, 32]. IL-6 trans-signaling leads to the upregulation of adhesion molecules and the regulation of lymphocyte trafficking in endothelial cells, these promoting a proatherogenic phenotype [23]. IL-6 also stimulates the production of matrix metalloproteinases, contributing to plaque vulnerability/rupture and arterial remodeling [4, 8]. While tocilizumab, an IL-6 inhibitor, has shown improvement in endothelial function and reduced arterial stiffness [25]. Therefore, anti-IL-6 therapies are considered a double-edged sword in atherosclerosis management [25, 31]. Monitoring chemerin levels and inflammatory markers may help identify individuals at increased risk for coronary artery disease in Iraqi subjects with metabolic syndrome.

4. CONCLUSION

The present study confirmed that chemerin, IL-6, hs-CRP, and TNF-alpha levels are significantly elevated in individuals with metabolic syndrome and have a close correlation with different metabolic risk factors. It has been demonstrated that chemerin is linked to indicators of inflammation and predictors that play a significant role in determining coronary artery disease in metabolic syndrome patient. This chemerin impact introduces a new chapter in cardiovascular disease prevention.

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