

In individuals with unstable angina, insulin resistance has multiple connecting arms

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Abstract

Introduction: Insulin resistance (IR) and unstable angina (UA) are two global public health threats. When UA patients have comorbid IR, they would suffer from serious complications, including atherosclerosis and dysregulation of some important pathways.

Aim of the research: The present study used biomarkers of multiple pathways for the detection of IR in UA patients.

Material and methods: We examined biomarkers of lipid profile, IR, endogenous opioids (β-endorphin (βEP) and μ-opioid receptor (MOR)) and vitamin D₃ in patients with IR (UA + IR) (*n* = 35), without IR (UA-IR) (*n* = 41), and healthy controls (*n* = 45).

Results: The triglycerides (TG), total cholesterol, very low-density lipoprotein cholesterol, HOMA index of β-cell function percentage (HOMA2%B), HOMA index of sensitivity (HOMA2%S), and Homeostatic Model Assessment of Insulin Resistance Index (HOMA2IR) were significantly different between the three diagnostic groups. There was a significant increase in uric acid, blood urea, creatinine, low-density lipoprotein cholesterol, κ-opioid receptor (KOR), endomorphin 2 (EM2), Castelli's Risk Index I (CRI-I), Castelli's Risk Index II (CRI-II), AG, Atherogenic Index of Plasma (AIP), interleukin (IL) 6 (IL-6), IL-10, IL-10/IL-6 ratio, βEP, MOR, and fasting blood sugar. Toll-like receptor 4 (TLR4) is higher in patient groups than controls, while there is a significant decrease in estimated glomerular filtration rate (eGFR), vitamin D (VD), βEP/MOR, and high-density lipoprotein cholesterol in both patient groups compared with the control group.

Conclusions: The presence of IR state in UA patients is associated with various changes in serum biomarkers of some systemic arms.

Introduction

Unstable angina (UA) is a common form of acute coronary syndrome (ACS), which is a disorder that affects a large portion of the population and continues to be the primary cause of mortality globally [1]. It is characterized by reduced blood flow to the cardiac muscle during periods of rest or moderate physical exercise, without causing immediate damage or death to the heart muscle cells [2]. The primary factors leading to the development of ACS, UA, and acute myocardial infarction (MI), include atherosclerosis (ATS) and thrombosis [3]. Insulin resistance (IR) and cardiovascular disease (CVD) are two global public health threats, in a cause-effect relationship [4].

The opioid receptors μ (MOR), kappa (κ) (KOR), and delta (δ) (DOR) are activated by endogenous opioids [5]. Immune activation, the endogenous opioid system, antioxidants, trace elements, and macrominerals all have an impact on increased UA, atherogenicity (the tendency to promote the formation of fatty deposits in arteries), and IR [6].

The theory that inflammation plays a role in the development of ATS is supported by the observation of elevated levels of inflammatory markers in the blood of patients with coronary artery disease. Coronary artery disease (CAD) patients had substantially higher plasma interleukin (IL) 6 (IL-6) levels [7]. Moreover, it was discovered that increased concentrations of IL-6 in the bloodstream have a significant ability to predict the occurrence of acute coronary syndromes [8]. IL-10 is a powerful anti-inflammatory protein. It helps form and break atherosclerotic plaques. An increased risk of early or severe CAD is linked to the IL-10–1082G/A polymorphism [9].

Deficiency of vitamin D (VD) is believed to contribute to the prognosis of CVD [10]. Coronary ATS was shown to be more prevalent in patients with multivessel effects who had low VD levels [11]. Toll-like receptor 4 (TLR4) is a transmembrane protein that possesses the capacity to identify several internal ligands and is correlated with IR due to the significant correlation observed of TLR4 expression with obesity

[12], and IR [13]. TLR4 also has a role in the progression of atherosclerotic CVD [14].

Aim of the research

This study aims to distinguish between UA patients with and without IR by using of endogenous opioid system (EOS), lipid profile, atherogenic indices, proinflammatory and anti-inflammatory markers, TLR4, and IR characteristics.

Material and methods

Participants

The current study included 76 patients diagnosed with UA, divided into two groups: 35 patients with IR (UA + IR) and 41 patients without IR (UA-IR). The participants were recruited at the Sadr-Teaching Hospital-Najaf City, Iraq, from November 2021 to January 2022. The identification of patients with UA was conducted according to medical history, physical examination, Doppler sonography, electrocardiogram, echocardiography, and blood pressure [15]. All patients had coronary angiography within the first 24–48 h of hospitalization to detect lesions that may require

treatment. Fourteen patients underwent the stenting procedure, while nineteen patients underwent a coronary artery bypass grafting. We recruited 45 healthy individuals who have similar age and sex characteristics as the patient groups. The sample size calculation was performed with G*Power 3.1.9.4. All subjects in the study provided written informed consent.

Methods

Ten milliliters of venous blood were obtained from patients and controls at 8–10 a.m. after overnight fasting. After coagulation and centrifugation, sera were stored at a temperature of -80°C until analysis. The spectrophotometric methods, using kits supplied by Biolabo® (France), were used to assess the levels of total cholesterol (TC), triglycerides (TG), glucose, albumin, urea, and creatinine. Serum IL-6, IL-10, TLR4, and insulin were measured using commercial ELISA kits from Melsin® (China). MOR and β -endorphin (β EP) were measured using a kit from MyBioSource® (USA). The Homeostasis Model Assessment 2 (HOMA2) calculator® was used to calculate insulin sensitivity (HOMA2%S), β -cell function percentage (HOMA2%B), and insulin resistance

Table 1. Socio-demographic and clinical biomarkers data in healthy controls (HC), and patients with insulin resistance (UA + IR) and patients without insulin resistance (UA-IR)

Parameter	ControlA N = 45	UA-IRB N = 41	UA + IRC N = 35	F/ χ^2	P-value
Age	49.76 $\pm$ 4.24	48.49 $\pm$ 6.33	49.23 $\pm$ 6.17	0.553	0.577
BMI	26.42 $\pm$ 3.08	27.65 $\pm$ 4.57	27.14 $\pm$ 5.07	0.905	0.407
Sex (M/F)	16/29	15/26	17/18	1.64	0.440
Hypertension (N/Y)	45/0	19/22	23/12	31.507	< 0.001
TUD (N/Y)	36/9	28/13	26/19	1.543	0.462
Canadian stages III/IV	–	27/14	19/15	0.779	0.377
SBP [mm Hg]	120 $\pm$ 1.35 B,C	132.93 $\pm$ 13.59A	134.14 $\pm$ 42.21A	12.701	< 0.001
DBP [mm Hg]	79.98 $\pm$ 1.44 B	84.63 $\pm$ 7.08A	82.57 $\pm$ 8.27	6.257	0.003
Trimetazidine (N/Y)	–	19/22	16/19	0.003	0.956
Isosorbide (N/Y)	–	22/19	14/21	1.413	0.235
Clopidogrel (N/Y)	–	12/29	15/20	1.522	0.217
Bisoprolol (N/Y)	–	23/18	25/10	1.907	0.167
Atenolol (N/Y)	–	29/12	24/11	0.042	0.838
Aspirin (N/Y)	–	0/41	1/34	1.187	0.276
Atorvastatin (N/Y)	–	22/19	14/21	1.413	0.235

Results are shown as mean (SD). ^{A,B,C}comparisons between group means (significant at $p = 0.05$). TUD – tobacco use disorder, DBP – diastolic blood pressure, SBP – systolic blood pressure.

Table 2. Measurements of the biomarkers in healthy controls (HC), and patients with insulin resistance (UA + IR) and patients without insulin resistance (UA-IR)

Biomarkers	Control ^A N = 45	UA-IR ^B N = 41	UA + IR ^C N = 35	F/ χ^2	P-value
Uric acid [mg/dl]	4.46 ±1.16 ^{B,C}	5.90 ±1.14 ^A	5.59 ±1.00 ^A	20.048	< 0.001
Urea [mg/dl]	32.27 ±4.91 ^{B,C}	37.24 ±9.58 ^A	37.03 ±9.94 ^A	4.909	0.009
Creatinine [mg/dl]	0.74 ±0.15 ^{B,C}	0.91 ±0.17 ^A	0.91 ±0.18 ^A	15.006	< 0.001
eGFR [ml/min]	97.26 ±21.95 ^{B,C}	97.26 ±21.95 ^A	77.23 ±18.88 ^A	11.346	< 0.001
Total cholesterol [mM]	4.35 ±0.67 ^{B,C}	6.42 ±1.37 ^{A,C}	5.43 ±1.07 ^{A,B}	54.929	< 0.001
TG [mM]	1.9 ±0.38 ^{B,C}	3.76 ±1.14 ^{A,C}	3.15071 ^{A,B}	40.730	< 0.001
VLDLc [mM]	0.87 ±0.17 ^{B,C}	1.72 ±0.52 ^{A,C}	1.44 ±0.36 ^{A,B}	58.215	< 0.001
HDLc [mM]	1.14 ±0.17 ^{B,C}	1.00 ±0.18 ^A	0.92 ±0.21 ^A	58.215	< 0.001
LDLc [mM]	2.35 ±0.67 ^{B,C}	3.70 ±1.03 ^A	3.07 ±0.91 ^A	15.131	< 0.001
CRI-I	2.10 ±0.70 ^{B,C}	3.79 ±1.16 ^A	3.52 ±1.44 ^A	28.461	< 0.001
CRI-II	1.70 ±0.43 ^{B,C}	3.81 ±1.13 ^A	3.64 ±1.31 ^A	58.655	< 0.001
AC	3.88 ±0.78 ^{B,C}	6.53 ±1.44 ^A	6.18 ±1.80 ^A	47.856	< 0.001
AIP	0.22 ±0.12 ^{B,C}	0.56 ±0.13 ^A	0.53 ±0.16 ^A	89.337	< 0.001
FBS [mM]	5.48 ±0.39 ^{B,C}	6.29 ±0.61 ^A	6.28 ±1.48 ^A	11.428	< 0.001
Insulin [pM]	79.29 ±13.65 ^B	142.37 ±22.35 ^A	78.54 ±22.58	141.340	< 0.001
Log(Glu/Ins)	7.84 ±0.07 ^C	7.60 ±0.22 ^{A,C}	7.85 ±0.40 ^B	12.373	< 0.001
HOMA2%B	104.60 ±16.74 ^{B,C}	123.38 ±31.90 ^{A,C}	90.18 ±42.90 ^{A,B}	10.795	< 0.001
HOMA2%S	68.61 ±13.78 ^B	37.28 ±5.54 ^{A,C}	75.86 ±15.03 ^B	20.042	< 0.001
HOMA2IR	1.51 ±0.26 ^B	2.74 ±0.39 ^{A,C}	1.52 ±0.41 ^B	161.185	< 0.001
TLR4 [ng/ml]	4.60 (1.88–5.99) ^{B,C}	7.30 (5.25–12.21) ^A	6.15 (4.99–10.94) ^A	KWT	< 0001
VD [nM]	67.59 (54.15–78.15) ^{B,C}	56.39 (34.17–65.31) ^A	47.77 (33.67–62.31) ^A	KWT	0.005
IL-6 [pg/ml]	8.01 (5.30–9.42) ^{B,C}	8.00 (5.77–14.33) ^A	12.78 (6.73–17.28) ^A	KWT	0.045
IL-10 [pg/ml]	7.34 (5.44–8.42) ^{B,C}	18.69 (14.34–25.94) ^A	18.61 (13.95–25.87) ^A	KWT	< 0.001
IL-10/IL-6	0.82 (0.50–1.17) ^{B,C}	1.73 (1.00–3.21) ^A	1.62 (1.01–1.97) ^A	KWT	< 0.001
βEP [pg/ml]	19.75 (16.17–26.54) ^{B,C}	30.06 (21.20–44.97) ^A	26.96 (21.33–33.48) ^A	KWT	< 0.001
MOR [ng/ml]	4.49 (3.00–5.24) ^{B,C}	9.45 (5.11–11.53) ^A	7.56 (5.15–10.00) ^A	KWT	< 0.001
EM2 [pg/ml]	320.28 (193.12–602.51) ^{B,C}	357.91 (220.95–824.58) ^A	497.03 (383.22–940.25) ^A	KWT	0.015
KOR [pg/ml]	5.66 (3.08–8.54) ^{B,C}	7.54 (6.06–8.95) ^A	7.54 (5.99–10.53) ^A	KWT	0.005

^{A,B,C}Pairwise comparisons between group means (significant at $p < 0.05$), CRI-I& II – Castelli's Risk Index (I & II), AIP – Atherogenic Index of Plasma, AC – atherogenic coefficient, FBS – fasting blood sugar, LDL – low-density lipoprotein, HDL – high-density lipoprotein, HOMA2IR – homeostatic model assessment of insulin resistance index, HOMA%S – HOMA index of sensitivity, HOMA%B – HOMA index of β-cell function percentage.

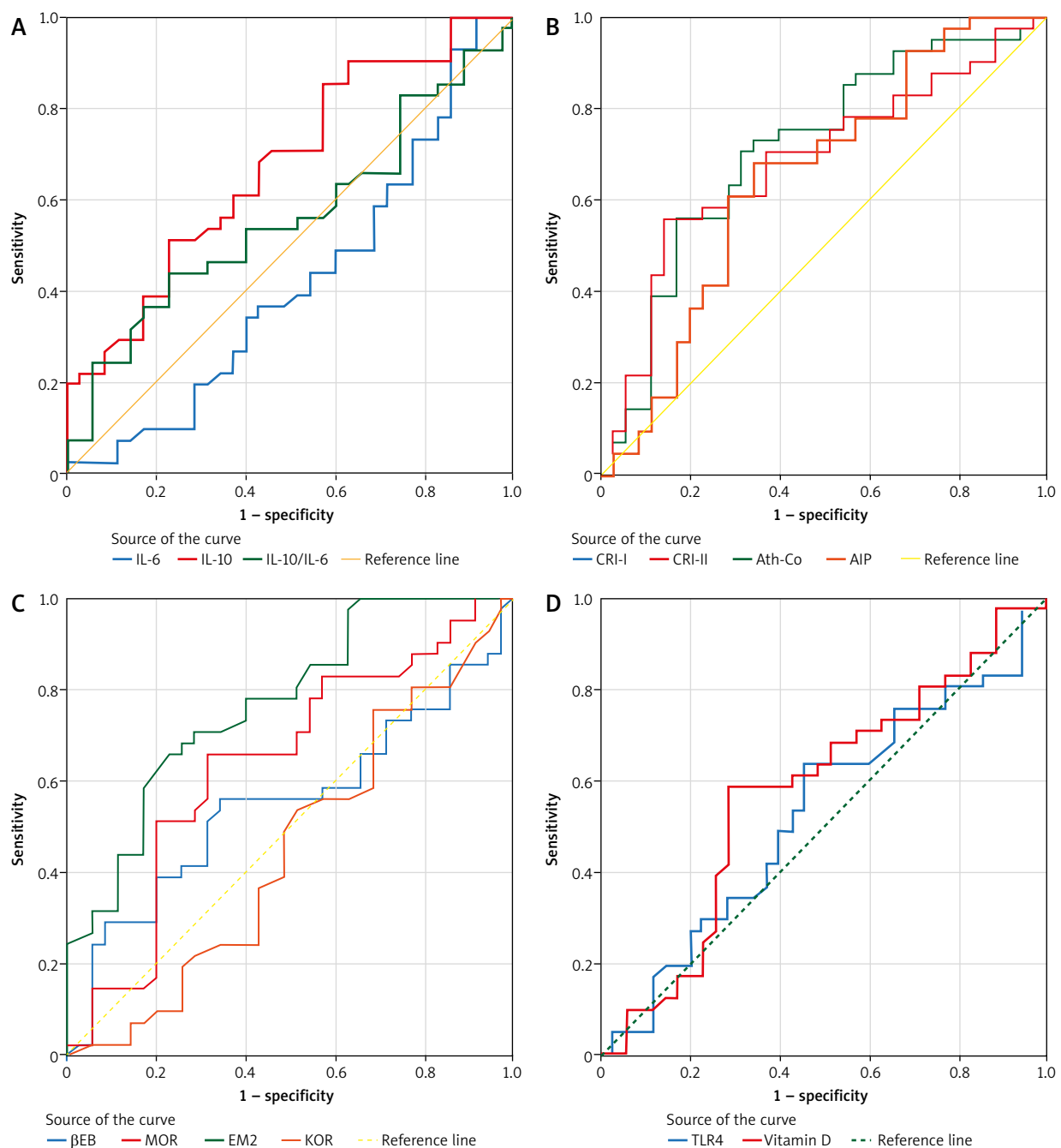


Figure 1. Receiver operating characteristic curves for differentiating between patients with and patients without insulin resistance. **A** – Pro- and anti-inflammatory interleukins, **B** – atherogenic indices, **C** – endogenous opioids and their receptors, **D** – vitamin D and TL-4

(HOMA2IR) from the fasting serum insulin and glucose levels [16].

Biostatistical analysis

The normality of continuous data was evaluated using the Kolmogorov-Smirnov test. Continuous variables are represented by the mean value accom-

panied by the standard deviation. An analysis of variance (ANOVA) was used to examine the disparities in continuous variables across the study groups. The Mann-Whitney *U* test was employed to compare the measurement parameters between the control and patient groups. By calculating Spearman's correlation coefficients (ρ), we may approximate the level

Table 3. Receiver operating characteristic-area under curve (AUC) analysis of measured biomarkers for differentiating between patients with and patients without insulin resistance. Only the biomarkers that produce acceptable discrimination ($AUC > 0.6$, $p < 0.05$) are cited in the table

Variables	Cut off	Sensitivity %	Specificity %	Youden J statistic	AUC (95% CI)	P-value
EM2 [pg/ml]	535.535	0.707	0.714	0.421	0.770 (0.666–0.875)	< 0.001
CRI-I	6.457	0.683	0.686	0.369	0.711 (0.592–0.830)	0.002
AC	5.457	0.683	0.686	0.369	0.711 (0.592–0.830)	0.002
AIP	0.574	0.659	0.657	0.316	0.649 (0.521–0.776)	0.026
MOR [pg/ml]	8.476	0.659	0.657	0.316	0.639 (0.511–0.676)	0.038
Total cholesterol [mM]	5.769	0.634	0.629	0.263	0.675 (0.553–0.797)	0.009
IL-10 [pg/ml]	18.336	0.610	0.629	0.239	0.674 (0.554–0.795)	0.009
LDLc [mM]	3.337	0.610	0.629	0.239	0.652 (0.529–0.776)	0.023
CRI-II	3.756	0.610	0.629	0.239	0.684 (0.562–0.805)	0.006

of correlation between the parameters. ROC analysis was employed to evaluate the diagnostic efficacy of the identified biomarkers.

Results

Socio-demographic data

Table 1 shows that the UA + IR group had a notably greater prevalence of hypertension compared to the UA-IR group. The systolic blood pressure exhibited a statistically significant increase in patients with UA compared to the control group. Patients with UA-IR had markedly elevated diastolic blood pressure compared to the control group.

Comparison of biomarkers among groups

Table 2 shows the measurements of the biomarkers in the study groups, there was a significant increase in uric acid, blood urea, creatinine, low-density lipoprotein cholesterol (LDLc), KOR, endomorphin 2 (EM2), Castelli's Risk Index I (CRI-I), Castelli's Risk Index II (CRI-II), atherogenic coefficient (AC), Atherogenic Index of Plasma (AIP), IL-6, IL-10, IL-10/IL-6 ratio, β EP, MOR, fasting blood sugar (FBS), TLR4 in patients' groups compared to controls, while a significant decrease in estimated glomerular filtration rate (eGFR) in UA + IR and significant decrease in VD, β EP/MOR, high-density lipoprotein cholesterol (HDLc) in both patient groups. Furthermore, insulin was significantly increased in the UA + IR group compared to controls. The TG, TC, HOMA2%B, HOMA2%S, and HOMA2IR, were significantly different between the three groups.

ROC study

Figure 1 displays the ROC curves of the biomarkers utilized to distinguish across groups. Table 3 contains the coordinates and biomarkers, cut-off values, and all

ROC statistics. The results suggest that an increase in EM2 levels beyond the cut-off value of 535.535 pg/ml indicates that the participants may have a sensitivity of 70.7% and a specificity of 71.4%. The results reveal that an increase in CRI-I above the cut-off value of 6.457 suggests that the participants may have an underlying condition, with 68.3% sensitivity, and 68.6% specificity. Furthermore, the results reveal that AC, AIP, MOR, TC, IL-10, LDLc, and CRI-II were higher than the cut-off value (5.457, 8.476, 5.769 pg/ml, 5.769 mM, 18.336 pg/ml, 3.337 mM, 3.756 ng/ml, and 2054.953 ng/ml, respectively).

Discussion

The main findings of this study are the coexistence of high levels of uric acid, urea, atherogenicity, IR, IL-6, IL-10, MOR, and low VD in patients which can serve as external confirmation for the clinical diagnosis of UA-related conditions. Furthermore, the results reveal that UA also demonstrates additional attributes such as increased levels of β EP and creatinine, while concurrently decrease eGFR [17].

The second result of this research is that UA is affected by the following factors: IR, atherogenicity, immunological diseases, the body's natural opioid system abnormality, trace element imbalance, and low antioxidant levels [6]. A recent study provided evidence that β EP and substances that activate the MOR might be involved in the formation of ATS and contribute to the instability of plaque [18]. The authors provided evidence that β EP is associated with IR and endothelium dysfunction. β EPs are mostly produced and stored in the anterior pituitary gland from their precursor protein, pro-opiomelanocortin [5]. The consequences of T2DM on cardiovascular health have been carefully evaluated [19]. Overall, opioids reduce the effects of catecholamines on the heart. Opioid receptors are

activated during hypoxia and heart ischemia injury, reducing the severity of cardiac damage [20].

Currently, there is no existing data that establishes a connection between UA and any alterations in the stated trace elements and the EOS system [21].

The third major finding in the current study revealed reduced levels of serum VD levels in UA patients. These findings were found previously in patients admitted for ACS compared to those with stable coronary artery disease [22, 23]. Additionally, it has been shown that VD affects the processes of inflammation, and a lack of VD has consequences for the risk factors associated with cardiovascular disease [24]. Furthermore, the provision of VD supplements to persons suffering from ACSs [25], and CVD lowers markers of cardiac fibrosis [26]. Various observational studies have revealed a link between VD and HDLc concentration, however, the precise cause-and-effect relationship has not yet been established [27, 28]. The relatively low sample size is the study's main limitation, and it would be better to be repeated with a larger sample size.

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Ethical approval

The study obtained approval from the Institutional Review Board (IRB) of the University of Kufa (487/2019), in compliance with the Declaration of Helsinki.

Conflict of interest

The authors declare no conflict of interest.

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