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Study the correlation between plasma soluble corin and hypertention in ischemic heart disease in male patients

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Abstract

The Plasma soluble corin is a key transmembrane serine protease, its principal functions is the synthesis of mature atrial natriuretic peptide (ANP) and B-type natriuretic peptide (BNP), these proteins have important functions in maintaining salt–water balance, blood pressure and cardiac function.

Plasma soluble corin has been suggested to be associated with hypertension and obesity by cell and animal-based studies. However, the relationship remained unclear. In the present study, an attempt is carried out to estimate the level of plasma soluble corin in ischemic heart disease (IHD) patients and compare their levels with the healthy control group in addition to the study the correlation between plasma soluble corin and hypertention and body mass index in ischemic heart disease in male patients.

One hundred and thirty six patients male patients with ischemic heart diseases including stable angina (AS), unstable angina (UA) and myocardial infarction (MI) (aged 35->60 years) were involved in the present study during their admission to Al- Sader Teaching Hospital / Al- Najaf Al- Ashraf. Also patients groups were divided according to hypertention for the purpose of study the correlation between plasma soluble corin and this risk factor in ischemic heart disease. Body mass index, blood pressures and plasma soluble corin were determined in 176 participants aged above 35 years. Age matched forty healthy men were included as control group.

Results of the present study in general revealed that there was significant decrease ($P<0.05$) in plasma soluble corin in MI, UA and SA patients in comparing with healthy control group. The blood pressure (systolic and diastolic) revealed a significant negative correlation ($P<0.05$) with plasma soluble corin in all IHD patients groups. The body mass index showed a significant negative correlation ($P<0.05$) with plasma soluble corin in all IHD patients groups.

From the results of the study, we can conclude that the early detection of abnormal biochemical parameters include plasma soluble corin can limit complication and deterioration of hypertensive patients with ischemic heart disease. This finding suggests that corin may play a role in the pathology of hypertension and obesity.

***Keywords*:** plasma soluble corin; blood pressure; hypertension; body mass index.

Introduction: Ischemic heart diseases are a common name for a group of associated syndromes resulting from myocardial ischemia {an imbalance between cardiac blood perfusion and myocardial oxygen demand}. Though ischemia can result from diminished oxygen- carrying capacity (e.g., anemia, carbon monoxide poisoning), increased demand (e.g., increased heart rate or hypertension), or in the vast majority of cases, IHD is due to a decline in coronary blood flow caused by obstructive atherosclerotic disease. IHD is also often called coronary artery disease (CAD) [1].

Atherosclerosis is the main causes of coronary heart disease (CHD) [2], atherosclerosis is a gradual build up of fatty deposits in the walls of the coronary arteries [3].

At first formed as a consequence of damage to the inner lining of the artery (endothelium), these fatty deposits; known as plaques, cause the artery to narrow and obstruct the flow of blood to the heart [4]. Eventually, the artery may become so narrow that blood supply to the heart is inadequate and can lead to angina [3]. Also, if a fragment of the plaque breaks away from the endothelium it can result in the development of a clot, which blocks the artery and starves the heart of blood and oxygen, this is known as a myocardial infarction (MI) [3].

The cardiac Corin (proatrial natriuretic peptide convertase corin), is a key transmembrane serine protease, its primary function is the synthesis of mature atrial natriuretic peptide (ANP) and B-type natriuretic peptide (BNP), these proteins have important functions in maintaining salt–water balance, blood pressure, and cardiac function [5] [6]. The human corin gene, located on the short arm of chromosome 4 at p12-13, has 22 exons and spans >200 kb in length. Corin is greatly expressed in the heart, mainly in the ANP-expressing atrial cardiomyocytes and, to a lesser extent, in the BNP-expressing ventricles. It has been well-acknowledged that intracellular protein trafficking, transcriptional control, zymogen activation, cell surface targeting, and ectodomain shedding are essential mechanisms regulating corin expression and activity in the heart [7].

Recently, much evidence has confirmed that corin might serve as a potential prognostic factor in ischemic heart disease [8][9][10]. Peleg *et al*. (2013), indicated that patients with non–ST-segment elevation acute coronary syndrome had lower serum corin levels and corin could be a important biomarker for cardiovascular risk stratification and outcome prediction in patients with coronary disease.

The present study has been designed to evaluate and compare the levels of the plasma soluble corin in patients suffering from ischemic heart diseases and control healthy subjects, also to the study the correlation between plasma soluble corin and hypertention and body mass index in ischemic heart disease in male patients.

Materials and Methods

Patients: One hundred and thirty six patients were divided into three study groups**:** myocardial infarction patients group included 60 subjects aged 35-69 years, unstable angina patients group included 40 subjects aged 35-69 years and stable angina patients group included 36 subjects aged 35-69 years. The samples were collected from Al- Sader Teaching Hospital/Al- Najaf Al-Ashraf during the period from September, 2016 till February, 2017. Each patients group of the study was divided into subgroups according to the, hypertension and body mass index.

Control group consists of 40 healthy non smoker males with normal blood pressure and their age range is between (35-69) years old. Exclusion criteria included a history of infection, inflammation, cancer, diabetes mellitus, and congestive heart failure.

Blood (2 ml) samples were taken from the antecubital vein of the patients as well as control individuals. Blood was allowed to clot and serum was separated by centrifugation at 2500 rpm for 15 minutes. Serum was stored at -20 ºC until analyzed for study parameters.

The levels of Plasma soluble corin was determined by using enzyme-linked immunosorbent assay (ELIZA) method, according to procedure provide by the from Elabscience, China, Catalog No: E-EL-H0042 96T.

Blood pressure was measured by sphygmomanometer (SK-MINIATUR300B-Germany). Both systolic and diastolic blood pressure was recorded in mm Hg, the value of the last reading of the blood pressure was taken for each subject.

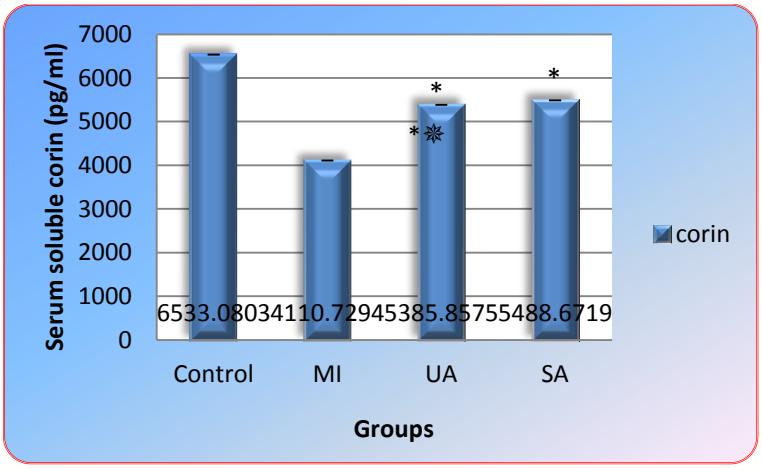
The anthropometric measure including the height (to the nearest centimeter) and weight (to the nearest kilogram). Then the body mass index (BMI) was calculated according to the following equation:

BMI= Weight (kg)/Height(m2)

Statistical Analysis: The results were expressed as (mean ± standard deviation). ANOVA test has been used for the comparison between the patients and control groups. Pearson's correlation coefficients (r) were calculated to estimate the correlation between parameters. All statistical analysis was performed using SPSS Statistics version 19.0.1 Multilingual program (2010), IBM-USA. While the figures constructed using EXELL program of Microsoft Office 2010.

Results:

Plasma soluble corin levels in the groups under study are plotted in fig. (1). The results showed a variation in plasma soluble corin concentrations among the different patients and control groups, the results revealed a significant (P< 0.05) decrease in concentration of plasma soluble corin in MI group (4110.729±331.718 pg/ml), UA group (5385.857± 198.693 pg/ml) and SA group (5488.671 ±101.753 pg/ml) as compared with control group (6533.080±211.309 pg/ml). On the other hand, there has been a significant (P< 0.05) difference in plasma soluble corin level in MI group as compared with other patients groups (UA and SA).



* denote a significant (p< 0.05) difference compared to control group.

❋denote a significant (p< 0.05) difference compared to other groups.

Figure (1): Serum soluble corin in MI, UA, SA patients and control group

The present study revealed a significant negative correlation (r= -0.599(**)), (p=0.000) between serum soluble corin and diastolic pressure in MI patients (fig. 2A).

Additionally, the results in the (fig. 2B) showed a significant negative correlation (r= -0.699(**)), (p= 0.000) between serum soluble corin and systolic pressure in MI patients.

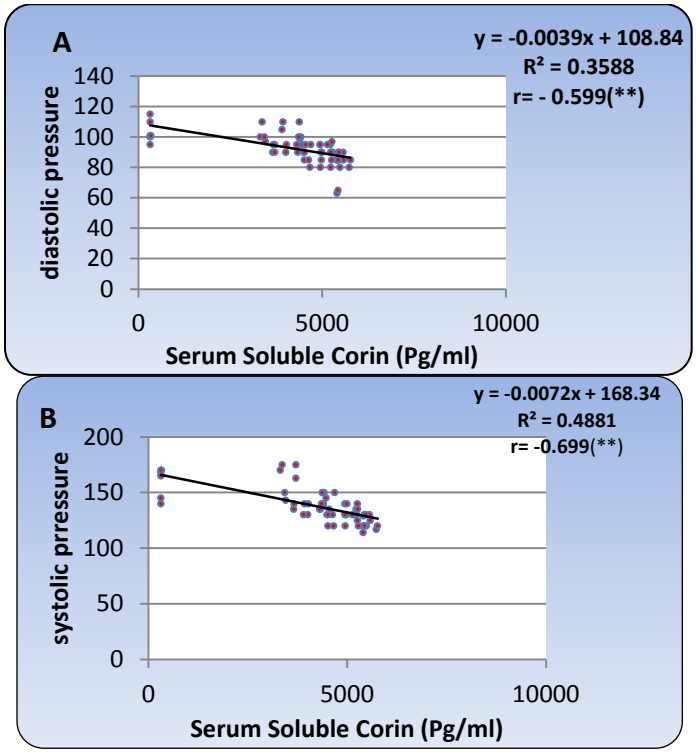


Figure (2): Correlation between serum soluble corin and blood pressure in MI patients. (A) diastolic pressure. (B) systolic pressure.

The present study indicated a significant negative correlation (r= -0.612(**)), (p= 0.000) between serum soluble corin and diastolic pressure in UA patients (fig. 3A).

Additionally, the results in the (fig. 3B) showed a significant negative correlation (r= -0.638(**)), (p= 0.018) between serum soluble corin and systolic pressure in UA patients.

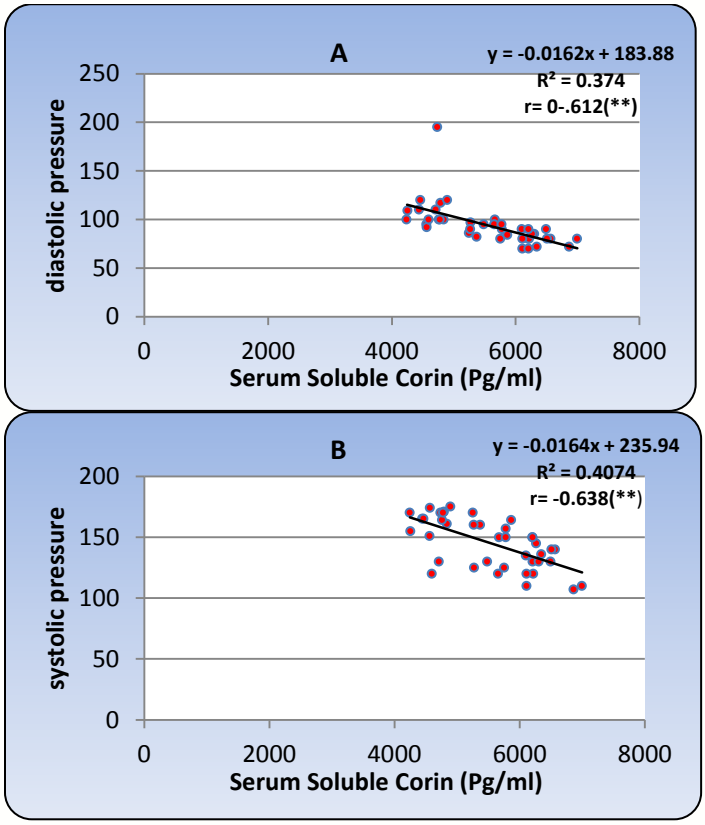


Figure (3): Correlation between serum soluble corin and blood pressure in UA patients. (A) diastolic pressure. (B) systolic pressure.

Data of the study showed a significant negative correlation (r= -0.670(**)), (p=0.000) between serum soluble corin and diastolic pressure in SA patients (fig. 4A).

Also, the results in the fig. (4B) showed a significant negative correlation (r= -0.410(*)), (p= 0.013) between serum soluble corin and systolic pressure in SA patients.

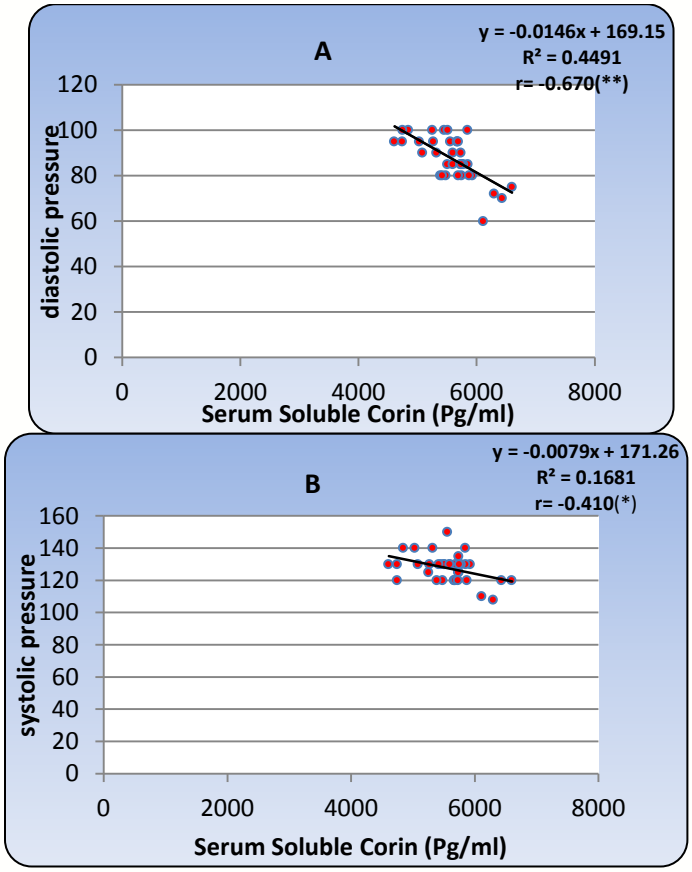


Figure (4): Correlation between serum soluble corin and blood pressure in SA patients. (A) diastolic pressure. (B) systolic pressure.

Results of study showed a significant negative correlation (r= -0.271(*)), (p= 0.036) between serum soluble corin and BMI in MI patients (fig. 5A). The results in the fig. (5B) showed a significant negative correlation (r= -0.760(**)),(p= 0.000) between serum soluble corin and BMI in UA patients. The results in the fig. (5C) showed a significant negative correlation (r= -0.399(*)), (p= 0.016) between serum soluble corin and BMI in UA patients.

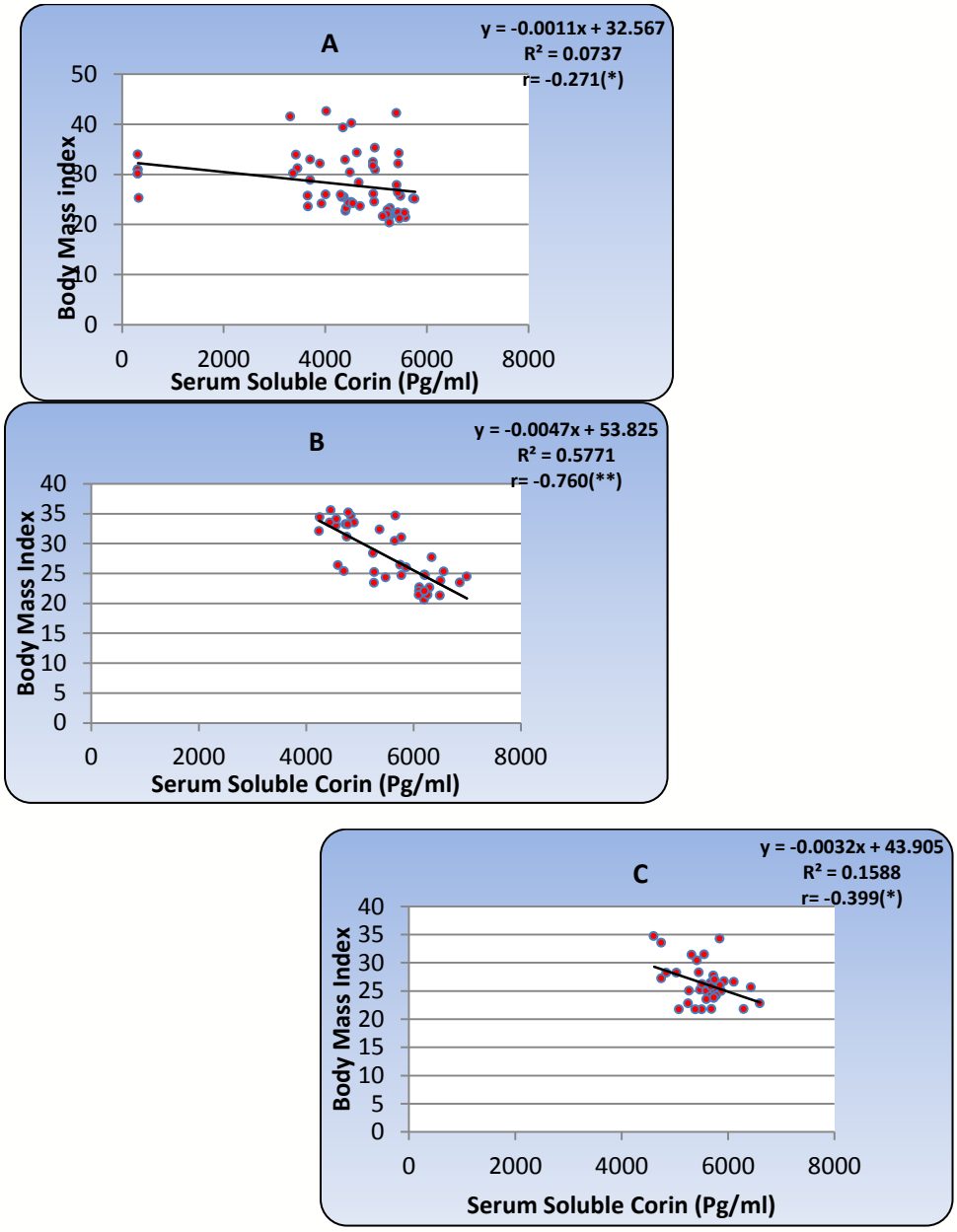


Figure (5): Correlation between serum soluble corin and body mass index in MI patients (A), UA patients (B), SA patients (C).

Discussion:

In this study, results showed a variation in serum soluble corin concentrations among the different patients and control groups, the results revealed a significant ($P< 0.05$) decrease in concentration of serum soluble corin in all patients groups as compared with healthy group and this results came in agreement with recent other studies [10][11][12] that have documented a relationship between lower serum soluble corin concentrations and increase cardiovascular disease risk.

The prospective study of [10] was revealed that serum corin was significantly decrease in patients with non- ST elevation myocardial infaraction (NSTEMI) acute coronary syndrome and could be a possible predictor for myocardial acute coronary events (MACE).

Study of [11] was generated corin-deficient mice and found that mice finally developed spontaneous hypertension and exhibited cardiac hypertrophy and dysfunction, suggesting that corin is vitally involved in the regulation of cardiac function and blood pressure.

Gladysheva *et al*. (2013) was generated a mouse model of dilated cardiomyopathy and found that the mice displayed increased myocardial fibrosis and impaired contractile function in the situation of low corin expression, whereas corin overexpression resulted in the improvement in cardiac structure and function. Pang *et al*. (2015) demonstrated that corin exerted cardioprotection by activating the ANP pathway in diabetic cardiomyopathy, and that down-regulation of corin led to endothelial dysfunction and vascular remodeling, as well as to experimental studies in animal models, clinical studies have investigated the importance of corin in cardiovascular diseases.

Dong *et al*. (2010) discovered that corin insufficiency might contribute to the pathogenesis of heart failure (HF) and that plasma corin could be used as a biomarker in the diagnosis of HF. Rame *et al.* (2009) discovered that the dysfunctional corin i555(p568) allele was associated with adverse outcomes and impaired BNP processing in blacks with systolic HF.

The present study revealed a significant negative correlation ($P< 0.05$) between serum soluble corin and blood pressure in all patients groups.

The main reason for these results was explained by the researchers who found that the ANP pathway is essential in regulating blood pressure. Many studies found that Knockout mice lacking ANP or NPR-A are hypertensive [14] [15]. Mice with corin deficiency are expected to have a similar hypertensive phenotype since corin is essential for pro-ANP activation. By using radiotelemetry, Chan *et al.* (2005) found that corin-null mice, which are viable and fertile, indeed were hypertensive. Together male and female corin-null mice had elevated systolic, diastolic, and mean arterial blood pressure as compared to that in wild-type controls. Blood pressure increased additional when the mice were fed a high-salt diet. John *et al*. 1995 was reported such a phenotype in ANP-null mice. The results are consistent with corin being the pro-ANP convertase and show the importance of corin in maintaining normal blood pressure in vivo.

Many studies [16 [17] [5] suggesting that defects in the ANP pathway may contribute to hypertensive disease, because of single nucleotide polymorphisms (SNPs) in the ANP gene promoter or a deletion in the NPR-A gene promoter are associated with patients with hypertension and cardiac hypertrophy .

Various epidemiological studies of large population-based cohorts, including the Chicago Genetics, the Multi-Ethnic Study of Atherosclerosis (MESA) and the Dallas Heart of Hypertension Study, have shown that the minor corin I555/P568 allele is more familiar in African Americans than in Caucasians (~12 vs <0.2% carrying one or more copies of the allele) and linked with an increased risk for hypertension [18][5].

Additionally, the I555/P568 corin minor allele was reported to be connected with an improved concentric cardiac hypertrophy in response to high systolic blood pressure in African Americans from the Dallas Heart and MESA cohorts [19]. Patients how have this corin allele had a greater left ventricular mass compared to that of healthy patients with a wild-type allele but similar systolic blood pressure. The result linking the corin gene variant to myocardial pathology in patients is fascinating [20].

Former animal researches have showed that the ANP pathway has a local anti-hypertrophy function in the heart, which is independent of its systemic action on blood pressure [21]. Constantly, Chan *et al*. (2005) revealed that corin-null mice developed cardiac hypertrophy. These results propose that corin deficiency may contribute to hypertension and heart failure in African Americans, a population known for its high occurrence of these cardiovascular diseases.

Wang *et al.* in 2008 [22] examined the effect of corin variant on blood pressure by using a transgenic mouse model that expressed the T555I/Q568P variant in a corin null background, in this transgenic mouse model, corin activity was significantly reduced, resulting in elevated levels of pro-ANP in the heart. The results confirmed that the corin variant is defective in vivo. Notably, the transgenic mice developed hypertension and cardiac hypertrophy, which were exacerbated upon high salt-diet challenge [23]. The hypertensive phenotype of the transgenic mice mimics the clinical features in the African Americans carrying the variant allele [18]. These data suggest that the corin variant allele, which is present in ~10–12 % of African Americans [18], may contribute to hypertension and heart disease in this high-risk population.

Zhou and Wu in 2014[24] has been used knockout (KO) mice to study the consequence of corin in controlling natriuretic peptide production and blood pressure, in this study the biochemical analysis revealed that heart tissues from corin KO mice were found to contain high levels of unprocessed pro-ANP, but no measurable amounts of mature ANP, reflecting a defect in pro-ANP processing [11]. Other studies indicated that intravenous injection of a soluble active corin into the KO mice restored pro-ANP processing and increased plasma cGMP levels [11], the results illustrate that corin is essential for pro-ANP processing and that its activity cannot be compensated by other proteases in vivo.

Results of study showed a significant negative correlation between serum soluble corin and BMI in MI, UA and SA patients.

The study of Peng *et al.* [25] indicated that the association between serum soluble corin and obesity in adults. Numerous studies point to that there is some factors that lead to dysregulation of the homeostasis mechanism of energy regulation. It is well-known that the melanocortin-mediated pathway plays an essential role in energy homeostasis [26].

Mayfield *et al.* [27] indicated that agouti and agouti-related protein (AGRP) inhibit the melanocortin-mediated pathway, thereby inducing obesity. Human corin, a type II transmembrane serine protease greatly expressed in the heart [28], was found to promote AGRP degradation by a cell-based study [29]. The study of Chan *et al.* (2005) revealed that an animal experiment found that knockout corin gene induced increased body weight in mice. These results indicated a possible role of corin in obesity, as results, soluble corin in the circulation may be used as a marker or potential risk factor for obesity, although the

mechanism of the production of corin in the circulation is unidentified. To investigate this hypothesis, the relationship between circulating soluble corin and obesity should be studied in humans. The association between obesity and plasma corin was unsuccessful to be observed in 126 patients with heart failure [30].

Animal and Cell based studies found that corin degraded agouti and agouti-related protein (AGRP) proteins [29]. Because AGRP proteins play an essential role in stimulating food intake, lack of or low levels of corin may lead to higher AGRP concentrations, thereby promoting more eating and causing obesity [26] [27] . These results propose a possible role of corin protein in obesity.

Lately, Jiang *et al.* [31] discussed that corin was shed from the cardiomyocyte surface by metalloproteinase-mediated hydrolysis and corin autocleavage. It appears that, shed corin molecules could enter the blood. Soluble corin in the circulation is detectable [7] and was found to have the same activity as the membranebound corin [32]. As a result, serum soluble corin is hypothesized to be lower in obese individuals and this result was inconsistent with our study which showed significant negative correlation between serum soluble corin and body weight in MI, UA and SA patients.

To assessment the theory of [25], he was conducted a cross-sectional study designed to investigate the association between serum soluble corin and prevalent obesity in 2498 adults in Suzhou, China. Unpredictably, Peng *et al.* (2015) did not find a occurrence of serum soluble corin reduction in obese individuals compared with nonobese individuals. Peng *et al.* (2015) results showed a raised level of serum soluble corin in overweight or obese or central obese individuals. In addition, serum soluble corin positively and considerably correlated to BMI and WC, and they was found that overweight or obesity and central obesity significantly increased with the increase in serum soluble corin. Consequently, these results did not provide population-based supportive evidence for the above hypothesis that serum soluble corin is decreased in obesity.

From the results of the study, we can conclude that the early detection of abnormal biochemical parameters include plasma soluble corin can limit complication and deterioration of hypertensive patients with ischemic heart disease. This finding suggests that corin may play a role in the pathology of hypertension and play a role in weight gain.

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