

## Association of Serum C-reactive Protein Levels with Gamma Glutamyl Transferase and Cardiometabolic Risk Factors in Middle Aged People

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### ABSTRACT

*C-reactive protein (CRP) is an inflammatory marker shown to predict future cardiovascular morbidity and mortality. The aim of the present study was to investigate the association of serum CRP level as a marker of chronic inflammation with gamma glutamyl transferase (GGT) as early marker of oxidative stress and their association with cardiometabolic risk factors among a diverse community sample of mid-life people, also to examine whether these relationships might vary by age, sex and body mass index. The investigation was based on data derived from 100 apparently healthy volunteers (male 40, female 60) aged 20-50 years, had a BMI between 24.2 and 37.7 kg/m<sup>2</sup>. Fasting serum CRP, GGT, uric acid and cardiovascular risk factors were measured and assessed in relation to CRP. Significant gender differences exist in the population distribution of CRP and GGT. In addition, higher BMI was significantly associated with higher CRP and uric acid. There was linear trend for increased prevalence of cardiovascular risk factors across CRP categories representing medium (1-<3mg/L) and high (3-10 mg/L). After adjustment for sex, age and body mass index, serum concentration of CRP was positively associated with serum concentration of GGT and Uric acid ( $P<0.05$ ). Body mass index and systolic blood pressure had the strongest association with CRP. The prevalence of metabolic syndrome (MS) progressively increased with elevated CRP levels. In conclusion, these data suggest that CRP is associated with two markers of oxidative stress, GGT and UA and elevation of both CRP and GGT may be worsening the atherogenic state. Furthermore, elevated CRP levels were associated with adverse lipid profiles and metabolic syndrome.*

**Key Words:** Metabolic syndrome, cardiovascular diseases, C-reactive protein, BMI.

### INTRODUCTION

C-reactive protein (CRP) is a cited marker of inflammatory status, shown to predict cardiovascular morbidity and mortality<sup>(1)</sup>. The CRP level is, also correlated with cardiovascular disease (CVD) risk factors in healthy men and women<sup>(2)</sup>.

Low-grade inflammation has, also been linked to the development of metabolic disorders regarding diabetes, hypertension and MS<sup>(3)</sup>. Furthermore, slightly elevated gamma glutamyl transferase (GGT) that is almost within the normal range is associated with all cause mortality<sup>(4)</sup>, and has emerged as an independent

predictor of CVD, which is increasingly viewed as an inflammatory disease<sup>(5)</sup>. These associations can be partly explained by the known correlation of GGT with cardiovascular risk factors such as obesity<sup>(6)</sup>, dyslipidemia<sup>(7)</sup> and MS<sup>(8)</sup>.

Serum GGT is, also an independent marker of oxidative stress<sup>(9)</sup> and increased GGT reflects increased oxidative stress<sup>(10)</sup>. Elevated GGT could, also reflect subclinical inflammation and several studies showed that serum GGT concentration predicted concentration of inflammation and oxidative stress markers, such as uric acid, CRP<sup>(11)</sup>.

Therefore, the present study was conducted to evaluate the association of elevated serum CRP with serum GGT and their relation to the atherogenic abnormalities. In addition, the association of CRP with the metabolic syndrome components and CVD in middle-aged Egyptian adults will be examined.

## MATERIALS & METHODS

The present study was based on data derived from 100 apparently healthy volunteers participating in Ain Shams University Hospitals: 40 men and 60 women, classified as either age 20-30 years,  $n = 60$ , mean  $\pm$  SD,  $23.8 \pm 2.2$  years and 31-50 years,  $n = 40$ , mean  $\pm$  SD,  $39.43 \pm 5.4$  years or CRP categories<sup>(12)</sup>; medium CRP 1-3 mg/L,  $n = 45$ ,  $2.16 \pm 1.6$  mg/L and high CRP 3-10 mg/L,  $n = 55$ ,  $4.09 \pm 1.9$  mg/L and further according to body mass index (BMI) (calculated as weight / height in  $m^2$ ): normal weight ( $18.5-24.9$  Kg/ $m^2$ ,  $n=10$ ), overweight ( $25-29.9$  Kg/ $m^2$ ,  $n= 65$ ), or obese ( $\geq 30$

Kg/ $m^2$ ,  $n=25$ )<sup>(13)</sup>. Waist circumference was obtained at the mid-point between the lowest rib and the iliac crest to the nearest 0.1 cm, after inhalation and exhalation. Blood pressure was measured using an electronic blood pressure monitor on the right arm of the participant in a comfortable sitting position after at least 5 min rest

Subjects were premenopausal, were not currently pregnant, and were not under medication that effected weight or body composition. Other exclusions included a reported history of atherosclerotic cardiovascular disease, subjects with diagnosed metabolic abnormalities and who were taking medications known to affect CRP levels. Data of participants having circulating CRP levels  $> 10$  mg /L (given extreme CRP values are usually not associated with cardiometabolic disorders) were not included in the study. All volunteers were informed about the research design and gave their written informed consent to participate in the study, which was approved by the ethical committee.

In the present study, metabolic syndrome (MS) was defined according to International Diabetes Federation (IDF) definition<sup>(14)</sup>. Subjects were considered to have the MS if they met at least three of the following: high waist circumference ( $\geq 80$ cm), raised blood pressure ( $\geq 130/85$  mm Hg), reduced HDL cholesterol ( $< 50$ mg/dl), raised triglycerides ( $\geq 150$ mg/dl), and raised fasting plasma glucose ( $\geq 100$  mg/dl) or previously diagnosed type 2 diabetes.

Ten ml fasting venous blood samples were taken. Two ml of the

sample were added to sodium fluoride containing tube, then centrifuged at 3000 rpm for 10 minutes at 40C and the separated plasma was used for blood glucose analysis. Another two ml of the sample were added to EDTA containing tube for measurement of blood HbA1c. Serum was obtained from the remaining blood by centrifugation & stored in aliquots at -80 °C until the time of assay of lipids and other analyses.

Glucose<sup>(15)</sup>, total cholesterol (TC) level<sup>(16)</sup>, triacylglycerol (TAG) level<sup>(17)</sup>, high-density lipoprotein cholesterol (HDL-C) level<sup>(18)</sup> and uric acid (UA) level<sup>(19)</sup> were measured using enzymatic methods. Low-density lipoprotein cholesterol (LDL-C) was calculated by the Friedwald formula<sup>(20)</sup>. Glycosylated hemoglobin (HbA1c) was determined in whole blood using chromatographic-Spectrophotometric methods<sup>(21)</sup>.

Enzyme activity for gamma glutamyl transferase (GGT) was measured using commercial reagent kit according to<sup>(22)</sup>. C-reactive protein (CRP) level was measured by (BioCheck high sensitivity CRP ELISA kit; Foster City). All samples were examined in duplicate, and the mean values of individual samples were used for statistical analysis.

#### Statistical Analysis:

Values were analyzed, as means  $\pm$  SD. Differences between groups were determined with student's t-test for independent samples and by one-way analysis of variance (ANOVA). The analyses were carried out using SPSS 11.0 for Windows statistical software (Chicago, IL, USA). Tests were considered statistically significant at  $p < 0.05$ . Correlation

between variables was calculated by Pearson's correlation coefficient "r". Receiver operating characteristic curve (ROC curve) was constructed to evaluate the sensitivity and specificity of the markers, and to determine the best cut-off value for each marker.

## RESULTS

The basic clinical characteristics of the male and female subjects are presented in table (1). The mean ages were  $24.5 \pm 3.89$  years for males and  $32.5 \pm 7.9$  years for females. Compared with men, women had higher systolic and diastolic blood pressure ( $P < 0.001$ ) and lower TC ( $P < 0.05$ ), while men had higher TG than women ( $P < 0.001$ ).

The median CRP values were 2.5 (interquartile range: 1-4) mg/L for males and four (interquartile range: 1-6) mg/L for females. The median GGT values were 12 (interquartile range: 11.6-12.75) IU/L for males and 15 (interquartile range: 13.2-16) IU/L for females. Serum UA concentration in male was significantly higher ( $P < 0.01$ ) than those in female, table (2). When the study subjects were further classified according to age and BMI, the highest concentrations of CRP, GGT and UA were found in aging and obese individuals, table (2).

Table (3) shows the associations between the two CRP categories and biological risk factors. The results demonstrate a linear trend for an increased prevalence of cardiovascular risk factors across the CRP categories.

Pearson's correlation analysis represented in table (4) revealed that,

serum CRP was negatively correlated with SBP ( $r=-0.37$ ), BMI ( $r=-0.33$ ) and positively correlated with the biomarkers of oxidative stress, GGT ( $r=0.56$ ) and UA ( $r=0.33$ ).

In separate analyses for men and women, the Pearson's correlation between CRP and BMI was significantly ( $P<0.05$ ) stronger in women ( $r=0.53$ ) than in men ( $r=0.41$ ), table (5).

We next compared study subjects based on the number of metabolic syndrome criteria which were present. As subjects with five components of MS were rare (8), they were combined with subjects displaying four criteria. Fig (1) displays the distribution of CRP levels according to presence of total number of components of the MS. As shown, there was a strong linear increase in CRP levels as the number of components of the MS increased; mean CRP levels for those

with 0, 1, 2, 3, 4 characteristics of the MS were 1.83, 2.2, 3.46, 4.33, and 5.6 mg/L, respectively ( $P < 0.001$ ).

The receiver operating characteristic curve (ROC) analysis was used to evaluate the sensitivity, specificity and the best cut-off values of CRP and GGT for early prediction of cardiometabolic risk in aging subjects (31-50 years). It was indicated that the GGT was the best test with an area under the curve (AUC) equal 0.85, the sensitivity was 87.5 % and specificity was 79.17 % at the cut-off value = 16 IU/L (95 % confidence interval, 0.702-0.943) as shown in fig (2). The next most useful test was CRP with AUC equal 0.78, the sensitivity was 87.5% and specificity was 66.67 % at the cut-off value= 3 mg/L (95 % confidence interval, 0.612 - 0.895) as shown in fig (3).

**Table (1):** Clinical characteristics of the male and female subjects (Mean  $\pm$  SD)

Characteristics	Total (n=100)	Male (n=40)	Female (n=60)
Age (years)	29.3 $\pm$ 7.6	24.5 $\pm$ 3.89	32.5 $\pm$ 7.9*
SBP (mmHg)	127.7 $\pm$ 13.9	120.4 $\pm$ 4.6	138 $\pm$ 16.4*
DBP(mmHg)	81.8 $\pm$ 10.7	77.08 $\pm$ 8.1	89 $\pm$ 10.3*
BMI (Kg/m <sup>2</sup> )	28.5 $\pm$ 4.5	27.4 $\pm$ 4.3	30.25 $\pm$ 4.5
WC (cm)	84.7 $\pm$ 14.03	85.04 $\pm$ 17.3	84.2 $\pm$ 7.14
TC (mg/dl)	138.6 $\pm$ 22.6	147.5 $\pm$ 36	125.3 $\pm$ 26**
LDL-c (mg/dl)	93.6 $\pm$ 35	89.4 $\pm$ 27.9	99.8 $\pm$ 62.3
HDL-c (mg/dl)	43.6 $\pm$ 5.5	43.4 $\pm$ 4.3	44 $\pm$ 9.8
TG (mg/dl)	126.5 $\pm$ 17	159.08 $\pm$ 2.03	77.8 $\pm$ 37.7*
Glucose (mg/dl)	111.8 $\pm$ 16.2	113.7 $\pm$ 6.8	109.09 $\pm$ 3.9
HbA1c (%)	7.25 $\pm$ 1.5	7.8 $\pm$ 3.05	6.4 $\pm$ 3.3

\* $P < 0.001$ , \*\* $P < 0.05$

**Table (2):** CRP, GGT and UA concentrations according to gender, aging, and BMI (Mean  $\pm$  SD)

Total	N	CRP (mg/L)	GGT (IU/L)	UA (mg/dl)
Gender				
Men	40	2.75 $\pm$ 1.98	12.4 $\pm$ 1.56	5.7 $\pm$ 0.8
Women	60	4.04 $\pm$ 2.2*	14.5 $\pm$ 2.01*	4.9 $\pm$ 0.64*
Aging				
20-30 years	60	2.41 $\pm$ 1.86	15.07 $\pm$ 4.2	5.04 $\pm$ 0.6
31-50 years	40	4.43 $\pm$ 1.6*	18.41 $\pm$ 2.1*	5.65 $\pm$ 0.48*
BMI(Kg/m <sup>2</sup> )				
Normal	10	1.7 $\pm$ 1.5	15.9 $\pm$ 3.5	4.4 $\pm$ 0.85
Overweight	65	2.69 $\pm$ 1.87	16.7 $\pm$ 3.9	5.2 $\pm$ 0.68†
Obese	25	4.7 $\pm$ 1.63††	18 $\pm$ 2.9	5.5 $\pm$ 0.39†

\**P* < 0.01.†*P* < 0.05, significantly different from normal BMI group.††*P* < 0.001; significantly different from normal and overweight BMI. groups**Table (3):** Association between CRP categories, GGT and biological risk factors (Mean  $\pm$ SD)

Variable	CRP category	
	Medium (n=45)	High (n=55)
GGT (IU/L)	13.53 $\pm$ 2.1	18.75 $\pm$ 3.4*
BMI (Kg/m <sup>2</sup> )	25.9 $\pm$ 1.2	30.6 $\pm$ 5.1*
WC (cm)	79.6 $\pm$ 9.3	88.8 $\pm$ 15.9**
HDL-c (mg/dl)	45.16 $\pm$ 2.7	43.2 $\pm$ 6.9
LDL-c (mg/dl)	90.4 $\pm$ 29	91.6 $\pm$ 40
TC (mg/dl)	138 $\pm$ 28	140.6 $\pm$ 17
SBP (mmHg)	120.5 $\pm$ 5.3	134.13 $\pm$ 15*
DBP (mmHg)	76.9 $\pm$ 10.4	85.9 $\pm$ 9.3*
Glucose (mg/dl)	115.2 $\pm$ 7.1	115.9 $\pm$ 21
HbA1c (%)	5.7 $\pm$ 0.98	6.56 $\pm$ 1.8

\**P* < 0.01, \*\**P* < 0.05

**Table (4):** Pearson correlation coefficient of CRP with Atherosclerotic risk factors and oxidative stress markers

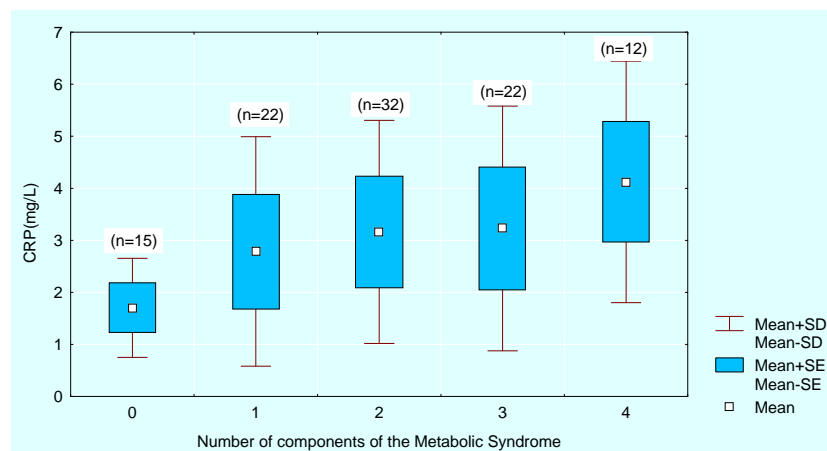
	CRP	GGT	UA	SBP	DBP	BMI	WC	HDL-c	TAG
GGT	0.56*								
UA	0.33*	0.5*							
SBP	-0.37*	0.27	0.27						
DBP	-0.11	0.3	0.15	0.66*					
BMI	-0.33*	0.2	0.15	0.58*	0.31*				
WC	-0.15	-0.02	0.21	0.14	0.08	-0.7*			
HDL-c	-0.3	-0.08	-0.14	0.02	-0.02	0.27	0.17		
TAG	0.28	0.2	-0.21	-0.6*	-0.43	-0.3*	-0.05	-0.06	
Glucose	0.02	-0.11	0.07	-0.06	-0.01	-0.09	0.05	0.01	0.05

\*P-value: Correlation is significant at the 0.05 level.

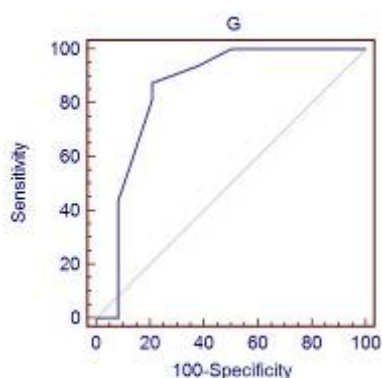
**Table (5):** Pearson correlation coefficient of CRP with biological risk factors in male and female subjects

	Men	Women
Age	-0.29	-0.47
BMI	0.41*	0.53*
SBP	0.23	0.6*
DBP	0.26	0.1
TC	0.05	-0.02
HDL-c	-0.01	0.11
TAG	0.33	-0.69
Glucose	-0.5*	-0.34

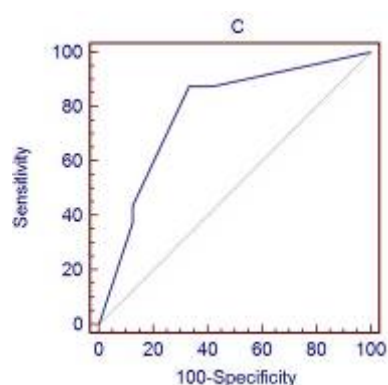
\*P-value: Correlation is significant at the 0.05 level.



**Fig. (1):** Distribution of CRP levels according to the numbers of components of the metabolic syndrome.



**Fig. (2):** ROC curve of GGT. Area under the curve equal 0.85.



**Fig. (3):** ROC curve of CRP. Area under the curve equal 0.78.

## DISCUSSION

C-reactive protein (CRP) is the most extensively inflammatory risk marker and higher levels of it are associated with cardiac events in healthy men and women<sup>(23)</sup>. The present study aimed to evaluate the relationships between serum CRP levels with GGT as marker of oxidative stress and the cardiometabolic risk factors among healthy adult people.

Low grade systemic inflammation is common in aging people and may cause chronic disease, the present results add to previous studies by investigating an association between increasing level of CRP and other clinical markers of cardiovascular risk. Gaining more information about novel biomarkers in aging peoples is important because the accurate value of classic risk factors is decreased with advancing age<sup>(12)</sup>. Furthermore, the current findings demonstrated that CRP level varies by sex, age and

BMI. That result is, however, consistent with other studies on western samples that show higher CRP levels in females<sup>(24)</sup>, whereas one cross-sectional study of Japanese males and females aged 30 years and over showing higher CRP in men<sup>(25)</sup>. The reason for these sex discrepancies is unclear but suggests that race and environmental factors should be considered in association with CRP. Of the total population, 50 % of men and 41.6 % of women had CRP levels less than 3 mg/L, whereas only 50 % of men and 58.3 % of women had CRP levels above 3 mg/L.

Recent studies have suggested a role for uric acid as a mediator of cardiovascular and metabolic syndrome<sup>(26)</sup>. Elevated uric acid concentrations are, also associated with increased serum antioxidant capacity and reduced oxidative stress during acute physical exercise among healthy subjects<sup>(27)</sup>. Previous works reported that obesity increase GGT in an additive manner. GGT is

responsible for the extracellular metabolism of glutathione, the main antioxidant in mammalian cells and GGT enzyme induction may be specifically associated with the generation of reactive oxygen species. Obviously, the links between serum uric acid, oxidative stress, and biomarkers of liver status, which associate with various biochemical and anthropometric features of the metabolic syndrome, also warrant future studies<sup>(28)</sup>.

The current data further showed a linear trend for an increased prevalence of cardiovascular risk factors across CRP categories, which included a marker of diabetes risk, blood pressure and cholesterol. In addition, the current results recorded that high CRP that was defined as >3mg/L was associated with components of metabolic syndrome, and this was largely explained through the effects of central adiposity<sup>(12)</sup>.

There are several mechanisms underlying the association of GGT with MS. First, GGT has a central role in glutathione homeostasis by initiating the breakdown of extracellular glutathione. As glutathione, an antioxidant protects cells from toxins such as free radicals, increases in GGT may be a marker of oxidative stress and increased GGT reflects increased oxidative stress<sup>(10)</sup>. Increased oxidative stress, also, impaired insulin secretion by promoting  $\beta$ -cell dysfunction, and reduced insulin action by activation of multiple stress-serine/threonine kinase signaling cascades. The significant relationship that has been found between GGT and CRP is possibly due to their association with oxidative

stress, which is a cardiovascular risk factor<sup>(29)</sup>.

Consistent with the previous studies<sup>(30)</sup>; BMI is a mediator for the association between CRP and the MS. However, even though, BMI has a predominant influence on the CRP profile and the overall risk of MS, the present data showed that the increased CRP levels were highly associated with the individual features of MS. CRP also, has several direct effects at the level of the vessel wall and its measurement adds important prognostic information to clinical definitions of the MS is thus consistent with this that hypothesis.

In addition, to BMI, CRP was also found to be closely correlated with SBP in female subjects. The mechanisms underlying the association of CRP with BMI might be as follows; the adipose tissue is a source of cytokines such as tumor necrosis factor and interleukin-6, and these cytokines stimulate the production of acute-phase proteins such as CRP in the liver<sup>(31)</sup>.

ROC analyses showed the predictive power of GGT was larger than CRP in aging subjects. That result shows that GGT could be used as the predictive marker for future risk of cardiometabolic diseases.

In conclusion, these results suggest that GGT might be associated with increased CRP levels in males and females. Given that, GGT is easily measured and is extensively used. In addition, elevated CRP is highly associated with the metabolic syndrome. Further work is required to investigate the role of very high-elevated CRP in cardiovascular risk diseases in elderly peoples and to



clarify whether GGT is related to atherosclerotic disease after adjustment for cardiovascular risk factors.

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خلود صلاح الدين عبد العال رمضان  
قسم الكيمياء الحيويه-كلية العلوم-جامعه عين شمس

يعد بروتين سي المتفاعل من البروتينات المرتبطه بالاصابه بالالتهابات كما ان له علاقته وطيدته بالعديد من الأمراض مثل أمراض القلب والتهاب المفاصل. ويهدف هذا البحث الي دراسه علاقته بين بروتين سي المتفاعل وأنزيم الجاما جلوتاميل ترانسفيريز كمؤشر للاجهاد التأكسدي ودراسه مدي ارتباطهم بالعوامل الخطره لأمراض القلب الوعائيه في الرجال والسيدات في المرحله المتوسطه من العمر. وأيضا لبيان أختلاف هذه العلاقه بأختلاف السن والجنس ومعامل كتله الجسم. وقد اشتملت هذه الدراسه علي ١٠٠ امراه ورجل من المتطوعين تتراوح أعمارهم ما بين ٢٠ الي ٥٠ عاما، وتتراوح أوزانهم من ٢٤ الي ٤٠ كجم. تم جمع عينات دم وريديه بعد صيام لمدة ١٢ ساعه وتم قياس كل من مستوي بروتين سي المتفاعل ، انزيم الجاما جلوتاميل ترانسفيريز، حمض البوريك والقياسات الخاصه بأمراض القلب الوعائيه. أوضحت الدراسه بعد اجراء التحليل الأحصائي للنتائج أن هناك أختلاف في تركيز بروتين سي المتفاعل مع أختلاف السن والجنس والوزن. كما وجد أن هناك زياده خطيه بين العوامل الخطره لأمراض القلب الوعائيه وزياده مستوي بروتين سي المتفاعل كما أن هناك علاقته ارتباط ايجابي وثيقه بين مستوي كل من بروتين سي المتفاعل واثنين من مؤشرات الأجهاد التأكسدي ، مستوي انزيم الجاما جلوتاميل ترانسفيريز وحمض البولييك. كما أظهرت النتائج أيضا أن زياده بروتين سي المتفاعل يزيد من معدل الاصابه بالمتلازمه الأستقلابيه. كما وجد أن هناك علاقته ارتباط ايجابي أيضا بين بروتين سي المتفاعل وكل من الكتل الوزنيه للجسم ومعدل ضغط الدم. ويتضح من هذه النتائج أن هناك ارتباط وثيق بين مستوي بروتين سي المتفاعل ومؤشرات الأجهاد التأكسدي ممثلا في انزيم الجاما جلوتاميل ترانسفيريز وحمض البولييك ويمكن اعتبارهم أهم المؤشرات البيوكيميائيه للتنبؤ بخطر الاصابه بالتعقيدات القلبيه الوعائيه الخطره وايضا المتلازمه الأستقلابيه وخاصه مع تقدم العمر ووجود زياده في الوزن.