# Relationship between hs-C- reactive protein and some biochemical variables in Cardiovascular and Type -2- Diabetic Mellitis patients

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**Objective:**

Study the effect of bio-invariant hs-C-reactive proteins as participate marker in Cardiovascular and Type -2-Diabetes Mellitus patients, with related to other biochemical variables .

**Subjects**

1- Preparation formation list which include (Name .Age ,Length ,Weight

2- Determination the body mass index (BMI ),by divided weight/ length square.

3- Determine the serum level of hs-C-reactive protein .

4- Determine the serum level of fasting serum sugar , Glycohemoglobin A1c ( HbA1c%) , lipid profile and lipoproteins . 5-Evaluation the Insulin and insulin resistance .

6- Determination the relationship between hs- C-reactive protein and biochemical variables in three study groups (Type -2 diabetes mellitus, Type-2- Diabetes Mellitus with cardiovascular diseases, cardiovascular diseases only) patients .

**Abstract**

C-reactive protein (CRP) is a protein found in the blood, the levels of which rise in response to inflammation. its' study as a risk marker for Cardiovascular and Type -2- Diabetes Mellitus patients . This study was done in the period from 1st July 2011 to 1 st November 2012 in Al-Hussein hospital in Karballa government . The study groups were divided into four groups ,one is control ,the others were patients ( Type -2- Diabetic , Type - 2- Diabetic with Cardiovascular and Cardiovascular disease only . The results were showed, there were lowering in Fasting serum adiponectin hormone concentration for (three study groups ) Type -2- Diabetic , Type - 2- Diabetic with Cardiovascular, and Cardiovascular diseases groups with respect to than normal subjects . Significant different ( $p< 0.001$ ) as shown in tables 1 ,2 ,3 . When use hs-CRP measurement as a marker to limitation the kind of pathogenic case and from L.S.D statistical system were observed there were highly significant different between (DMII with CVD and CVD )groups compared to control group and medium significant different with DMII group .There weren't significant different between (DMII with CVD and CVD) groups ,while there were significant different between DMII group and control group less than two previous groups (DMII with CVD and CVD). Therefore measurement of hs-CRP were considered as a predictor to incident by Cardiovascular diseases more than Type -2- Diabetes .

**الخلاصة**

لقد تمت دراسة العامل البايلوجي البروتين الفعال–ج– عالي الحساسية كأحد العلامات الدالة على مرضى القلب في مرضى السكر نوع 2– . أجريت هذه الدراسة على ثلاث مجاميع من المرضى سكر نوع –2– فقط والمجموعة الثانية مرضى سكر نوع –2– بالإضافة إلى مرض القلب والمجموعة الثالثة مرضى قلب فقط بالإضافة إلى مجموعة السيطرة ؛عدد المرضى لكل مجموعة (50) مريضا .أجريت الدراسة في مستشفى الحسيني التعليمي في محافظة كربلاء وشخصت ألعينات من قبل الدكتور عمار كاني اختصاص باطنية و سكر والدكتور حيدر سلوم اختصاص قلب .لقد تمت مقارنة النتائج لكل مجموعة من المرضى مع نتائج مجموعة السيطرة وأوضحت ألنتائج ان مستوى العامل البايلوجي ج– البروتين الفعال كان عاليا نسبيا في المجاميع الثلاثة مقارنة بمجموعة السيطرة وان التأثير كان معنويا, وعند استخدام العامل البايلوجي ج–البروتين الفعال عالي الحساسية كأحد العلامات الدالة لتحديد نوع الحالة المرضية ومن استخدام النظام الإحصائي (أ–أ–م) لتحديد أقل اختلاف معنوي تبين إن هذا العامل البايلوجي هو عالي ألمعنوية بالنسبة لمجموعة ألقب ومتوسط ألمعنوية بالنسبة مجموعتي ( سكر نوع –2– و سكر نوع –2–وقلب )مقارنة بالسيطرة ،ولا يوجد اختلاف معنوي بين مجموعتي (سكر نوع –2– و قلب سكر نوع –2)

**Introduction**

Type -2- Diabetes Mellitus (DMII) is not one disease –but rather is heterogeneous group of syndromes characterized by an elevation of fasting blood glucose caused by a relative or absolute deficiency in insulin .Diabetes Mellitus is the leading cause of adult blindness and amputation and a major cause of renal failure,heart attack, strokes ,Most cases of diabetes mellitus can be separated into two groups type 1,type 2( Champe .C *et al* 2008). One of the very important parameters to follow up DMII is HbA1c as monitor (Gilliland, S. S., J. S. Carter, *et al.* (2002).Cardio vascular disease(CVD)a group of medical problems that effect the heart and surrounding blood vessel .CVD can take many forms such as high blood pressure ,Coronary artery disease, Valvular heart disease or rheumatic heart disease .There are many factors affect at CVD such as cholesterol,triglycerides ,and lipoproteins (HDL-C,VLDL-Tg. ,LDL-C(Maton ,Anthea 1993).C-Reactive protein (CRP) is a liver protein composed of five identical non glycosylated subunits with a total molecular weight of 105 kDa. CRP has a variety of powerful effects related to immunology,

inflammation, and coagulation( Ridker, P.M. *et al*). As a marker of low-level inflammation, CRP appears to predict future cardiovascular disease events among apparently healthy individuals High plasma concentration of CRP was associated with increased risk of stroke ,infarction, and peripheral vascular disease [Ridker, P.M. *et al*. (1997): Ridker, P.M. *et al*.(1998)] hs-CRP has also been associated with increased risks of fatal coronary events among high-risk male smokers and incident coronary disease among the elderly[Kuller, L.H. *et al*. (1996);Tracy, R.P.*et al*. (1997)]other Studies have established the prognostic usefulness of (CRP) in the setting of angina [Liuzzo, G. *et al*.(1994)] .Originally used as a marker of acute inflammation,(CRP)has become a leading candidate as the measure of choice for estimating the inflammatory component of Cardiovascular disease risk

***Methods***

This study was done in the period from 1st July 2011 to 1 st November 2012 in Al-Hussein hospital in Karballa government .The study groups were divided into four groups ,one is control and the others were patients as follow:

**Control group** included as a 50 healthy subjects (25 males and 25females).The ages of the apparently healthy individuals were range from 35-up to 65 years.They were collected from my family,medical staff and relatives who were free from signs and symptoms of any chronic diseases like diabetes ,hypertension and others

**patients groups:-** This include three groups, each one have 50 subjects , the ages were range from 35-up to 65 years, as shown below :- 1- DMII patients only (30 females ,20 males) .

2- DMII with CVD patients (24 females, 26 males). 3 - CVD patients (23 females, 27 males).

Patients suffered from kidney failure or/and liver diseases were not included and excluded from the current study. All samples were diagnosed by supervisor ,dr .Amar Cani sugar specialist and dr. Heider Sallom heart specialist .

**1-Collection of samples**

the patients and healthy volunteers after an over night fasting. The samples were put in plain tubes without any additives. Disposable syringes and needles were used for blood collection . After allowing the blood to clot at 37°C for about 15 min, blood samples were centrifuged at 1800xg for 15 min . Sera were separated in a disposable tubes divided into ten parts in sterile eppendrofs and frozen at ( -18 °C ) .

and stored at(-18 °C ).

**2-Assay Procedure of hs-C-reactive protein**

hs-C-reactive protein was assayed according to the procedure of the manufactures of its' kit (Ridker 1998 ) .

***Calculations***

- The absorbance for each set of references standard ,control and sample were measured at wave Length 450 nm as duplicate using Bio-ELISA reader Elx 800 .
- A standard curve was constructed by plotting the mean absorbance obtained for each reference standard against its concentration in ng/l on graph paper.
- The corresponding concentration of CRP (ng/l) from the standard curve was determined.
- The obtain values of the samples and control sera were multiplied by the dilution factor of 1000 to obtain CRP result in mg/l.
- A serial dilutions were done (16 , 8, 4 ,2 ,1 , 0. 50 , 0.25 , 0.00 ) ng/ml of CRP standard as shown in figure . 1 .

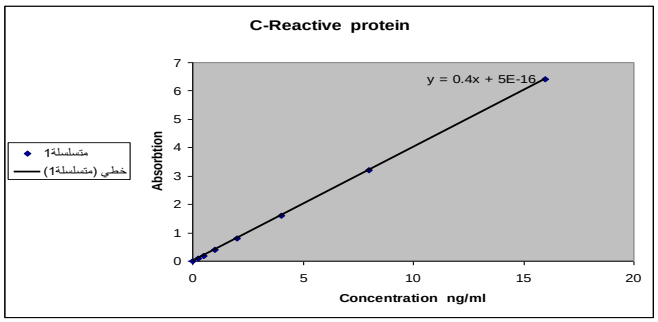


**Fig 1 :** Standard curve of hs-CRP

**3-Fasting serum sugar (FSG)**( Bablock W.1988 ), glycolated hemoglobin(HbA1C) (Varley H, 1980) ,triglycerides , (Tg.)(Fossati P., Prencipe L 1980) , total cholesterols (TC.) (Young DS. 1995), high density lipoprotein cholesterol (HDL-C) (Tietz. NW. 1995) and insulin hormone were assayed according to the procedure of the manufactures of its' kits[ (Nahla S. *et al* 2006) .

***4-Very low density lipoprotein triglycerceride*** (VLDL-Tg) concentration was calculated by divided triglycerceride concentration by five VLDL = Tg**./5** ( Friedwald WT. 1972) .

***5-Low density lipoprotein cholesterol (LDL.C)*** = TC –(HDL+TG/**5** ) (Ram A. 1996).

***6-insulin resistance*** in type 2 diabetic patients was estimated by Homeostasis model assessment (HOMA-IR): (Kirsten A. *et al* 2001, DeFronzo MRA 1999)

HOMA = [glucose in (mmole/L) x insulin in (microIU/mL ) ] **/ 22.5**.

**Statistical analysis**

student 't' test was applied to assess the significance and linear regression analysis ( Bivariats correlation analysis) was done to determine the relationships between adiponectin and other risk variables and Least Significant Different (L.S.D) statistical system to limitation significant.

**Results &Discussion**

**Table-1-Clinical and Biochemical variables of study subjects *Type -2 - Diabetic Mellitis*.**

| Parameters | Healthy normal subjects ,n=50 | Type 2 diabetic n=50 | P-Value |
|---|---|---|---|
| BMI (kgs/m²) | 23.979±0.659 | 31.894±4.237 | < 0.001 |
| Fasting glucose (mmol /L) | 4.994±0.650 | 9.245±3.009 | < 0.001 |
| HbA1c (%) mg/dl | 5.112±0.286 | 10.966±2.755 | < 0.001 |
| S.Cholesterol (mmol/L) | 4.066±0.701 | 4.838±1.535 | < 0.002 |
| S.Triglyceride (mmol/L) | 1.510±0.468 | 2 .354±0.849 | < 0.001 |
| High density lipoproteins (mmol/L) | 1.130±0.156 | 0.860±0.137 | < 0.001 |
| Low density lipoproteins | 2.680±0.819 | 3.454±0.120 | < 0.001 |
| Very low density lipoproteins | 0.272±0.105 | 0.450±0.166 | < 0.001 |
| Insulin (µIU/ml) | 6.557±1.742 | 18.787±15.874 | < 0.001 |
| Insulin resistance(HOMA.IR) | 1.458±0.381 | 7.556±5.962 | < 0.001 |
| Hs-CRP ( mgs/L) | 0.412±0.272 | 4.166±2.039 | < 0.001 |
| Systolic BP(mm Hg) | 118.4±4.4 | 129.6±10.7 | < 0.001 |
| Diastolic BP (mm Hg) | 78.6±3.3 | 89.8±11.4 | < 0.001 |

**Table-2-Clinical and Biochemical variables of study subjects, Type -2- Diabetic Mellitis with Cardiovascular.**

| Parameters | Healthy normal subjects,n=50 | DMII-CVD subjects n=50 | P-Value |
|---|---|---|---|
| BMI (kgs/m²) | 23.979±0.659 | 31.162±5.602 | <0.001 |
| (Fasting glucose mmol/L) | 4.994±0.650 | 11.816±4.433 | < 0.001 |
| HbA1c (%) mg/dl | 5.112±0.286 | 12.394±2.401 | < 0.001 |
| S.Cholesterol (mmol/L) | 4.066±0.701 | 4.838±1.523 | <0.002 |
| S. (mmol/L) Triglyceride | 1.510±0.468 | 2.406±1.420 | < 0.001 |
| High density lipoproteins.C(mmol/L) | 1.130±0.156 | 0 .872±0.122 | < 0.001 |
| Low density lipoproteins.C | 2.680±0.819 | 3.538 ±1.546 | = 0.001 |
| Very low density lipoproteins | 0.272±0.105 | 0.458±0.279 | < 0.001 |
| Insulin(µIU/ml) | 6.557±1.742 | 24.908±28.77 | < 0.001 |
| Insulin resistance(HOMA,IR) | 1.458±0.381 | 12.896±18.032 | < 0.001 |
| hs-CRP ( mgs/L) | 0.412±0.272 | 4.693±2.625 | < 0.001 |
| Systolic BP(mm Hg) | 118.4±4.4 | 137.1±13.6 | < 0.001 |
| Diastolic BP (mm Hg) | 78.6±3.3 | 93.6±12.5 | < 0.001 |

**Table-3-Clinical and Biochemical variables of study subjects, Cardiovascular .**

| Parameters | Healthy normal subjects n=50 | CVD subjects n=50 | P-Value |
|---|---|---|---|
| BMI (kgs/m²) | 23.979±0.659 | 31.659±5.702 | < 0.001 |
| Fasting glucose (mmol/L) | 4.994±0.650 | 5.370±0.698 | < 0.006 |
| HbA1c (%)mg/dl | 5.112±0.286 | 6.736±1.361 | < 0.001 |
| S.Cholesterol(mmol/L) | 4.066±0.701 | 5.058±1.104 | < 0.002 |
| S.Triglyceride(mmol/L) | 1.510±0.468 | 2.394 ±1.290 | < 0.001 |
| High density lipoproteins.C(mmol/L) | 1.130±0.156 | 0.874±0.376 | < 0.001 |
| Low density lipoproteins.C(mmol/L) | 2.680±0.819 | 3.828±1.124 | < 0.001 |
| Very Low density lipoproteins | 0.272±0.105 | 0.454±0.256 | < 0.001 |
| Insulin(µIU/ml) | 6.557±1.742 | 17.85 ±14.26 | < 0.001 |
| Insulin resistance(HOMA.IR) | 1.458±0.381 | 4.932±5.433 | < 0.001 |
| Hs-CRP ( mgs/L) | 0.412±0.272 | 4.838 ±2.563 | < 0.001 |
| Systolic BP(mm Hg) | 118.4±4.4 | 136.4±15.2 | < 0.001 |
| Diastolic BP( mm Hg) | 78.6±3.3 | 93.4±14.3 | < 0.001 |

**Table- 4- Bivariats correlation analysis of hs-CRP with high risk variables in DMII patients .**

| Parameters | r | P-Value |
|---|---|---|
| BMI (kgs/m²) | 0.891** | < 0.01 |
| Fasting glucose (mmol /L) | 0.150 | 0.298 |
| HbA1c (%)mg/dl | 0.245 | 0.086 |
| S.Cholesterol (mmol/L) | 0.050 | 0.711 |
| S.Triglyceride (mmol/L) | 0.285* | 0.045 |
| High density lipoproteins (mmol/L) | -0.167 | 0.248 |
| Low density lipoproteins | 0.070 | 0.630 |
| Very low density lipoproteins | 0.287* | 0.043 |
| Insulin (µIU/ml) | 0.819** | < 0.01 |
| Insulin resistance(HOMA.IR) | 0.902** | < 0.01 |
| Systolic BP(mm Hg) | 0.212 | 0.140 |
| Diastolic BP( mm Hg) | 0.217 | 0.130 |

***Correlation is significant at the 0.05 (2-tailed )**
***Correlation is significant at the 0.01 (2-tailed )**

**Table- 5- Bivariats correlation analysis of hs-CRP with high risk variables in DMII with CVD patients.**

| Parameters | r | P-Value |
|---|---|---|
| BMI (kgs/m²) | 0.784** | < 0.01 |
| Fasting glucose (mmol/L) | 0.155 | 0.284 |
| HbA1c (%)mg/dl | 0.142 | 0.326 |
| S.Cholesterol (mmol/L) | - 0.229 | 0.110 |
| S.Triglyceride (mmol/L) | -0.27 | 0.057 |
| High density lipoproteins (mmol/L) | 0.239 | 0.094 |
| Low density lipoproteins | -0.181 | 0.207 |
| Very low density lipoproteins | -0.265 | 0.063 |
| Insulin (µIU/ml) | -0.636** | < 0.01 |
| Insulin resistance(HOMA.IR) | 0.680** | < 0.01 |
| Systolic BP(mm Hg) | 0.049 | 0.734 |
| Diastolic BP( mm Hg) | -0.027 | 0.853 |

***Correlation is significant at the 0.05 (2-tailed )**
****Correlation is significant at the 0.01 (2-tailed )**

**Table- 6- Bivariats correlation analysis of hs-CRP with high risk variables in CVD patients.**

| Parameters | r | P-Value |
|---|---|---|
| BMI (kgs/m²) | 0.821** | 0.01 < |
| Fasting glucose ( mmol/L) | 0.158 | 0.272 |
| HbA1c (%)mg/dl | 0.507** | 0.01 < |
| S.Cholesterol (mmol/L) | 0.125 | 0.389 |
| S.Triglyceride (mmol/L) | 0.043- | 0.765 |
| High density lipoproteins (mmol/L) | 0.025 | 0.862 |
| Low density lipoproteins | 0.136 | 0.345 |
| Very low density lipoproteins | -0.062 | 0.667 |
| Insulin (µIU/ml) | 0.779** | 0.01 < |
| Insulin resistance(HOMA.IR) | 0.680** | 0.01 < |
| Systolic BP(mm Hg) | 0.084- | 0.734 |
| Diastolic BP( mm Hg) | 0.122- | 0.853 |

***Correlation is significant at the 0.05 (2-tailed )**Correlation is significant at the 0.01 (2-tailed )**

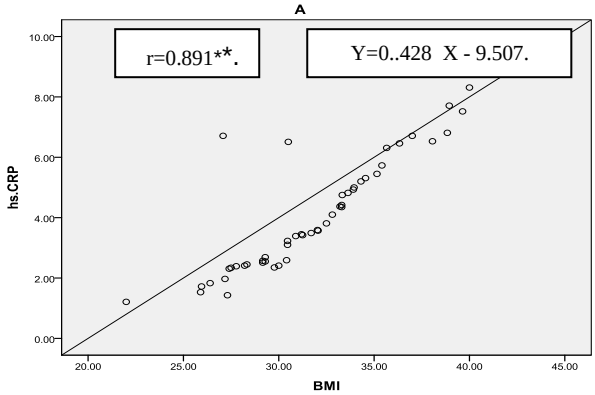


Figure -2- Relationship between high sensitive C-reactive protein and body mass index in Type -2- Diabetic Mellitis group ( DMII),

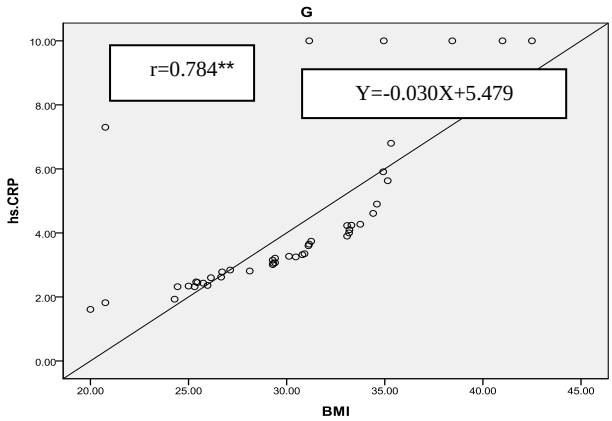


Figure -3- Relationship between high sensitive C-reactive protein and body mass index in Type -2- Diabetic Mellitis with Cardiovascular diseases group ( DMII-CVD ) .

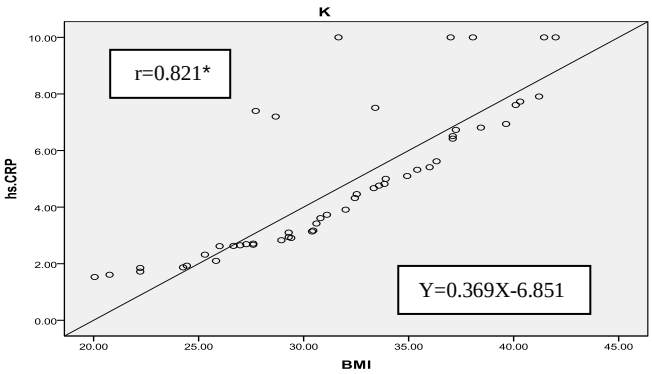


Figure -4- relationship between high sensitive C-reactive protein and body mass index in cardiovascular diseases only group ( CVD ) .

1- **Evaluation of high sensitive CRP ( hs-CRP) in (three study groups) Type- 2 - Diabetic, Type - 2- Diabetic with Cardiovascular , Cardiovascular patients comparison with control group:**

The results in this study were showed there were increase in concentration of hs-CRP in the three study groups when compared with normal subjects,as in table1,2 ,3.High significant differences ( P< 0.001).When use hs-CRP measurement as a marker to limitation the kind of pathogenic case and from Least Significant different(L.S.D)statistical system were observed there were highly significant different between CVD group compared to control group and medium significant different with [DMII , DMII-CVD]groups, while the results show no significant different between (DMII-CVD group and (CVD) group, while there were significant different between DMII group and DMII-CVD group compared to control group less than previous group (CVD). Therefore concentration of hs-CRP were considered as predictor to incident by Cardiovascular diseases more than Diabetes.Several studies have earlier shown that hs-CRP predicts diabetes, Cardiovascular disease in western populations as a biomarker of inflammation [Pradhan *et al.*(2001);**.** Haffeiner SM. (2003); Hanley AJ(2004)].The results obtained in this study is comparatively similar to the earlier work that emphasis's the prediction of incident with Diabetes,Cardiovascular diseases by hs- CRP level [David C *et al.* (2007)].The present study which showed increased of hs-CRP in Diabetes, Cardiovascular diseases was supported by the previous study results[ Li CZ (2004) ; Mendall MA et al. (2000 )]

The clinical and biochemical variables which were related to hs-CRP of the three study groups were shown in the tables 1,2.3 . In comparison with control subjects, the (diabetic, diabetic with Cardiovascular and Cardiovascular only ) subjects were significant different and had higher body mass index (BMI p<0.001). They also had higher systolic blood pressure p<0.001 and diastolic pressure Blood pressure(P<0.001).HbA1C% (P<0.001), fasting insulin (P<0.001) and insulin resistance( P<0.001 )were also higher in (DMII, DMII-CVD, CVD only) subjects with compared to healthy subjects Significant different. Fasting serum glucose (P<0.001 )was higher in subjects with(DMII, DMII-CVD)only compared to healthy subjects (significant different), but Its´ normal in CVD only subjects (P<0.006) compared to healthy ( no significant different ) subjects ,{LDL- C (P<0.001 ). VLDL-Tg (P<0.001), triglycerides (P<0.001)}were significantly higher among the three study groups, HDL-C were lower in three study groups than control group, significant different (P<0.001), total cholesterol (p=0.002 ) ( no significant different)

**2-Relationship between hs-CRP and biochemical variables in (three study groups):-** The linear regression analysis was used to examine the relationship of the levels of hs-CRP with biochemical variables which found the relationship of the levels of hs-CRP with (fasting serum glucose,T.C.,LDL.C,) variables of the patients in three study groups ,( no significant correlations) (positive correlations) were observed .These results were in agreement with [ Cosin Aguilar J et al. (2007); Francisco G. et al. ( 2005) ; Taniguchi A. et al. ( 2002 )]There were low significant correlations between levels of (Tg ,VLDL.Tg) and hs-CRP levels (positive correlations) in DMII group ,while no significant correlations in (DMII -CVD, CVD) groups (negative correlations ) .There were no Significant correlations between levels of HbA1c%and hs-CRP levels in (DMII, DMII-CVD) groups ,while high Significant correlations in CVD group (positive correlations).There were

no Significant correlations between levels of HDL-C and hs-CRP in three study groups,(negative correlations) with DM group and (positive correlations ) with (DMII and DMII with CVD) groups . All results were in tables. 4 ,5 ,6 .In current study and from linear regression analysis , There were high significant correlations(positively correlation) between of ,insulin , insulin resistance (HOMA-IR ) and hs-CRP levels. Some study have explored the relation of hs-CRP with insulin resistanc, which precedes diabetes,Cardiovascular diseases[Chambers JC.et al.( 2001);Nakanishi S.et al ( 2001); (Visser et al 2000); Wu DM et al. (2006) ]. Though the hs-CRP was identified as one of the most sensitive marker of inflammation, there are many studies which have looked at the association of insulin resistance with hs-CRP . In the present study serum hs-CRP levels were positively related and significant correlations, tables No.(4 ,5 ,6 ) and figures No.( 2 ,3, 4 ) to anthropometric variables such as Body Mass Index (BMI ) among the three study groups, Previous analysis found high concentration of hs- CRP was significantly associated with Obesity.[ Visser et al (2000);Chambers et al.( 2001);Forouchi et al.( 2001)]. Serum hs-CRP levels were positively related to Systolic and Diastolic blood pressure in Diabetic group and positively related to Systolic and negative related to Diastolic blood pressure in Diabetic with Cardiovascular diseases group , negative related to Systolic and Diastolic blood pressure in *Cardiovascular* diseases group ,these results were in agreement with [Chambers JC. et al. ( 2001);( Visser et al. (2000) ; Li CZ *et al.* (2004) ; Francisco G. et al. ( 2005); Earl S. F and Wayne H.G. (2004)].

**Conclusion**

The present study was showed that hs-CRP has a strong association with Diabetes , *Cardiovascular* diseases in Iraqi population. It is also concluded that a body mass index , hyper insulin resistance and body weight has strong association with diabetic individuals an high levels of hs-CRP groups predicts the high risk of diabetes mellitus type 2, *Cardiovascular* diseases. It is very well understand that the levelsof hs-CRP significantly associated and positively related to insulin resistance, BMI, systolic and diastolic pressure. similarly, low HbA1c strong related to negative hs-CRP levels. It is also observed that hs-CRP levels are the sensitive marker for inflammation .

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