Original Article

Role of Serum Retinol Binding Protein-4 and Insulin Resistance as Cardiovascular Risk Factors in Non Diabetic Post-Menopausal Women.

Samia A.Ebied,[1] Gihane I.Khalil,[2] Hanan M.Mostafa,[3]

Departments of Applied Medical Chemistry,[1] Chemical Pathology[2] & Internal Medicine[3], Medical Research Institute - Alexandria University. Alexandria; Egypt

Abstract:

Background: Retinol binding protein-4 (RBP-4) is a newly discovered adipokine, which is mainly secreted by liver and originally known to be the only specific transport protein for vitamin A in the circulation. Recently, RBP-4 is found to be expressed in adipose tissue and correlated with obesity, insulin resistance (IR) and type 2 diabetes mellitus (T2DM). **Objective:** The aim of the present work was to study the role of serum RBP-4 concentration and IR as cardiovascular risk factors in non diabetic post-menopausal women. **Subjects and Methods:** The present study included 25 apparently healthy premenopausal women (group I), 25 apparently healthy postmenopausal women (group II) and 25 postmenopausal women with cardiovascular diseases (CVD) (group III). Informed consents were obtained from all females. The following were done for all participants: history taking, complete physical examination, laboratory tests including lipid profile, fasting (FG)and postprandial plasma glucose(PPG) level, fasting plasma insulin , assessment of IR by homeostasis model assessment (HOMA score) and determination of plasma RBP-4. **Results:** Data showed that, the mean fasting plasma insulin levels and mean HOMA-IR in postmenopausal women with CVD were statistically significantly higher than those without CVD ($p_2 < 0.05$). There was a significantly higher mean level of RBP-4 in postmenopausal without CVD than in the premenopausal women ($p_1 < 0.05$). In addition, the mean value of RBP-4 levels of postmenopausal women with CVD was statistically significantly higher than those without CVD ($p_2 < 0.05$). Plasma RBP-4 was positively correlated with the age, serum total cholesterol (TC), serum triglycerides (TG), serum TG/HDL-C ratio, plasma (FG), plasma (PPG), plasma insulin and (HOMA-IR) in postmenopausal women with CVD. **Conclusions:** RBP-4 is significantly elevated in postmenopausal women with CVD as compared to postmenopausal women without CVD. RBP-4 is positively correlated with lipids and HOMA-IR in postmenopausal women with CVD. It affects glucose and lipid homeostasis and contributes to the onset of IR which may play a role in the development of CVD. RBP-4 might serve as a novel biomarker of CVD.

Keywords: Retinol binding protein-4, insulin resistance, cardiovascular disease, Postmenopausal women.

Introduction:

Cardiovascular disease is a class of diseases that involve the heart or blood vessels (arteries and veins), principally cardiac disease, vascular diseases of the brain and kidney, and peripheral arterial disease. The causes of cardiovascular disease are diverse but atherosclerosis and/or hypertension are the most common.(1) Cardiovascular diseases (CVD) are a principal cause of death worldwide and are linked to obesity and metabolic syndrome. Several adipokines secreted by the increased adipose tissue mass, together with the infiltrating macrophages, have been identified as key components of the 'adipo-cardiovascular axis' and are main contributors to the pathogenesis of atherosclerosis and other cardiovascular diseases. Among these, RBP4 has been identified as an adipokine associated with obesity, type 2 diabetes (T2DM) and metabolic syndrome. (1)

Retinol binding protein-4 (RBP-4) is a newly discovered adipokine, which is mainly secreted by the liver and excreted by the kidneys. It is the sole carrier of retinol (vitamin A) in blood, and serves to transport it from liver stores to the peripheral tissues. Circulating RBP4 levels have been shown to rise and positively correlated with body mass index (BMI) (2,3) and

to be associated with insulin resistance (IR).[2-5] Growing evidence suggests that RBP4 plays a role in lipid metabolism to an even greater extent than insulin resistance. In fact, many human studies have found a strong relationship between RBP4 and triglycerides; some have found associations with insulin resistance [3, 6] and others have failed to do so. [7-9]

Menopause is defined as the permanent cessation of menses as a consequence of the loss of ovarian follicular function or of surgical removal of ovaries. During this period, many psychological, physiological, and pathological modifications occur; in particular cardiovascular disease (CVD). It is well known that there is a high prevalence of cardiovascular risk factors and metabolic syndrome (MS) in postmenopausal women. Postmenopausal status is believed to be a risk factor for IR in women. IR has a causal role in the development of T2DM. Even in the absence of hyperglycemia or diabetes, IR contributes to an increased risk of CVD. [1, 10]

The aim of the present work was to study the role of serum RBP-4 and IR as CVD risk factors in non-diabetic post-menopausal women.

Subjects and Methods:

The present study included 25 apparently healthy premenopausal women (group I), 25 apparently healthy postmenopausal women (group II) (both groups were chosen from the staff members of MRI), and 25 postmenopausal women with CVD (group III) (recruited from the Internal Medicine Department, Cardiology unit MRI). All the subjects were matched as regards body mass index. Informed consents were obtained from all females. Exclusion criteria: patients with impaired kidney function, liver cirrhosis, diabetes mellitus and hypertension.

The following were done for all participants: history taking with special stress on family history of diabetes mellitus and any drug intake, complete physical examination including body mass index (BMI) which was calculated as body weight (kg) divided by body height squared (m^2), Waist to hip ratio (WHR) and blood pressure measurement and laboratory investigation including determination of serum total cholesterol (TC), high density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol, Triglycerides (TG), calculated TG/HDL-C ratio, fasting and postprandial plasma glucose level, and fasting plasma insulin by chemiluminescence method.[11] Assessment of IR was done using homeostasis model assessment HOMA score (HOMA-IR = fasting plasma insulin (mU/ml) × fasting plasma glucose (mmol/l)/22.5.[12] Plasma creatinine was determined[11] and the estimated glomerular filtration rate (eGFR) was calculated using Cockcroft Gault equation:

eGFR = (140-age) × body weight (kg) × 0.85 if female / 72 × serum creatinine (mg/dl). [13] Liver enzymes including serum aspartate aminotransferase (AST) and serum alanine aminotransferase (ALT)[11] were determined. Plasma RBP-4 was estimated by ELISA method using commercially available kit.[14] Special studies included; echocardiography and ECG for suspected cases with ischemic heart diseases (IHD), or Doppler on carotid arteries and CT brain for suspected cases with cerebrovascular strokes (CVS).

Statistical analysis:

Statistical analysis was performed with the SPSS version 19 software package. Statistical significance was defined as a 2-sided P-value of ≤0.05.The comparison between the studied groups was done using Mann-Whitney and t-test. Correlation analysis was done using Pearson coefficient and Spearman coefficient tests.

Results:

Out of the 25 postmenopausal women with CVD, 16 cases were diagnosed as IHD and 9 cases were diagnosed as CVS. As regard BMI, there was no statistical significant difference between the three studied groups (p_1&p_2 > 0.05). Table I

Data showed that, there were statistical significant differences in the mean TC and mean TG between group I&II (p_1 < 0.05). In

contrast, there were no statistical significant difference between group I&II as regard mean HDL-C, mean LDL-C levels and TG/HDL-C ratio ($p_1 > 0.05$). It was also observed that the mean TC, mean LDL-C, mean TG levels and TG/HDL-C ratio were statistically significantly higher in group III than group II ($p_2 < 0.05$), while there was no statistical significant difference between the two groups in the mean HDL-C ($p_2 > 0.05$).(Table II)

There were no statistical significant difference in the mean plasma FG, mean plasma post prandial glucose, mean insulin levels and mean HOMA-IR between group I&II ($p_1 > 0.05$). On the other hand, the mean plasma insulin levels and mean HOMA-IR in group III were statistically significantly higher than in group II ($p_2 < 0.05$). (Table III)

There was a statistical significant difference in the mean serum RBP-4 between groupI&II ($p_1 < 0.05$). In addition, the mean serum RBP-4 was statistically significantly higher in group III than in group II ($p_2 < 0.05$). (Table IV)

Correlation analysis of the plasma RBP-4 levels with clinical and biochemical parameters in premenopausal women and postmenopausal women with and without CVD revealed that; plasma RBP-4 was positively correlated with serum total cholesterol (TC) ($r = 0.409$, $p = 0.042$) and post prandial glucose ($r = 0.412$, $p = 0.041$) in postmenopausal women without CVD. Also it positively correlated with the age ($r = 0.540$, $p = 0.005$), serum total cholesterol (TC) ($r = 0.442$, $p = 0.027$), serum triglycerides (TG) ($r = 0.654$, $p < 0.001$),serum triglycerides / high density lipoprotein-cholesterol ratio ($r = 0.627$, $p = 0.001$), fasting plasma glucose (FG) ($r = 0.475$, $p = 0.017$), plasma post prandial glucose ($r = 0.404$, $p = 0.045$), plasma insulin ($r_s = 0.431$, $p = 0.032$), and homeostasis model assessment insulin resistance level (HOMA-IR) ($r_s = 0.455$, $p = 0.022$) in postmenopausal women with CVD. While there were no correlation between the plasma RBP-4 levels with clinical and biochemical parameters in premenopausal women. (Table V)

Table I: The age (year) and body mass index (kg/m^2), of the three studied groups

	Premenopausal women (gp1) (n = 25)	**Postmenopausal women without cardiovascular disease(gpII) (n = 25)**	**Postmenopausal women with cardiovascular diseases(gpIII) (n = 25)**
Age (year)			
Range	27.0 – 52.0	47.0 – 59.0	52.0 – 66.0
Mean ± SD	37.60 ± 7.65	52.56 ± 3.28	59.52 ± 4.72
p_1		$p_1 < 0.001^*$	
p_2			$p_2 < 0.001^\#$
BMI (kg/m^2)			
Range	20.69 – 36.79	25.30 – 35.38	24.03 – 40.31
Mean ± SD	29.13 ± 4.48	30.03 ± 2.79	32.48 ± 3.44
p_1		$p_1 = 0.684$	
p_2			$p_2 = 0.064$

p_1 : p value compared postmenopausal women without CVD to premenopausal women.

p_2 : p value compared postmenopausal women with and without CVD.

* : Significant difference between postmenopausal without CVD and premenopausal groups.

\# : Significant difference between postmenopausal groups.

Significance was considered at the level of $p < 0.05$.

Table II: Serum total cholesterol (TC), High density lipoprotein-cholesterol (HDL-C), triglyceride (TG) and TG/HDL-C ratio of the three studied groups.

	Premenopausal women (gpI) (n = 25)	**Postmenopausal women without cardiovascular diseases(gpII) (n = 25)**	**Postmenopausal women with cardiovascular diseases (gpIII) (n = 25)**
TC (mg/dl)			
Range	132.0 – 229.0	124.0 – 276.0	188.0 – 321.0
Mean ± SD	181.96 ± 26.36	204.20 ± 30.42	227.80 ± 28.97
p_1		$p_1 = 0.028^*$	
p_2			$p_2 = 0.018^\#$
HDL-C (mg/dl)			
Range	34.0 – 74.0	31.0 – 77.0	31.0 – 85.0
Mean ± SD	52.36 ± 9.92	57.56 ± 11.39	50.58 ± 11.74
p_1		$p_1 = 0.256$	
p_2			$p_2 = 0.089$
LDL-C (mg/dl)			
Range	66.6 – 156.8	51.0 – 192.8	97.2 – 213.6
Mean ± SD	114.36 ± 24.81	122.82 ± 30.31	143.18 ± 30.05
p_1		$p_1 = 0.579$	
p_2			$p_2 = 0.047^\#$
TG (mg/dl)			
Range	48.0 – 128.0	60.0 – 291.0	85.0 – 287.0
Mean ± SD	76.24 ± 23.77	119.12 ± 53.76	170.20 ± 46.89
p_1		$p_1 = 0.004^*$	
p_2			$p_2 < 0.001^\#$
TG/HDL-C Ratio			
Range	0.65 – 3.15	0.78 – 8.08	1.29 – 8.39
Mean ± SD	1.54 ± 0.69	2.35 ± 1.78	3.58 ± 1.46
p_1		$p_1 = 0.133$	
p_2			$p_2 = 0.010^\#$

p_1 : p value compared postmenopausal women without CVD to premenopausal women.

p_2 : p value compared postmenopausal women with and without CVD.

* : Significant difference between postmenopausal without CVD and premenopausal groups.

\# : Significant difference between postmenopausal groups.

Significance was considered at the level of $p < 0.05$.

Table III: Fasting plasma glucose (mg/dl), post prandial glucose (mg/dl),fasting insulin (µIU/ml) and homeostasis model assessment- insulin resistance in the three studied groups.

	Premenopausal women (gpI) (n = 25)	**Postmenopausal women without cardiovascular diseases (gpII) (n = 25)**	**Postmenopausal women with cardiovascular diseases (gpIII) (n = 25)**
FG (mg/dl)			
Range	61.0 – 101.0	77.0 – 99.0	78.0 – 118.0
Mean ± SD	84.92 ± 9.69	91.32 ± 6.01	98.0 ± 12.58
p_1		$p_1 = 0.076$	
p_2			$p_2 = 0.061$
Post prandial glucose (mg/dl)			
Range	70.0 – 117.0	78.0 – 139.0	77.0 – 131.0
Mean ± SD	97.72 ± 10.33	104.28 ± 16.65	105.28 ± 12.56
p_1		$p_1 = 0.232$	
p_2			$p_2 = 0.966$
Insulin (µIU/ml)			
Range	2.10 – 9.40	2.05 – 18.80	3.0 – 22.60
Mean ± SD	4.52 ± 2.21	5.54 ± 4.04	7.54 ± 4.40
p_1		^{MW} $p_1 = 0.587$	
p_2			^{MW} $p_2 = 0.012^{\#}$
HOMA-IR			
Range	0.49 – 2.02	0.42 – 4.55	0.58 – 6.42
Mean ± SD	0.94 ± 0.49	1.27 ± 0.97	1.90 ± 1.33
p_1		^{MW} $p_1 = 0.265$	
p_2			^{MW} $p_2 = 0.007^{\#}$

p_1 : p value compared postmenopausal women without CVD to premenopausal women.
p_2 : p value compared postmenopausal women with and without CVD.
* : Significant difference between postmenopausal without CVD and premenopausal groups.
\# : Significant difference between postmenopausal groups.
Significance was considered at the level of $p < 0.05$. MW *:* Mann-Whitney test.

Table IV: Serum retinol binding protein–4 (mg/L) in the three studied groups

	Premenopausal women (gpI) (n = 25)	**Postmenopausal women without cardiovascular diseases(gpII) (n = 25)**	**Postmenopausal women with cardiovascular diseases (gpIII) (n = 25)**
RBP-4 (mg/L)			
Range	29.61 – 68.71	53.33 – 91.79	62.05 – 120.00
Mean ± SD	54.28 ± 10.36	70.06 ± 11.81	90.09 ± 13.02
p_1		$p_1 < 0.001^{*}$	
p_2			$p_2 < 0.001^{\#}$

p_1 : p value compared postmenopausal women without CVD to premenopausal women.
p_2 : p value compared postmenopausal women with and without CVD.
* : Significant difference between postmenopausal without CVD and premenopausal groups.
\# : Significant difference between postmenopausal groups.
Significance was considered at the level of $p < 0.05$.

Table V: Correlation of plasma RBP-4 levels with clinical and biochemical parameters in the three studied groups.

	Group I		Group II		Group III	
	Coeff.	**P**	**Coeff.**	**P**	**Coeff.**	**P**
Age	r = -0.072	0.733	r = -0.143	0.496	r = 0.540**	***0.005#***
BMI	r = -0.077	0.715	r = 0.007	0.974	r = 0.117	0.576
TC	r = -0.052	0.806	r = 0.409*	***0.042#***	r = 0.442*	***0.027#***
HDL-C	r = -0.340	0.096	r = -0.107	0.610	r = -0.211	0.312
LDL-C	r = 0.043	0.839	r = 0.380	0.061	r = 0.305	0.139
TG	r = 0.200	0.338	r = 0.200	0.339	r = 0.654**	***<0.001#***
TG/HDL-C ratio	r = 0.271	0.189	r = 0.212	0.309	r =0.627**	***0.001#***
FG	r = -0.001	0.995	r = 0.174	0.406	r = 0.475*	***0.017#***
Post prandial glucose	r = -0.240	0.249	r = 0.412*	***0.041#***	r = 0.404*	***0.045#***
Insulin	r_s = -0.144	0.588	r_s = 0.162	0.440	r_s = 0.431*	***0.032#***
HOMA-IR	r_s = -0.127	0.544	r_s = 0.157	0.453	r_s = 0.455*	***0.022#***

r :Pearson coefficient

rs :Spearman coefficient

** :Correlation is significant at the 0.01 level (2-tailed).

* :Correlation is significant at the 0.05 level (2-tailed).

:Statistically significant at $p \leq 0.05$

Discussion:

RBP4 has long-been known to be released by the liver ,but recently, it has been shown that approximately 15% of circulating RBP4 levels results from adipose tissue secretion.[15] RBP4 down-regulates GLUT4 ,[2] the insulin-activated glucose transporter responsible for translocation of glucose into both muscle and fat cells , and has also recently been shown to induce expression and secretion of pro-inflammatory cytokines in primary human macrophages known to induce insulin resistance.[16] In humans, circulating RBP4 levels were found to be highly negatively correlated with levels of insulin sensitivity, and to be increased with obesity and in those with type 2 diabetes.[3,17,18] However, discrepant results from other studies have questioned these associations, failing to demonstrate associations with either obesity or indicators of glucose homeostasis.[4,19,20]

The aim of the present work was to study the role of serum RBP-4 concentration and IR as CVD risk factors in non diabetic post-menopausal women. The present study included 25 apparently healthy premenopausal women (group I), 25 apparently healthy postmenopausal women (group II) and 25 postmenopausal women with CVD (group III).

The present data revealed that RBP-4 concentration in postmenopausal women without CVD was higher than those in premenopausal women. This result agreed with that reported by Suh JB[21] suggesting that menopausal status might be a major determinant of plasma RBP-4 concentrations. As women reach menopause, estrogen decreases. As such, fat amount or body fat percentage change; and visceral fat increase. As a result, lipid metabolism becomes dysregulated. This change of lipid metabolism may affect plasma RBP-4 concentrations that come from adipocytes. [22]

Accumulating data strongly support the association of RBP4 circulating levels with traditional cardiovascular risk factors (e.g. dyslipidemia, hypertension, albuminuria) and non-traditional cardiovascular risk factors (e.g. cytokines) mainly through the impairment of glucose and lipid metabolism and adipose tissue dysfunction, despite that opposite findings put RBP4 changes in dispute.[23] Although, the involvement of RBP4 in the development of subclinical atherosclerosis has been proven,[24] its prognostic value in carotid or coronary atherosclerosis progression is still obscure. [25]

The present work showed that RBP-4 concentration in postmenopausal women with CVD was higher than those without CVD. In agreement with our work, Pala et al [26] suggested that, for the first time, a major effect of visfatin, adipocyte fatty acid binding protein (aFABP), and RBP4 in the development of cardiovascular disease in their work. Also Lambadiari et al [27] concluded that patients with CAD showed elevated RBP4 serum levels. Notably, increased RBP4 concentration seemed to independently correlate with CAD severity. And regarding the underlying mechanisms, they observed the independent correlation of RBP4 with insulin resistance indices and established markers of inflammation, like CRP. RBP4 levels independently predicted early endothelial dysfunction, linking adipose tissue, inflammation and subclinical atherosclerosis in non diabetic individuals. [28]

Insulin resistance is the main pathologic mechanism that links the constellation of clinical, metabolic and anthropometric traits with increased risk for cardiovascular disease and type II diabetes mellitus. These traits include hyperinsulinemia, impaired glucose intolerance, endothelial dysfunction, dyslipidemia, hypertension, and generalized and upper body fat redistribution. This cluster is often referred to as insulin resistance syndrome. The progression of insulin resistance to diabetes mellitus parallels the progression of endothelial dysfunction to atherosclerosis leading to cardiovascular disease and its complications. In addition, insulin resistance assessed by HOMA has been shown to be independently predictive of CVD in several studies and a one unit increase in insulin resistance is associated with a 5.4% increase in CVD risk.[29&30] The San Antonio Heart Study (SAHS)[30] demonstrated that insulin resistance assessed by HOMA was significantly and independently associated with risk of CVD outcomes among Mexican-American and non-Hispanic white men and women. Logistic regression analysis in SAHS indicated that the risk of a cardiovascular event increased across quintiles of HOMA-assessed insulin resistance after the adjustment for age, sex and ethnicity. [30]

In agreement with the previous reports,[29&30] our data also revealed that the mean plasma insulin levels and mean HOMA-IR in postmenopausal women with CVD were statistically significantly higher than in postmenopausal women without CVD.

Also fasting glucose positively correlated with serum RBP-4 concentrations in postmenopausal women with CVD. The association between plasma RBP-4 concentrations and fasting glucose may be explained by the mechanism through which RBP-4 develops IR in liver. Retinol binding protein-4 induces the expression of the gluconeogenic enzyme PEPCK in the liver.[2] The present results could be due to this mechanism.

In addition, RBP-4 correlate positively with postprandial glucose in the postmenopausal women with CVD. This could be explained by findings of Broch et al [19] who concluded that RBP-4 may impair β cell function in human subjects. As RBP-4 circulates in plasma form a complex with transthyretin, which constitutes a functional component in pancreatic β cell stimulus secretion coupling. Thus it is possible that increased serum RBP-4 prevents transthyretin from exerting its β cell stimulus secretion effects.

Results from the present study also found positive association between RBP-4 and HOMA-IR. A mechanism whereby RBP-4 modulates insulin sensitivity in muscle and liver has been suggested. In skeletal muscle, RBP-4 reduces insulin sensitivity by inhibiting both insulin receptor substrate-1 phosphorylation and phosphatidylinositol 3-kinase activation, while increasing hepatic glucose production by increasing PEPCK expression.[2] Another contributing factor for IR is that RBP-4 down-regulates GLUT4,[2,15] the insulin activated glucose transporter responsible for translocation of glucose into both muscle and fat cells,[15] and has also recently been shown to induce expression and secretion of pro-inflammatory cytokines in primary human macrophages known to induce IR. [16]

Insulin resistance is well established as one of the risk factors for CVD suggesting that RBP-4 might serve as an alternative biomarker of CVD.[31] This need confirmation of some future prospective studies.

Dyslipidemia is a major cause of CVD, which in turn, is the most common cause of female morbidity and mortality.[32] The incidence of CVD increases after menopause due to changes in the plasma lipid and lipoprotein

levels that occur following menopausal transition.[33,34]

In this study it is evident that postmenopausal women had significantly higher concentrations of total cholesterol with respect to premenopausal women ($p<0.001$). These findings are similar to other studies. [35-37] Gorodeski GI and his colleague [38] reported that TC was 19% higher in postmenopausal women compared to premenopausal women, and 1% increase in TC is associated with at least 2% increase in the incidence of CVD. [39] They attributed the elevated concentrations of TC to estrogen deficiency in postmenopausal women.

In our study, postmenopausal women with CVD were having high levels of LDL; this finding is in agreement with other studies. [35,40] Circulating estrogen is a regulator of lipoprotein lipase (LPL), which catalyzes the hydrolysis of very low density lipoprotein (VLDL) to form intermediate density lipoprotein (IDL) and later LDL. After menopause due to estrogen deficiency, there will be increased plasma LPL activity causing increased level of LDL and also leads to down-regulation of LDL receptors.[37,41] The higher the small dense LDL proportion which characterizes the atherogenic shift, the higher is the LDL oxidation,[37] and these particles are associated with a threefold increase in CVD risk. [42]

In the present study when compared to premenopausal women, postmenopausal women showed high TG. This finding is in accordance with that reported by Razay et al. [39] who stated that TG in postmenopausal women was higher by 31% when compared to premenopausal women. The elevated levels of TG observed in postmenopausal women could be interpreted in view of Razay and colleagues,[39] they stated that in the postmenopausal women, the increased fat accumulation, resulting in increased release of free fatty acids into the circulation and excessive free fatty acids provide substrate for hepatic triglyceride and triglyceride rich lipoprotein production.[43]

Furthermore, the ratio between TG and HDL-C was also estimated in post -menopausal women. It was found that TG/HDL-C ratio (atherogenic index) in postmenopausal women with CVD was higher than in the postmenopausal women without CVD. Since increased TG/HDL-C ratio is considered as independent risk factor for CVD,[44, 45] therefore our result may throw light on the possibility of using this ratio in predicting CVD which is more common among postmenopausal women. The importance of TG/HDL-C ratio in CVD risk assessment has been established by previous study. [46]

In the present study, serum RBP-4 correlate positively with TC, TG and TG/HDL-C ratio in postmenopausal women with CVD. Our results are in line with previous findings.[3,47,48] It was suggested that RBP-4 in postmenopausal women with CVD might have a direct role in the progression of lipogenesis by increasing the expression of the gene encoding fatty acid synthesis (FASN) in adipose tissue. [49]

Conclusion:

RBP-4 is significantly elevated in postmenopausal women with CVD as compared to postmenopausal women without CVD. RBP-4 is positively correlated with lipids and HOMA-IR in postmenopausal women with CVD. It affects glucose and lipid homeostasis and contributes to the onset of IR which may play a role in the development of CVD. RBP-4 might serve as a novel biomarker of CVD.

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