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Relationship of serum novel adipokine chemerin levels with body composition, insulin resistance, dyslipidemia and diabesity in Saudi women

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Abstract. – OBJECTIVE: Chemerin is believed to be a mediator for the adipose tissue inflammation that occurs in obesity. The present study compared chemerin levels between healthy and type 2 diabetic women matched for age and body composition. We also aimed to assess the relationship of serum chemerin levels with body composition, insulin resistance, dyslipidemia, and diabesity.

PATIENTS AND METHODS: This observational case-control study was conducted at the Departments of Physiology and Medicine, Saud University Riyadh, Saudi Arabia, from September 2013 to April 2014. A total of 100 subjects were recruited, including 51 adult diabetic females, and a control group consisting of 49 healthy females. Finally, 80 subjects were selected as per inclusion criteria. In the finally selected group, 45 of were type 2 diabetics and 35 were healthy subjects matched for age, body mass index (BMI) and body composition with age ranging between 30-65 years. Body composition analysis was estimated using bioelectrical impendence analyzer. Fasting venous blood samples were analyzed for glycemic markers, lipids, and chemerin. Insulin resistance and sensitivity indices were calculated by HOMA-IR and QUICKI using standard formulas.

RESULTS: The two groups were matched for age, BMI, body fat percentage (BF%), basal metabolic rate (BMR), truncal fat and waist hip ratio (WHR). Serum chemerin levels were higher in diabetics than controls (p=0.001). Systolic blood pressure, weight, fat mass and visceral fat were found to be significantly higher in diabetics when compared to controls. Fasting blood glucose (FBG), glycosylated hemoglobin (HbA1c), low-density lipoprotein (LDL), triglycerides (TG), insulin and HOMA-IR were significantly higher in diabetics compared to controls. While QUICKI and HDL were significantly lower in diabetics compared to controls. Chemerin levels correlated positively with age (r=0.300, p=0.007), waist hip ratio (r=0.250, p=0.026), weight (r=0.270, p=0.016), BMI (r=0.334, p=0.003), BF% (r=0.325, p=0.003), fat mass (r=0.250, p=0.026), visceral fat (r=0.356, p=0.001), truncal fat mass (r=0.245, p=0.030), truncal fat % (r=0.249, p=0.027), serum basal insulin levels (r=0.354, p=0.001) and HOMA IR (0.275, p=0.015), while it correlated inversely with QUICKI (r=-0.283*, p=0.012). In multiple linear regression analysis age (r=0.236, p=0.023), BF% (r=0.265, p=0.014) and basal insulin levels (r=0.265, p=0.014) were independent predictors of chemerin.

CONCLUSIONS: Serum chemerin levels are elevated in patients with type 2 DM compared to healthy control subjects and are positively correlated with adiposity and Insulin resistance in patients with type 2 DM.

Key Words

Chemerin, HOMA-IR, Type 2 diabetes mellitus, Body composition.

Abbreviations

Body mass index (BMI), homeostasis model assessment-estimated insulin resistance HOMA-IR and Quantitative insulin sensitivity check index (QUICKI), body fat percentage (BF%), basal metabolic rate (BMR), waist hip ratio (WHR), Fasting blood glucose (FBG), glycosylated hemoglobin (HbA1c), low density lipoprotein (LDL), triglycerides (TG), high density lipoprotein (HDL), type-2 diabetes mellitus (T2DM), coronary artery disease (CAD), Bioelectrical impendence analysis (BIA), G2H: Post Prandial (2 Hour) Glucose.

Introduction

Obesity and type-2 diabetes mellitus (T2DM) are related to dysregulation of adipokines. Recent researches have shown that novel adipokine chemerin is involved in regulation of inflammation,

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adipogenesis and glucose metabolism by functioning as an autocrine, paracrine and endocrine signaling molecule[1]. Data from an experimental study on human inflammatory fluids indicated that chemerin serves as a potent chemoattractant when acting as a ligand on cells expressing Chemerin receptors. Reports also identified chemerin as a potent chemoattractant of immature dendritic cells and macrophages[2]. In 2007, chemerin was officially identified as a novel adipokine. A study confirmed that human white adipose tissue had high expression of both chemerin and its receptor CMKLR1 (chemokine-like receptorl), confirming that they serve as a primary source of chemerin. Furthermore, Chemerin stimulates lipolysis by direct activation of hormone-sensitive lipase in mature white adipose cells[3,4]. Chemerin levels have been proven to have a direct positive correlation with adiposity indices. It has been linked with visceral obesity and resultant cardiovascular disease[5]. In another report[6] chemerin levels did not differ between normal subjects and type 2 DM. However, it correlated with BMI, blood pressure and triglycerides. Takahashi et al[7] observed that chemerin was significantly low in patients with T2DM compared with control subjects. The chemerin levels were significantly higher in male than in female control subjects. Chemerin influences adipose tissue development, inflammation, and glucose homeostasis and may contribute to the metabolic derangement characteristic of obesity and obesity-related diseases. Disruption of chemerin gene is associated with glucose intolerant and decreased glucose-stimulated insulin secretion as well as decreased skeletal muscle and white adipose tissue glucose uptake[8]. Moreover, it may be involved in cross-talk between adipose tissue and skeletal muscle contributing to the negative relationship between obesity and insulin sensitivity[9]. Gender- and adipose tissue-specific differences have been observed in chemerin mRNA expression levels, with expression significantly higher in women than men and in subcutaneous than visceral adipose tissue[10]. Chemerin is altered in prediabetic states also, suggesting that it may be an early pathogenic event is glucose gerangements[11]. Elevated serum chemerin levels could be considered as an independent predictive marker of the presence and severity of CAD[12-14]. It is reduced significantly by long-term endurance training programs in obese individuals[15].

Studying its link to diabetes and glucose intolerance has shown inconsistent results. However, there are still questions to be answered regarding this relationship. Having known that chemerin is affected by body adiposity and gender, we considered it appropriate to study it in a gender-specific population which is matched for body composition in addition to weight, height, BMI and WHR and BMR to show an independent association of chemerin with type 2 diabetes mellitus. The present study aimed to compare chemerin levels between healthy and type 2 diabetic women. We also aimed to assess the relationship of serum chemerin levels with body composition, insulin resistance, dyslipidemia and diabesity.

Patients and Methods

This observational case-control study was conducted at the Departments of Physiology and Medicine, Saud University Riyadh, Saudi Arabia, from September 2013 to April 2014. The Patients were recruited from the medical clinics at King Khalid University Hospital. The Institutional Review Board approved the study. All patients were informed about the required procedures and they were recruited after they signed the consent form.

A total of 100 subjects were recruited, including 51 adult diabetic females, and a control group consisting of 49 healthy females. Finally, 80 subjects were selected as per inclusion criteria. In the finally selected group, 45 were type 2 diabetics and 35 were healthy subjects matched for age, BMI, BF%, BMR, truncal fat and WHR with age ranging between 30-65 years. Type 2 diabetic patients were diagnosed with T2DM diabetes of at least one year duration according to the American Diabetes Association Guidelines[16]. All the patients were in stable metabolic condition. Patients with pregnancy and pre-diabetic states having impaired fasting glucose were excluded. Also, patients having any disease that could affect the metabolic status of the body and the parameters studied. For example, nephrotic syndrome, acute or chronic renal failure, thyroid disorders, acute infections, stroke, diabetic ketoacidosis and non-ketotic hyperosmolar coma were all excluded.

A detailed history was obtained from each patient. It included their diet, exercise habits, medications, smoking and any history of hypertension or dyslipidemia. Blood pressure was recorded in mmHg from the patients' left arm, in sitting position. Body composition was performed by Bioelectrical impendence analysis (BIA) using TINITA BC 418, IL, USA. Parameters recorded were

muscles mass, fat mass, body fat composition and fat distribution. The TINITA body fat analyzer is segmental impedance device which measures the voltage drop in the upper and lower body by using eight points of tactile electrodes.

Fasting 10 ml venous blood samples were collected after 10-12 hours of overnight fast. After centrifugation, plasma and serum were separated and stored at -70°C. Blood samples were analyzed for fasting blood glucose (FBG), total cholesterol (TC), Triglycerides (TG), high-density lipoprotein (HDL), low-density lipoprotein (LDL), as well as urea and creatinine by automated analyzers. Glycosylated hemoglobin (HbA1c) was analyzed by ion exchange resin separation method. Chemerin was measured by standard sandwich ELISA (Mediagnost, Reutlingen, Germany). Serum Insulin levels were measured by the chemiluminescence assay using the Cobas 8000 machine. Insulin resistance was calculated by Homeostasis model assessment of Insulin resistance (HOMA-IR) using the formula HOMA-IR = [FPI (mU/L) × FPG (mmol/L)]/22.5[17] and QUICKIE to calculate insulin sensitivity QUICKIE=1/log (FBS*FSI)[18].

Statistical Analysis

Statistical Package for Social Sciences (SPSS version 20) analyzed the data obtained. Mean and standard deviation were used for descriptive data analysis of the study sample. Independent Student *t*-test was used to analyze parametric variables while Mann-Whitney' test was used for the non-parametric variables. Spearman's correlations test was done for chemerin with univariate descriptive characteristics. To further understand the correlations with chemerin, a stepwise multiple regression analysis was conducted to examine which variables have the power to independently predict chemerin. Based on colinearity and variance inflation factors, some of the variables which were strongly correlated were removed and stepwise regression models were run to see the final significant predictors. A p-value of < 0.05 was considered to be statistically significant.

Results

Table I shows a comparison of the descriptive characteristics and body composition between control and diabetic patients. The two groups were matched for age, BMI, body fat percentage (BF%), basal metabolic rate (BMR), truncal fat and waist hip ratio (WHR). Systolic blood pressure, weight, fat mass and visceral fat were found to be significantly higher in diabetics when compared to controls. Table II compares glycemic status and lipid profile between diabetics and controls. Fasting blood glucose (FBG), glycosylated hemoglobin (HbA1c), low-density lipoprotein (LDL), triglycerides (TG), insulin and HOMA-IR were significantly higher in

Table I. Comparison of descriptive characteristics and body composition between control and diabetic patients.

	Control N=35	Diabetics N=45	*p*-value
Age	50.09 ± 7.33	55.53 ± 6.15	0.051
Pulse	79.11 ± 8.86	77.16 ±16.37	0.525
WHR	0.84 ± 0.11	0.85 ± 0.06	0.400
SBP	128.54 ± 17.98	148.16 ± 18.99	0.001
DBP	80.37 ± 11.11	83.93 ±12.95	0.198
Height (cm)	150.71 ± 21.70	155.04 ± 5.25	0.200
Weight (kg)	76.49 ± 14.55	82.15 ±12.99	0.040
BMI	32.08 ± 5.61	34.14 ± 5.48	0.104
BMR (kcal)	1367.77±161.00	1423.51 ± 143.60	0.106
BF%	41.13 ± 7.34	43.34 ± 4.99	0.113
Fat mass kg	31.61 ± 11.26	36.15 ± 9.55	0.045
Free fat mass (kg)	43.11± 7.02	45.31 ± 6.34	0.145
TBW kg	31.87 ± 4.37	34.03 ± 3.96	0.023
Visceral fat rating	10.12 ± 3.52	11.76 ± 2.85	0.025
Trunk fat mass (kg)	15.93 ± 5.04	17.40 ± 4.71	0.186
Trunk FFM	24.70 ± 2.65	25.76 ± 2.28	0.059
Trunk predicted muscle mass	23.61 ± 2.52	24.63 ± 2.17	0.057

p-values calculated by Mann-Whitney are followed by *, all other parameters were calculated by Student's t-test
WHR (Waist hip ratio), SBP: Systolic Blood Pressure, DBP: Diastolic Blood Pressure, BMI: Body Mass Index, BMR: Basal Metabolic Rate, TBW: Total Body Water, FFM: Free Fat Mass

Table II. Comparison of glycemic status and lipid profile between control and diabetic subjects (Mean ± SD).

	Control N=35	Diabetics N=45	*p*-value
G2H mmol/L	6.42 ± 1.34	13.43 ± 5.94	0.013
FBG mmol/L	5.09 ± 0.50	9.09 ± 3.75	<0.001
HbA1C %	5.34 ± 0.36	8.30 ±1.93	<0.001
Total cholesterol mmol/L	5.00 ± 0.57	4.72 ± 0.91	0.112
Triglycerides mmol/L	1.21 ± 0.70	1.46 ± .55	0.018
LDL mmol/L	2.73 ± 0.61	3.06 ± 0.83	0.057
HDL mmol/L	1.45 ± 0.34	1.31 ± 0.45	0.018
Insulin (µIUL)	12.14 ± 5.58	16.95 ± 8.66	0.014
Chemerin (ng/mL)	256.09 ± 57.01	305.63 ± 73.66	0.001*
HOMAIR	2.73 ± 1.18	6.50 ± 4.07	0.001
QUICKIE	0.33 ± 0.02	0.30 ± 0.03	<0.001

p-values calculated by Mann-Whitney are followed by * - all others by Student T-Test
G2H: Post Prandial (2 Hour) Glucose, FBG: Fasting Blood Glucose, LDL: Low Density Lipoprotein, HDL: High Density Lipoprotein, HOMA-IR: Homeostasis model assessment of Insulin resistance.

diabetics compared to controls. While QUICKIE and HDL were significantly lower in diabetics compared to controls. Serum chemerin levels were higher in diabetics than controls (p=0.001) while the difference for chemerin levels between good and poor glycemic subjects was non-significant (Figure 1). Table III shows Spearman's correlation coefficients of chemerin with body composition indices and other metabolic variables. Chemerin levels correlated positively with age (r=0.300, p=0.007), waist hip ratio (r=0.250, p=0.026), weight (r=0.270, p=0.016), BMI (r=0.334, p=0.003), BF% (r=0.325, p=0.003), fat mass (r=0.250, p=0.026), visceral fat (r=0.356, p=0.001),truncal fat mass (r=0.245, p=0.030), truncal fat % (r=0.249, p=0.027), serum basal insulin levels (r=0.354, p= 0.001) and HOMA IR (0.275, p=0.015), while it correlated inversely with QUICKI (r=-0.283*, p=0.012). We performed backward multiple linear regression analysis to find independent predictors of chemerin. Many of the variables that were significantly correlated with chemerin in multiple regression models became non-significant. It was observed that age (r=0.236, p=0.023), BF% (r=0.265, p=0.014) and basal insulin levels (r=0.265, p=0.014) were independent predictors of chemerin (Table IV). Table V shows the use of medications in patients with T2DM.

Discussion

Our study aimed to see the relationship between the adipokine chemerin, body composition indices, insulin resistance, dyslipidemia and diabesity within a population of Arab female type 2 diabetics. These variables included: BMI, waist-hip ratio,

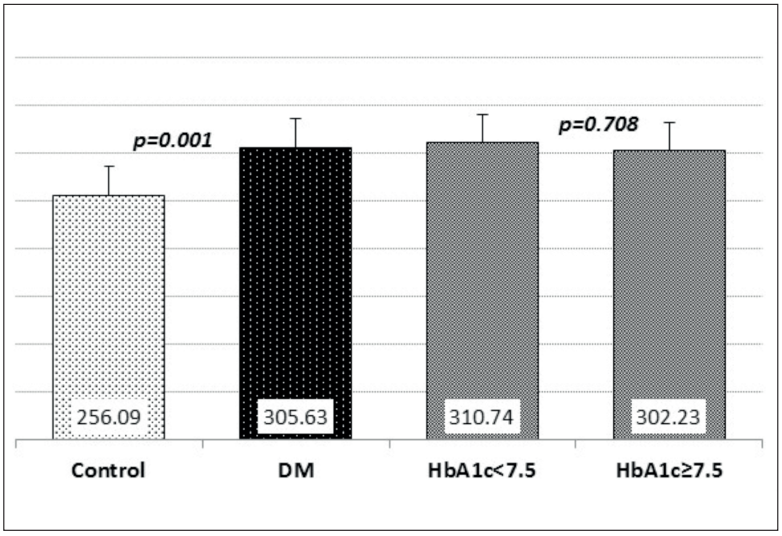

Figure 1. Comparison of chemerin levels (ng/mL) between control and T2DM patients including comparison of Chemerin levels in diabetic patients with good (HbA1c < 7.5) and poor (HbA1c ≥ 7.5) glycemic control.

Table III. Spearman's correlation coefficients of chemerin with body composition and metabolic variables.

	Correlation Coefficient	Confidence Interval Lower limits	Confidence Interval Upper limits	*p*-value
Age	.300**	.094	.488	.007
WHR	.250*	.017	.455	.026
SBP	.270*	.045	.498	.016
DBP	.278*	.052	.489	.013
Height cm	-.212	-.416	.008	.060
Weight kg	.270*	.044	.495	.016
BMI	.334**	.110	.558	.003
BMR kcal	.167	-.053	.401	.141
BF%	.325**	.102	.547	.003
Fat mass kg	.250*	.015	.491	.026
Fat free mass kg	.088	-.123	.323	.439
TBW kg	.133	-.079	.372	.244
Visceral fat rating	.356**	.125	.566	.001
Trunk fat	.249*	.030	.484	.027
Trunk fat mass	.245*	.018	.484	.030
Trunk FFM	.097	-.114	.344	.394
FBG	.134	-.106	.357	.242
HbA1C	.174	-.070	.408	.127
Total cholesterol	-.115	-.332	.098	.315
Triglycerides	.148	-.085	.358	.197
LDL	-.232*	-.421	-.033	.041
HDL	.018	-.212	.250	.878
Insulin (µIUL)	.354**	.026	.469	.001
HOMAIR	.275*	-.003	.118	.015
QUICKIE	-.283*	-.474	.009	.012

BMI, body mass index; % Fat, percent fat mass; HOMA-IR, homeostasis model assessment of insulin resistance; FBG, fasting blood glucose; TC, total cholesterol; TG, Triglycerides; LDL, Low density Lipoprotein; HDL, High density lipoprotein; Lp(a), Lipoprotein(a); high-sensitivity C-reactive protein (hsCRP)

body fat composition, lipid profile, serum insulin as well as insulin resistance and sensitivity. Many of these parameters showed a positive correlation with serum chemerin levels. Chemerin was found to be significantly higher in diabetic patients compared to control subjects. Recent papers have reviewed the possibility of a link between chemerin and diabetes. Most of these publications have focused on multiple components of metabolic syndrome[19,20]. As an adipokine, chemerin is affected by these components (obesity, dyslipidemia and high blood pressure), influencing the results of the aforementioned studies. In fact, a previously published article stated that chemerin levels increased with BMI among non-diabetic subjects. On the other hand, chemerin was not found to be different between obese and non-obese diabetic patients[21]. Weigert et al[21] reported elevated levels of chemerin in obesity and T2DM and was significantly associated with inflammatory marker high sensitivity C-reactive protein. Chemerin positively correlated with leptin, resistin and C-reactive protein (CRP) in their study. We also observed a positive association of chemerin with HOMA-IR and basal insulin levels[15]. Our aim towards finding a more independent relationship with type-2 diabetes mellitus showed that, FBG and HBA1C were not correlated with chemerin levels. However, in multiple regression analysis, basal insulin levels were identified as a significant predictor of

Table IV. Multiple linear regression analysis expressing independent predictors of serum chemerin levels.

	Beta standardized coefficients	t-values	*p*-value
BF%	0.265	2.530	0.014
Age	0.236	2.316	0.023
Basal Insulin (µIUL)	0.265	2.532	0.014

Table V. Use of medications in patients with T2DM (No. = number).

Anti-diabetic medication	No. (%)
• Biguanides	7 (15.5)
• Sulphonylureas	14 (31.1)
• Glinides	5 (11.1)
• Alpha-glucosidase inhibitors	12 (26.6)
• Thiazolidinedione	13 (28.8)
Lipid lowering medication	12 (26.6)
Antihypertensive medication	21 (46.6)

chemerin levels. This suggests that chemerin in these diabetic patients was elevated probably due to other significant factors, rather than elevated glucose levels. Moreover, supporting these results were similar chemerin levels in diabetics with high and low HbA1C, suggesting that chemerin is not directly affected by the glycemic control in diabetic individuals. It has been reported that giving recombinant chemerin to animals did not affect blood sugar levels[22].

Chemerin correlated positively with insulin in diabetic patients as an independent factor in our study. Insulin resistance and sensitivity (calculated using HOMA-IR and QUICKIE, respectively) also showed a significant correlation with chemerin. A study conducted on mice in which chemerin expression was disrupted by adenovirus-delivered short hairpin showed a decrease in other factors and adipokines that influence insulin sensitivity, suggesting chemerin to be an indirect cause of insulin resistance. Moreover, another work[9] reported a decrease in insulin-stimulated glucose uptake in skeletal muscle cells following chemerin supplementation. This consistency supports the proposed theory that chemerin is involved in the pathophysiology of insulin resistance. Stefanov et al[15] reported that chemerin correlated positively with total cholesterol, triglycerides, fasting insulin, HOMA-IR, systolic blood pressure and highly sensitive C-reactive protein, while it was an independent determinant of HOMA-IR.

Previous researches[9,12] have documented a direct correlation between chemerin and adiposity, which was measured by methods such as WHR ratio and BMI. This is in line with our results showing a significant relationship of chemerin levels with WHR and BMI. Additionally, we also observed a significant relationship of chemerin with adiposity indices like BF%, fat mass and visceral fat.

Studies[23,24,25] on adipokines and their potential effects in human obesity and type 2 DM have implicated them in the pathogenesis of metabolic syndrome and increased cardiovascular risk. We have already reported significant association among cardiovascular risk markers, adiponectin, resistin, BMI, waist hip ratio and BF% in the adult Saudi population. Shin et al[5] showed that abdominal visceral fat, blood pressure and lipid profile were significantly associated with serum chemerin levels. They used in their work CT imaging which is very costly and time-consuming. Our study was gender specific and confined to the Middle Eastern origin. Possible limitations of our study were relatively small sample size and its cross-sectional design. Future prospective studies are needed with a large sample size to explore the true links between chemerin, adiposity and cardiovascular risk.

Conclusions

Serum chemerin levels are elevated in patients with type 2 DM compared to healthy control subjects and are positively correlated with adiposity and Insulin resistance in patients with type 2 DM. Our study indicates that BF% may have a key role in the prediction of the increased cardiometabolic risk in Type 2 DM. The inclusion of body composition analysis together with morbidity evaluation in the routine medical practice for the diagnosis and the management decision-making is desirable.

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Conflict of Interests

The Authors declare that they have no conflict of interests.

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