

The unbalance of adiponectin oligomers, RvE1 and chemerin levels are associate with increase of adiposopathy *status* and insulin resistance in obesity

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Abstract

Objective: The aim was to establish if the balance adiponectin-oligomers, resolvin-E1 and chemerin levels could contribute to the insulin resistance (IR) setting of subjects with obesity, based on their serum levels and its relationship with inflammatory markers, metabolic profile and adiposopathy *status*.

Methods: This study included 230 individuals, classified according to World Health Organization criteria by body mass index (BMI) kg/m² in two groups: without-obesity (from 18.5 to 29.9) and with-obesity (from 30.0 to 39.9). Body fat mass distribution, metabolic and inflammatory markers were measured by anthropometric, enzymatic and immuno-turbidimetry methods, respectively. Serum insulin, resolvin-E1, chemerin, and adiponectin-oligomers were evaluating by ELISA method. Analysis performed were correlations IR-indexes with adiposity, receiver operating characteristic (ROC) curves and the adiponectin-oligomers, resolvin-E1 and chemerin tertiles.

Results: Subjects' with-obesity showed adiposopathy *status*, characterized by metabolic dysregulation and a subclinical inflammatory profile. They presented higher levels ($\bar{x} \pm SD$, ng/mL) of resolvin-E1 (1227 \pm 668 *versus* 909 \pm 769, $P=0.017$), chemerin (91 \pm 31 *versus* 79 \pm 23, $P=0.013$) and LMW-Adiponectin (2257 \pm 797 *versus* 1030 \pm 1055, $P=0.011$), whereas HMW-Adiponectin was lower (2470 \pm 1095 *versus* 3236 \pm 1848, $P=0.010$), compared to the without-obesity individuals. Individuals' with-obesity also displayed positive correlation of IR markers (*rho* from 0.163 to 0.479) along body fat measurements, metabolic and inflammation profiles. Moreover, a negative correlation of HMW-Adiponectin (*rho* from -0.564 to -0.214) with body fat measurements, metabolic and inflammation profiles. IR-indexes, LMW-Adiponectin and resolvin-E1/chemerin relationship showed differences between groups' with-obesity and without-obesity, but not with gender. ROC curves shown potential ability of the LMW-Adiponectin levels to differentiate IR from non-IR individuals, with AUC of 0.815, $P<0.0001$ (95% CI: 0.726-0.903).

Conclusion: The present study shown that LMW-Adiponectin-resolvinE1-chemerin serum unbalance establishes a specific relationship with adiposopathy in individuals with obesity, which could be a way to identify risk factors in early stages of IR.

Introduction

Obesity is characterizing by high storage and irregular distribution of white adipose tissue (WAT). It has dysmetabolic and subclinical inflammatory process with increase synthesis of adipokines and chemokines, these processes develop into an adiposopathy *status* (pathological function of WAT) that causes insulin resistance (IR) [1-4].

Inside of WAT, the interaction between immune cells and adipocytes favors releasing adiponectin and chemerin that stimulate,

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themselves or surrounded cells to further produce inflammatory mediators [5,6]. While, healing and pro-resolve processes are triggered by the production of lipid mediators (resolvins), through mechanisms of inflammation/resolution [7,8].

For instance, while resolvin-E1 (RvE1) is generated in response to inflammation by the interaction of endothelial cells with neutrophil leukocyte, chemerin has both active and inactive effects by an autocrine/paracrine mechanism, it plays an important role in adipocyte's differentiation [9-12]. Also, adiponectin is synthesized by WAT and suffers posttranscriptional changes, on three oligomeric forms: trimer (LMW), hexamer (MMW), and high (HMW) molecular weight. These variations display functional differences according on their levels and exert distinct biological effects and tissue-selective functions [13-15].

Although, RvE1 and chemerin are different in biochemical nature, with antagonistic properties, both shares the same receptor, CMKLR1 [16]. In obesity, the inflammatory response [17] promote a chronic subclinical inflammation and leads to the development of IR [6], it was linked with up-regulation of CMKLR1 expression which degenerates the signaling pathway when one (RvE1) or another (chemerin) ligand binds [1,18].

In the context of obesity, we search establish the balance of oligomeric adiponectin, RvE1/chemerin, which could better characterize the IR setting, based on their serum levels and relationship with inflammatory markers, metabolic profile and adiposopathy *status*.

Patients and methods

Study subjects

In this cross-sectional study 230 individuals (63.9% female) who had 20 to 59 years old, were eligible from general population. They were classify based on World Health Organization criteria by body mass index (BMI) in two groups as follows: study group (with-obesity $n = 77$) BMI from 30.0 to 39.9 kg/m² and comparison group (without-obesity $n = 153$) BMI from 18.5 to 29.9 kg/m².

Ethics conduct

Before the enrollment, all individuals gave their signature in a consent document after they were informed about to participate in the study. The consent form followed both, the Helsinki declaration and the institutional review boards' committees (Guadalajara University) guidelines, which has ensured appropriate ethical and conduct of biosecurity.

Clinical assessments

Physical examination and medical history were achieved from all participants, whom to answer a structured questionnaire as prerequisite to evaluate demographical and clinical variables; personal and family medical history were obtain. To enforce the quality of the groups, the questionnaire included questions about current health *status*, and whether they had body weight change in the last three weeks, if someone had an affirmative answer to the later these individuals were excluded from the study. The individuals who had pharmacological treatment, cardiovascular disease or previous diagnosis of metabolic diseases such as hypertension or diabetes, were also exclude.

Subjects' distribution and storage of body fat and status of adiposity

We evaluated the following measurements:

Storage and distribution of body fat: Body weight (kg), total body fat mass and trunk fat mass [absolute (kg) and relative (%)], were determined by using bioelectrical impedance analysis, (TANITA BC-418 segmental body composition analyzer. Tokyo, JPN) to the nearest 0.1 kg; five (abdominal, bicipital, tricipital, subscapular and suprailiac) skinfold thickness was obtain on the right side of the body by using a Harpenden skinfold caliper (opened 80 mm and precision of ± 0.2 mm, constant pressure: 10 g/mm²; Holtain Ltd. Crosswell, Crymych, Pembs., SA41 3UF, UK).

Body dimensions (cm): Height was measure to the nearest 1 mm by using a stadiometer (Seca GmbH & Co. KG. Hamburg, Germany), waist circumference (WC), hip circumference (HC) [19] and coronal abdominal diameter, were measured by using an anthropometric fiberglass tape (GULICK' length 0 - 180 cm precision ± 0.1 ; USA). At the level of the iliac crest (L4-L5) sagittal abdominal diameter was measured using a sliding-beam, abdominal caliper (precision ± 0.1 cm, Holtain Ltd. Crosswell, Crymych, Pembs, SA41 3UF, UK.) with the patient lying in a supine position in the examination table [20].

Status of adiposity: To determine obesity and adiposity indexes the following math calculations were used: BMI (kg/m²) = body weight (kg)/height (m)². Body fat ratio (kg/m²) = total body fat mass (kg)/height (m)². Waist to height ratio = WC (cm) /height (cm) [21]. Waist-hip ratio = WC (cm) /HC (cm). Conicity index = WC (m)/0.109^{1/3} (weight (kg)/height (m)). Total adipose area (cm²) = WC²/4 π Visceral area (cm²) = π (WC/2 π - abdominal skinfold)². Subcutaneous abdominal area (cm²) = total adipose area - visceral area [22]. Visceral adiposity index: for females, = (WC/36.58 + (1.896BMI))6(TG/0.81)6(1.52/HDLc) and males = (WC/39.68 + (1.886BMI)) 6(TG/1.03)6(1.31/HDLc) [23]. Abdominal volume index (L) = [2(WC² + 0.7 (WC - HC)²]/1000 [24].

All these measurements were carrying out by the same anthropometrist in duplicate following the procedures recommended by anthropometric indicators measurement guide.

Metabolic and inflammatory markers

Individuals included in the study were fasting 12 hours before blood samples were taken, allowing them to clot at room temperature, then were centrifuged at 1509 RCF (Rotanta 460R, Andreas Hettich GmbH & Co. KG.) for 10 minutes at 20°C. Serum was collected and stored at -80°C until further analysis.

With routine enzymatic, immuno-turbidimetry and colorimetric methods we quantified the serum concentration (mg/dL) of: fasting glucose, triglycerides (TG), total cholesterol (TC), HDLc, LDLc and VLDLc (with the Friedewald formula) [25], (high, low and very low density lipoprotein cholesterol, respectively), small dense LDLc (sdLDLc), apolipoproteins A-1 (Apo A-1) and B (Apo B), and nonesterified fatty acids (NEFAs mmol/L). High sensitivity C reactive protein (limit of detection of 0.15 mg/L) and complement component 3 (C3), (Randox Laboratories 55 Diamond Road, Crumlin Co. Antrim, Northern Ireland UK). Erythrocyte sedimentation rate (ESR, mm/h) by Wintrobe method [26].

Based on the lipid profile measurements we calculate the following cholesterol ratios: non-sdLDLc = LDLc - sdLDLc (mg/dL), %sdLDLc, sdLDLc/HDLc, TG/HDLc, TC/HDLc, LDLc/HDLc, and Apo B/ Apo A-1. Additionally, follow insulin indexes were estimating: the homeostasis model assessment (HOMA)-IR = [fasting serum glucose mg/dL \times (fasting serum insulin μ IU/mL)/405], Quantitative insulin sensitivity check index, QUICKI = [1/(log(fasting serum insulin μ IU/mL)+log(fasting glucose, mg/dL))], HOMA-adiponectin (AD) = [fasting

glucose (mmol/L) \times fasting serum insulin μ IU/mL)/[22.5 \times fasting adiponectin (μ g/mL)], HOMA-B = 20 \times insulin (μ IU/mL)/[glucose (mmol/L) - 3.5] and basal disposition index (DI), was calculate as HOMA-B/HOMA-IR [27,28].

Adiponectin oligomers, RvE1 and chemerin serum levels techniques

Following the manufactures instructions of commercial the quantitative enzyme-linked immunoassay technique (ELISA) kits were determined soluble levels of insulin (μ IU/mL), oligomers (HMW, MMW and LMW) and total adiponectin (ng/mL) (80-INSHU-E01.1, 47-ADPHU-E01. ALPCO 26-G Keewaydin Drive, Salem, NH 03079, respectively), chemerin (ng/mL) (DCHM00 R&D Systems Inc. 614 McKinley Place NE, Minneapolis, MN 55413, USA), and RvE1 (μ g/mL) (MBS286046. My BioSource, Inc. P.O. Box 153308 San Diego, CA 92195-3308 USA). The sensitivity of the assays are 0.399 μ IU/mL, 0.019 ng/mL, 4.13 pg/mL and 0.1 μ g/mL, respectively.

Based on biomarkers criteria, RvE1-chemerin relationship were perform as follows: RvE1/chemerin index = $[1 + \log_{10}(\text{RvE1 (ng/mL)}) - \log_{10}(\text{chemerin (ng/mL)})]$; RvE1/chemerin ratio = RvE1 (ng/mL)/chemerin (ng/mL).

Statistical analysis

Data were analyzed with statistical software packages SPSS v24 (IBM Inc., Chicago, IL, USA) and Graph-Pad Prism v6.01 (2014 Inc. 2236 Beach Avenue Jolla, CA 92037). The normal distribution of clinical and laboratory variables was evaluated with Z Kolmogorov-Smirnov test. Results were given as mean \pm SD, minimum and maximum or percentages.

Detailed test by tertiles was perform as follows: describing the first tertile as low levels, second tertile as intermediate levels, and third tertile as high levels. The clinical and laboratory characteristics of study groups were compared with the unpaired Student's *t*-test or ANOVA one-way test and Tukey *post hoc* test.

Data from serum concentrations of adiponectin-oligomers, RvE1, chemerin, IR indexes, metabolic and inflammatory markers assessment, and adiposity variables were subject to Spearman correlation tests. Receiver operating characteristic (ROC) curve was generate for LMW-Adiponectin levels and HOMA-AD and the area under curve (AUC) value and 95% confidence intervals (CI) were calculated to determine the specificity and sensitivity for IR or adiposopathy *status*. A two-tailed *P* value < 0.05 was consider statistically significant.

Results

Subjects with obesity showed adiposopathy status (high body dimensions and storage of body fat, and pathological distribution of adiposity)

Clinical characteristics and measurements of storage and distribution of body fat in study participants by gender are show in Table 1.

In this study, the frequency of individuals with obesity was 33%, they were individuals which showed increase in body fat storage (mean 19.3 kg), body dimensions, *status* of adiposity, and irregular abdominal fat distribution, while were similar in age with the without-obesity group. This anthropometric evaluation displayed those individuals with-obesity presented 2.02 times more quantity and 12.7% more in proportion of body fat (data no shown) compared with the without-

obesity group. It is important to note that in the trunk there is more quantity of the body fat stored (Table 1).

Group with-obesity present metabolic dysregulation and subclinical inflammatory profile

Group with-obesity show a lipids profile with metabolic dysregulation, it is important to mention that also presented higher insulin and lipids indexes compared to without-obesity group (Figure 1 and Figure 2C).

When inflammation markers were taken in consideration, group with-obesity present subclinical low-grade inflammation, represented by higher levels compared with group without-obesity of C reactive protein ($\bar{x} = 2.51 \text{ mg/L} \pm 3.26$ *versus* $5.65 \text{ mg/L} \pm 4.64$, $P < 0.0001$), C3 $\times \times = 194 \text{ mg/dL} \pm 73$ *versus* $251 \text{ mg/dL} \pm 95$, $P < 0.0001$) and ESR ($\bar{x} = 14.6 \text{ mm/h} \pm 10.0$ *versus* $19.5 \text{ mm/h} \pm 11.7$, $P = 0.002$), respectively.

Individuals' with-obesity presented high levels of RvE1, chemerin and adiponectin oligomers

Group with-obesity was presented higher levels of RvE1 compared with group without-obesity. Same fashion was observed with chemerin levels, and LMW-Adiponectin, whereas HMW-Adiponectin shown lower levels and RvE1-chemerin index and ratio were higher in obesity than without-obesity group (Figure 2A and B).

Unlike way was observe in without-obesity individuals when gender was acquiring in consideration, females shown higher levels than males (Figure 2D and E). Despite the fact insulin indexes were higher in the group with-obesity while in males *versus* females did not shown differences, with exception of QUIKI index (Figure 2C and F).

Resolvin E1, chemerin and adiponectin oligomers levels unbalance were associated with adiposopathy status

In whole group RvE1, chemerin and LMW-Adiponectin levels and HOMA-AD displayed positive correlations along body fat measurements, metabolic profile and inflammatory markers, even though HMW-Adiponectin correlated negatively, with the following pattern (Table 2)

- We observe correlations of levels of RvE1, chemerin and LMW-Adiponectin (positively, *rho* from 17.1 to 47.9) and HMW-Adiponectin (negatively, *rho* from -56.4 to -21.4) with IR indexes, trunk fat mass proportion, total adipose area and abdominal volume index, while HDLc and apolipoprotein A-1 correlate positively.
- Chemerin and LMW-Adiponectin levels displayed correlations in similar way along body fat measurements.
- The body dimensions, metabolic and inflammatory markers alternately were correlate with levels of RvE1 or chemerin and HMW-Adiponectin, it is when RvE1 correlated the chemerin and HMW-Adiponectin levels no shown correlation.
- We note that RvE1, chemerin and HMW-Adiponectin each correlate with a different inflammation marker.
- LMW-Adiponectin and HOMA-AD displayed positive correlations along body fat measurements and inflammatory markers, but not with metabolic profile.

Additionally, we performed multiple regression analysis, where we normalized (ln-transform) data and found that waist and hip circumferences, sagittal abdominal diameter and conicity index predict 14.5% of the variation in chemerin levels (Table 3). The model adjusted

Table 1. Clinical characteristics, and storage measurements and body fat distribution of study groups

Gender (n)	Study groups			
	Male (83)		Female (147)	
Obesity [BMI (kg/m ²)]	Without [19.6 – 29.4] n = 61	With [30.4 – 38.1] n = 22	Without [18.7 – 29.9] n = 92	With [30.1 - 39.0] n = 55
Measurements				
Age (years)	32 ± 12	36 ± 13	33 ± 13	44 ± 9
<i>Storage of body fat</i>				
Body weight (kg)*	76.4 ± 11.0	102.8 ± 22.4	62.1 ± 10.3	90.1 ± 12.8
Total body fat mass (%)*	21.0 ± 5.9	33.4 ± 6.9	31.9 ± 6.6	43.4 ± 4.4
Total body fat mass (kg)*	16.2 ± 5.3	35.6 ± 17.2	20.5 ± 7.2	39.4 ± 8.2
Trunk fat mass (%) ^{†,‡,§,¶}	26.2 ± 11.7	34.8 ± 7.5	31.1 ± 10.6	40.2 ± 9.3
Trunk fat mass (kg) ^{†,§,¶,***}	9.5 ± 3.5	19.3 ± 7.1	9.7 ± 4.3	18.7 ± 4.7
<i>Body dimensions (cm)</i>				
Height ^{†,‡,§,¶,***}	173 ± 7	170 ± 5	159 ± 7	159 ± 5
Waist circumference ^{†,§,¶,***,††}	92.0 ± 9.3	113.0 ± 15.1	86.8 ± 11.4	112.3 ± 11.3
Hip circumference ^{§,¶,***,††}	98.6 ± 6.0	114.4 ± 12.2	99.5 ± 7.0	118.4 ± 11.3
Coronal abdominal diameter ^{†,§,¶,***,††}	38.1 ± 7.0	48.1 ± 12.3	34.4 ± 6.4	42.9 ± 10.0
Sagittal abdominal diameter ^{†,§,¶,***,††}	19.4 ± 2.5	25.3 ± 3.6	18.0 ± 2.3	24.4 ± 2.8
<i>Status of adiposity</i>				
Body fat ratio (kg/m ²)*	5.4 ± 1.8	12.0 ± 5.0	8.0 ± 2.6	15.4 ± 2.9
Waist to height ratio ^{§,¶,***,††}	0.53 ± 0.05	0.66 ± 0.07	0.54 ± 0.07	0.70 ± 0.07
Waist-hip ratio ^{†,***,††}	0.93 ± 0.06	0.98 ± 0.05	0.87 ± 0.08	0.95 ± 0.11
Conicity index ^{¶,***,††}	1.27 ± 0.08	1.34 ± 0.07	1.27 ± 0.11	1.37 ± 0.09
Total adipose area (cm ²) ^{§,¶,***,††}	680 ± 137	1035 ± 297	610 ± 155	1020 ± 211
Visceral area (cm ²)	366 ± 346	514 ± 471	322 ± 323	459 ± 458
Subcutaneous abdominal area (cm ²) ^{§,¶,***,††}	529 ± 174	756 ± 360	456 ± 190	840 ± 299
Visceral adiposity index ^{†,***,††}	4.0 ± 2.7	4.3 ± 1.5	2.5 ± 1.9	3.8 ± 2.6
Abdominal volume index (L) ^{§,¶,***,††}	17.1 ± 3.4	26.0 ± 7.4	15.5 ± 3.7	25.7 ± 5.2
<i>Body fat distribution [Skinfold thicknesses (mm)]</i>				
Abdominal ^{§,¶,***,††}	20.3 ± 7.1	27.7 ± 7.1	20.5 ± 6.1	24.3 ± 7.8
Bicipital*	6.5 ± 2.8	13.3 ± 6.9	10.1 ± 4.5	18.4 ± 6.5
Tricipital ^{†,‡,§,¶,††}	13.0 ± 4.4	22.3 ± 8.0	20.0 ± 5.1	26.2 ± 6.0
Subscapular ^{§,¶,***,††}	17.9 ± 5.3	26.9 ± 7.5	18.1 ± 6.2	29.3 ± 7.6
Suprailiac ^{§,¶,***,††}	15.6 ± 6.5	27.9 ± 9.1	17.8 ± 6.4	27.4 ± 8.0

(Data are show in $\bar{x} \pm SD$. Differences between groups by One-way ANOVA and Tuckey post Hoc, $P < 0.05$, *: Differences between all groups

[†]: Male without obesity *versus* Female without obesity, [‡]: Male with obesity *versus* Female with obesity, [§]: Male without obesity *versus* Male with obesity, [¶]: Male without obesity *versus* Female with obesity, ^{***}: Female without obesity *versus* Male with obesity, ^{††}: Female without obesity *versus* Female with obesity)

Table 2. Adiponectin oligomers, resolvin E1 and chemerin correlations

Measurements	Rho Correlation coefficient of circulating levels									
	RvE1 (ng/mL)	P	Chemerin (ng/mL)	P	HMW-Adiponectin (ng/mL)	P	LMW-Adiponectin (ng/mL)	P	HOMA-AD	P
<i>Storage of body fat (%)</i>										
Total body fat mass	0.221	0.011	0.385	0.000	0.005	NS	0.260	0.009	0.385	0.000
Trunk fat mass	0.172	0.049	0.282	0.000	-0.102	NS	0.244	0.015	0.475	0.000
<i>Body dimensions (cm)</i>										
Waist circumference	0.126	NS	0.188	0.021	-0.199	0.048	0.290	0.004	0.508	0.000
Hip circumference	0.093	NS	0.216	0.008	-0.126	NS	0.323	0.001	0.496	0.000
Sagittal abdominal diameter	0.053	NS	0.157	NS	-0.235	0.021	0.304	0.003	0.532	0.000
<i>Status of adiposity</i>										
BMI (kg/m ²)	0.107	NS	0.153	NS	-0.222	0.026	0.335	0.001	0.536	0.000
Body fat ratio (kg/m ²)	0.190	0.029	0.315	0.000	-0.070	NS	0.297	0.003	0.466	0.000
Waist to height ratio	0.215	0.014	0.288	0.000	-0.106	NS	0.299	0.003	0.465	0.000
Conicity index	0.197	0.025	0.307	0.000	-0.070	NS	0.210	0.038	0.294	0.003
Total adipose area (cm ²)	0.126	NS	0.188	0.021	-0.199	0.048	0.290	0.004	0.508	0.000
Subcutaneous abdominal area (cm ²)	0.147	NS	0.204	0.031	-0.065	NS	0.240	0.047	0.298	0.011
Visceral adiposity index	0.070	NS	0.111	NS	-0.332	0.001	0.105	NS	0.411	0.000
Abdominal volume index	0.127	NS	0.192	0.018	-0.198	0.048	0.289	0.004	0.509	0.000
<i>Metabolic markers (mg/dL)</i>										
Triglycerides	0.147	NS	0.204	0.012	-0.252	0.011	0.152	NS	0.369	0.000
HDLc	0.112	NS	0.174	0.032	0.161	NS	0.038	NS	-0.138	NS

Measurements	<i>Rho</i> Correlation coefficient of circulating levels									
	RvE1 (ng/mL)	<i>P</i>	Chemerin (ng/mL)	<i>P</i>	HMW-Adiponectin (ng/mL)	<i>P</i>	LMW-Adiponectin (ng/mL)	<i>P</i>	HOMA-AD	<i>P</i>
LDLc	0.264	0.002	0.130	NS	-0.024	NS	0.015	NS	0.071	NS
VLDLc	0.147	NS	0.204	0.012	-0.252	0.011	0.152	NS	0.369	0.000
sdLDLc	-0.020	NS	0.441	0.035	-0.115	NS	0.017	NS	0.218	NS
Apolipoprotein A-1	-0.112	NS	0.093	NS	0.564	0.000	0.067	NS	-0.369	0.027
NEFAs (mmol/L)	0.324	0.001	0.302	0.002	0.074	NS	-0.108	NS	0.126	NS
Insulin (QIU/mL)	0.171	0.050	0.054	NS	-0.379	0.000	0.269	0.007	-	-
<i>Cholesterol ratios</i>										
LDLc/HDLc	0.136	NS	0.029	NS	-0.159	NS	-0.031	NS	0.176	NS
TG/HDLc	0.056	NS	0.099	NS	-0.335	0.001	0.111	NS	0.406	0.000
sdLDLc/HDLc	0.097	NS	0.524	0.010	-0.117	NS	-0.039	NS	0.272	NS
<i>Inflammation markers</i>										
C reactive protein (mg/L)	0.167	NS	0.257	0.002	-0.122	NS	0.187	NS	0.348	0.000
C3 (mg/dL)	0.133	NS	-0.056	NS	-0.329	0.005	-0.094	NS	0.517	0.000
ESR (mm/h)	0.106	NS	0.311	0.000	0.048	NS	-0.068	NS	0.149	NS
<i>Insulin resistance indexes</i>										
HOMA-IR	0.185	0.034	0.043	NS	-0.364	0.000	0.305	0.002	-	-
QUICKI	-0.185	0.034	-0.043	NS	0.364	0.000	-0.305	0.002	-	-
HOMA-B	0.114	NS	0.115	NS	-0.354	0.000	0.032	NS	-	-
DI	0.110	NS	0.155	NS	-0.352	0.000	0.022	NS	-	-

(*Rho* Spearman's correlations in bold numbers were consider significant. (n = 230). NS: non-significant; HMW and LMW: high and low molecular weight adiponectin; BMI: body mass index; HDLc, LDLc y VLDLc (lipoproteins of high, low and very low density cholesterol, respectively); NEFAs: nonesterified fatty acids; sdLDLc: small dense LDLc; ESR: erythrocyte sedimentation rate; HOMA: homeostasis model assessment; IR: Insulin resistance; B: beta cell function; QUICKI: quantitative insulin sensitivity check index; DI: basal disposition index)

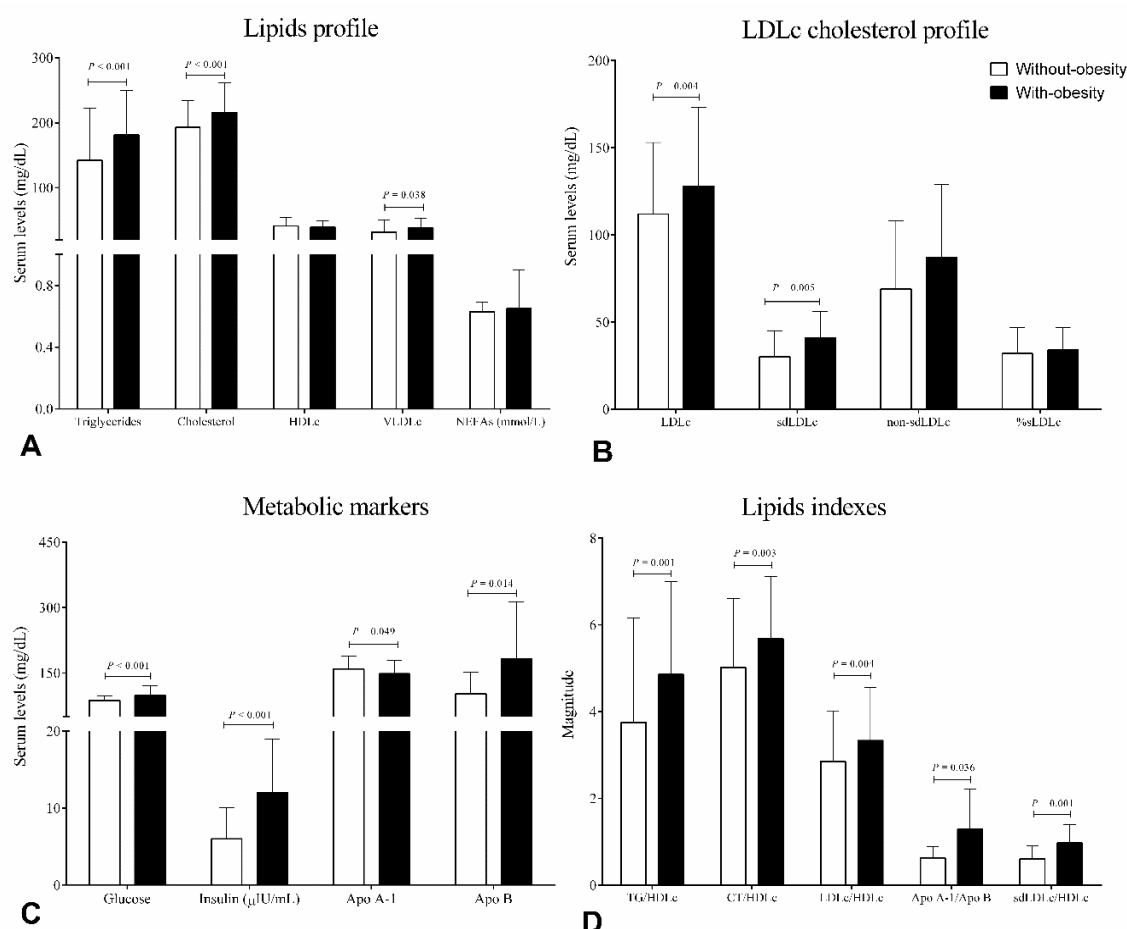


Figure 1. Metabolic markers and lipid profile. A. Lipids profile, B. LDL cholesterol profile, C. Metabolic markers, D. Lipids indexes. HDLc, LDLc and VLDLc (lipoproteins of high, low and very low-density cholesterol, respectively); sdLDLc: small dense LDLc; NEFAs: Non-esterified fatty acids. Data are shown in $\bar{x} \pm SD$. Difference of group with-obesity [n=77, BMI: 34.2 (30.1 – 39.0) kg/m²] versus without-obesity group [n= 153 BMI: 24.8 (18.7 – 29.9) kg/m²]. Unpaired Student's *t* test

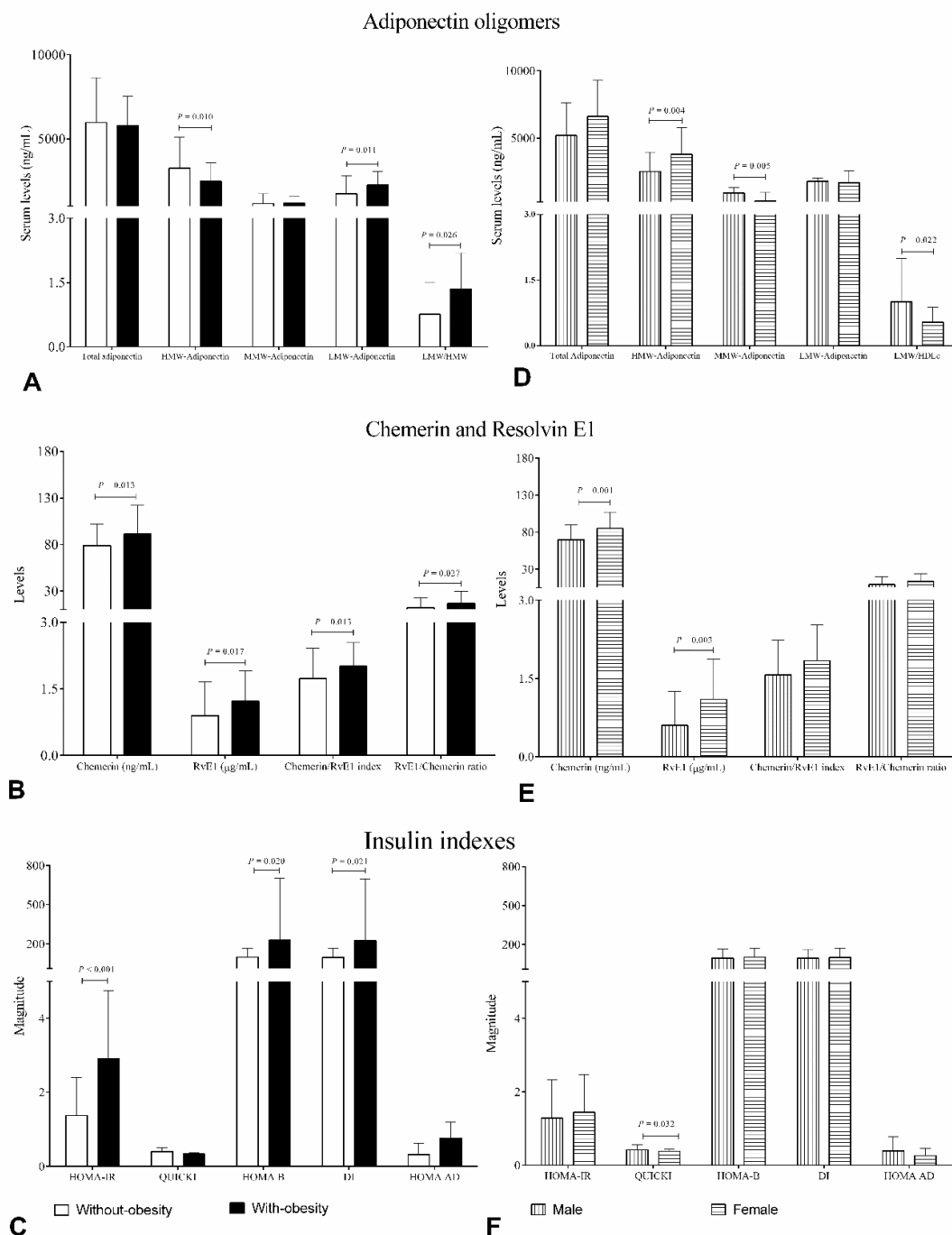


Figure 2. Serum levels of adiponectin oligomers, RvE1 and chemerin in study groups. A., B. and C. whole group, difference of group with-obesity [n=77, BMI: 34.2 (30.1 – 39.0) kg/m²] versus without-obesity group [n= 153, BMI: 24.8 (18.7 – 29.9) kg/m²]. D, E and F without-obesity group, difference of Males [n=61] versus Females [n= 55]. Data are show in $\bar{x} \pm SD$. Unpaired Student's t test

by BMI as covariable is $\ln \text{chemerin} = [\text{waist circumference} (-0.020) + \text{hip circumference} (0.007) + \text{conicity index} (1.921) + \text{sagittal abdominal diameter} (0.038) + 2.265]$.

Raise in the RvE1, chemerin and adiponectin oligomers unbalance are parallel to IR factors

A detailed data analysis by tertiles distribution in whole group shown that the high levels of RvE1 and chemerin were associated with

high storage of body fat mass, while only high chemerin levels were associated with high body dimensions, *status* of adiposity, ESR and sLDLc (Table 4).

On the other hand, higher levels of LMW-Adiponectin were associated with the increment of body fat storage, adiposity indexes, insulin levels and HOMA-IR. In the opposite, the higher levels of HMW-Adiponectin were associated with reduced content of adiposity, lipids (triglycerides, VLDLc and cholesterol indexes), insulin and HOMA-IR

Table 3. Multiple regressions between chemerin serum levels and adiposopathy *status* (Model was calculated after adjustment for BMI. Chemerin levels were transformed to natural logarithm for normality and was regressed on age and gender, which were presented as continuous variables, whereas BMI was categorized at two levels, namely, with-obesity and without-obesity)

Model natural logarithm of chemerin serum levels		
Total R^2	0.145	
	β -Coefficient (95% CI)	P
Constant	2.265 (1.374 – 3.184)	< 0.001
Waist circumference (cm)	-0.020 (-0.033 – -0.007)	0.003
Hip circumference (cm)	0.007 (-0.001 – 0.015)	0.071
Conicity index	1.921 (1.054 – 2.788)	< 0.001
Sagittal abdominal diameter (cm)	0.038 (0.006 – 0.070)	0.021

Table 4. Resolvin E1 and Chemerin levels associations

	Distribution levels by tertile group				
RvE1 (ng/mL) \bar{x} (min □ max)	Low 93 (5–323)	Intermediate 1121 (324–1450)	High 1816 (1451–2995)	* P	† P
Total body fat mass (%)	28.8 ± 9.6	33.6 ± 8.8	34.1 ± 9.2	0.021	NS
Conicity index	1.28 ± 0.09	1.33 ± 0.08	1.33 ± 0.11	0.044	NS
LDLc (mg/dL)	111 ± 42	134 ± 46	134 ± 41	0.022	NS
NEFAs (mmol/L)	0.48 ± 0.21	0.77 ± 0.83	0.69 ± 0.22	0.041	NS
	Distribution levels by tertile group				
Chemerin levels (ng/mL) \bar{x} (min □ max)	Low 57 (33–68)	Intermediate 80 (69–91)	High 115 (92–196)	* P	† P
BMI (kg/m ²)	29.4 ± 6.3	27.6 ± 5.6	31.2 ± 6.4	NS	0.008
<i>Storage of body fat</i>					
Total body fat mass (%)	29.9 ± 10.1	31.7 ± 8.7	38.3 ± 7.6	0.001	0.001
Total body fat mass (kg)	25.6 ± 15.0	24.4 ± 10.4	31.7 ± 12.0	0.041	0.010
Trunk fat mass (%)	29.7 ± 9.6	29.9 ± 8.7	34.8 ± 9.1	0.029	0.038
<i>Body dimensions</i>					
Waist circumference (cm)	98.7 ± 15.5	96.1 ± 14.1	104.5 ± 16.9	NS	0.021
Hip circumference (cm)	104.7 ± 1.8	104.0 ± 10.5	110.7 ± 14.3	0.043	0.019
Sagittal abdominal diameter (cm)	21.1 ± 3.7	20.2 ± 3.6	22.5 ± 4.3	NS	0.014
<i>Status of adiposity</i>					
Body fat ratio (kg/m ²)	9.2 ± 5.0	9.1 ± 3.9	12.3 ± 4.4	0.002	0.001
Waist to height ratio	0.59 ± 0.09	0.58 ± 0.08	0.64 ± 0.13	NS	0.036
Conicity index	1.29 ± 0.08	1.31 ± 0.10	1.35 ± 0.10	0.005	NS
Total adipose area (cm ²)	795 ± 64	751 ± 15	893 ± 288	NS	0.019
Abdominal volume index	20.0 ± 6.6	18.9 ± 5.3	22.5 ± 7.2	NS	0.016
<i>Biomarkers</i>					
sdLDLc (mg/dL)	40 ± 9	38 ± 11	49 ± 8	NS	0.046
ESR (mm/h)	14 ± 9	15 ± 10	22 ± 12	0.001	0.005

Data are show in $\bar{x} \pm SD$. ANOVA, Tukey post-hoc tertiles groups differences in bold numbers: *low *versus* high, †intermediate *versus* high. Difference of low *versus* intermediate tertiles in follows measurements: total fat mass % ($P = 0.039$), NEFAs ($P = 0.049$), LDLc ($P = 0.032$). LDLc: Low-density lipoprotein cholesterol; NEFAs: non-esterified fatty acids; BMI: body mass index; sdLDLc: small dense LDLc; ESR: Erythrocyte sedimentation rate

(Table 5) while Apo A-1 was increased. IR was evaluated by surrogate indexes, we used the QUICKI and additionally to estimate beta cell function we used HOMA-B and measure of secretory capacity of β -cell compensate for IR as basal disposition index (DI). Further strengthen these results of IR, the HOMA-AD index was assessed (Figure 2C). It has showed differences between individuals with-obesity and without-obesity, but not when compared males with females (Figure 2F).

LMW-Adiponectin and HOMA-AD associations show signs of specific shape of IR and adiposopathy status in individuals with obesity

In parallel way, we shown the correlation of the LMW-Adiponectin levels with the IR indexes (Figure 3A and C) and HOMA-AD with storage of body fat (Figure 3E). In addition, we carried out the construction of ROC curves to evaluate the performance of the LMW-Adiponectin levels within IR, and their potential ability to differentiate IR from non-IR individuals (Figure 3B and D).

These analyzes showed the values of AUC with IR discrimination. The result obtained in whole sample when LMW-Adiponectin levels positively correlate with HOMA-IR and negatively with QUICKI index (Figure 3A), the AUC was of 0.815, $P < 0.0001$ (Figure 3B). In addition, ROC curve analysis showed (95%CI, 0.726 - 0.903). While HOMA-AD positively correlate with adiposopathy *status*, the AUC for obesity discrimination was 0.801 $P < 0.0001$ (95%CI, 0.717 - 0.886) (Figure 3F).

Interestingly, in obesity group AUC for LMW-Adiponectin levels was 0.781, $P = 0.005$ (95% CI, 0.619 - 0.943), (Figure 3D) and an inverse correlation were observed, LMW-Adiponectin positively correlate with HOMA-IR and DI and negatively with QUICKI index (Figure 3C).

Discussion

Two main observations emerge from the current study. First, RvE1 and chemerin are both present in individuals with obesity, with such high levels a high lipid and inflammatory profiles, were noted and

Table 5. Adiponectin oligomers levels associations

LMW-Adiponectin (ng/mL) x̄ (min – max)	Distribution levels by tertile group			*P
	Low 975 (152 – 1458)	Intermediate 1870 (1466 – 2230)	High 2990 (2232 – 774)	
BMI (kg/m ²)	27.2 ± 5.8	29.3 ± 5.3	31.6 ± 6.5	NS
<i>Storage of body fat</i>				
Body weight (kg)	74.1 ± 17.7	77.4 ± 13.7	85.8 ± 22.8	0.032
Total body fat mass (%)	29.4 ± 9.1	32.3 ± 10.9	35.7 ± 9.5	0.031
Total body fat mass (kg)	22.4 ± 10.6	25.4 ± 10.8	31.9 ± 16.6	0.011
Trunk fat mass (kg)	11.9 ± 5.7	12.6 ± 5.4	16.1 ± 7.4	0.019
<i>Body dimensions (cm)</i>				
Waist circumference	93.9 ± 13.4	99.3 ± 14.9	105.2 ± 15.8	0.008
Hip circumference	102.0 ± 10.3	106.3 ± 10.8	110.0 ± 12.4	0.015
Sagittal abdominal diameter	20.1 ± 3.6	20.7 ± 4.1	23.1 ± 4.0	0.012
<i>Status of adiposity</i>				
Body fat ratio (kg/m ²)	8.3 ± 3.9	9.8 ± 4.7	11.7 ± 5.4	0.011
Waist to height ratio	0.57 ± 0.07	0.61 ± 0.10	0.63 ± 0.08	0.009
Total adipose area (cm ²)	716 ± 202	801 ± 252	900 ± 284	0.011
Abdominal volume index (L)	18.0 ± 5.0	20.2 ± 6.3	22.6 ± 7.1	0.011
<i>Biomarkers</i>				
Insulin (OIU/mL)	7.05 ± 4.41	10.37 ± 7.23	11.82 ± 7.65	0.012
HOMA-IR	1.56 ± 1.03	2.41 ± 1.81	2.91 ± 1.96	0.004
HMW-Adiponectin (ng/mL) x̄ (min – max)	Distribution levels by tertile group			*P
	Low 1302 (200 – 2048)	Intermediate 2806 (2055 – 3333)	High 4582 (3374 – 11016)	
Visceral adiposity index	4.94 ± 2.35	4.04 ± 2.77	3.17 ± 1.62	0.007
Triglycerides (mg/dL)	201 ± 90	161 ± 78	151 ± 81	0.045
VLDLc (mg/dL)	40 ± 18	32 ± 16	30 ± 16	0.045
TG/HDLc	5.49 ± 2.50	4.62 ± 3.03	3.60 ± 1.74	0.008
Apolipoprotein A-1 (mg/L)	127 ± 39	156 ± 27	173 ± 19	0.014
Insulin (OIU/mL)	11.55 ± 6.54	10.99 ± 7.46	6.85 ± 5.52	0.013
HOMA-IR	2.78 ± 1.72	2.48 ± 1.80	1.65 ± 1.49	0.021

Data are show in x̄ ± SD. ANOVA, Tukey post-hoc. Tertiles groups differences in bold numbers: *low versus high. HMW: high molecular weight; LMW: low molecular weight; BMI: body mass index; HOMA-IR; homeostasis model assessment-insulin resistance; HDLc, LDLc y VLDLc (lipoproteins of high, low and very low-density cholesterol, respectively); TG: triglycerides

associated with their adiposopathy *status*. Secondly, the amount of LMW-Adiponectin was able to differentiate individuals with IR from non-IR individuals, beside of correlations of HOMA-AD index in adiposity setting.

It is imperative to recognize that this study was design on bases of three conceptual points, labeled together as obesity-adiposopathy *status*, with unbalance of: 1) adiposity setting, 2) metabolic profile and 3) biomarkers of inflammation. On which clinical records were match with circulating levels of molecules characterized as immuno-metabolic regulators in obesity such as RvE1, chemerin and oligomeric complexes of adiponectin, with which was set of breakpoints for tertiles according to the normal distribution.

This is very important to take in consideration since the concept of low-grade inflammation present in obesity has been associated with chemerin, (known with pro-inflammatory properties). Moreover, at the same time, what has not expected from this study, the RvE1, (a lipid mediator known to present pro-resolutive and anti-inflammatory properties), was also present on high circulating serum levels in individuals with obesity. At this point it is essential to recall that the biological action of RvE1 and chemerin is through bind to the same receptor, the CMKLR1 [9]. Such receptor has been reported to play a crucial role with other comorbidities of obesity such as atherosclerosis [16].

One relevant result and not previously reported was the quantitative ratio of RvE1 and chemerin, and their positive correlations with body fat measurements, metabolic profile and

inflammatory markers in obesity. On this setting, the present study proposes the *RvE1/chemerin index* and *RvE1/chemerin ratio*, as early signs of adiposopathy *status* in obesity.

Our proposals are based on two observations: first, earlier in the disease, the common denominator is the metabolic dysregulation and inflammatory process along the subclinical manifestations in obesity such event occurs early in the adipose tissue, with pathological adipogenesis and recruitment of circulating monocytes enhanced by polarization of M1 macrophages in tissue. All of which is identified as subclinical low-grade inflammation [8,29,30] .

Secondly, late in the disease, a characteristic dyslipidemia and metabolic dysregulation, was observe. Such phenomenon was with subclinical inflammation along with high IR-indexes and RvE1, chemerin and LMW-Adiponectin and low HMW-Adiponectin levels.

On the context of obesity development, all results of this study can be explained because the adipose tissue becomes permanently dysfunctional, in the producing inflammatory adipokines, both have critical role in the develop of metabolic complications associated with obesity [31,32].

However, the underlying mechanisms of chronic inflammation unresolved in the development of obesity, has not been completely defined, in this scenario the evidence found shows a complex biological interrelationship between inflammatory immune response and metabolism of glucose and lipids [30].

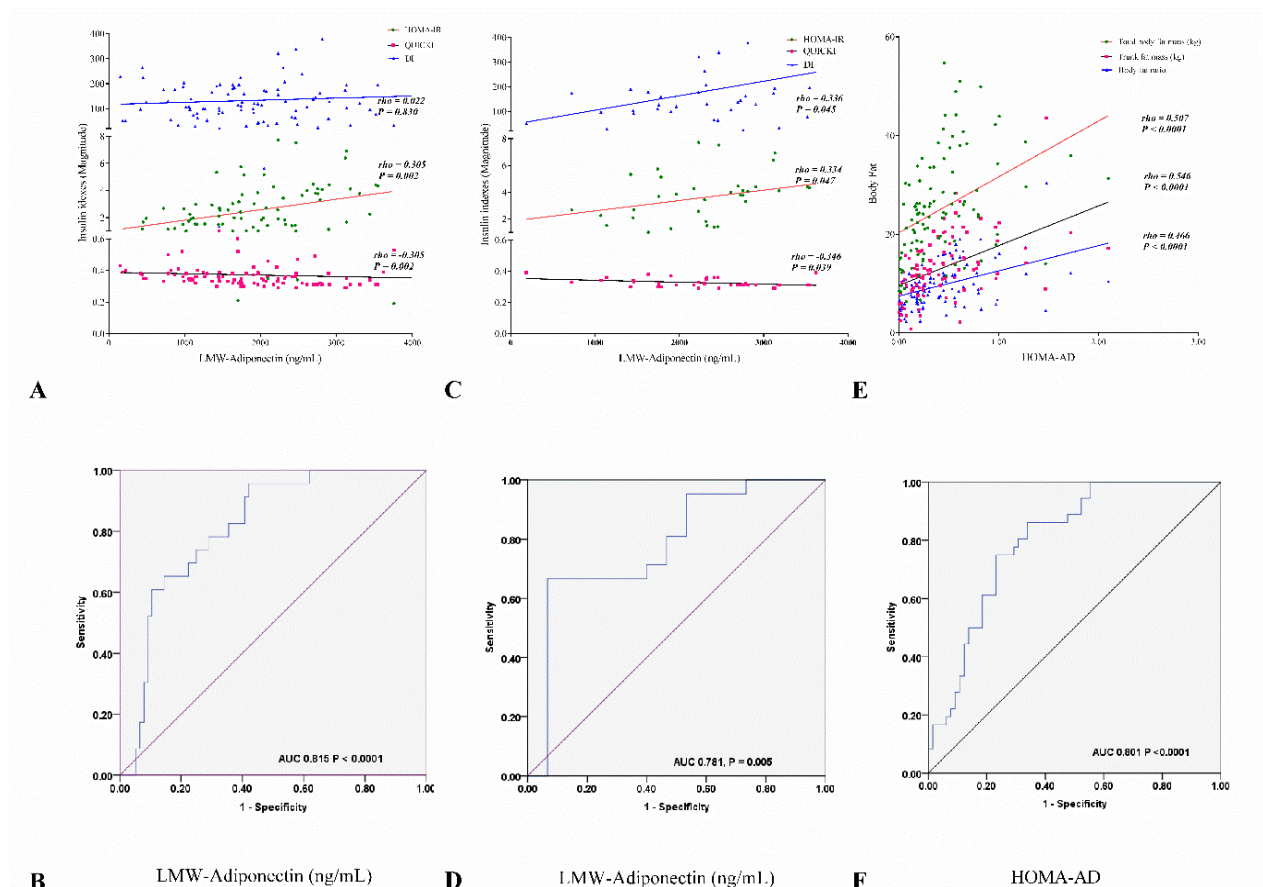


Figure 3. ROC curves for LMW-Adiponectin matching to insulin resistance indexes and body fat mass. Correlation of LMW-Adiponectin levels with IR indexes: A. whole group, C. group with-obesity. ROC curve of LMW-Adiponectin: B. whole group, D. group with-obesity. E. Correlation of HOMA-AD with body fat mass. F. ROC curve of HOMA-AD in whole group. Rho Spearman's correlation, $P < 0.05$ was consider significant. LMW: low molecular weight; HOMA: homeostasis model assessment; IR: insulin resistance; QUICKI: quantitative insulin-sensitivity check index; DI: basal disposition index; AD: adiponectin; ROC: receiver operating characteristic curve; AUC: area under curve

The correlation of RvE1, chemerin, HMW and LMW-Adiponectin levels with the IR setting in our study group is consistent with previous studies indicating that the metabolic changes associated with obesity are largely attributable to the amount of intra-abdominal fat, instead of the amount of total body fat [33-36].

One interesting point of this study is that chemerin is an adipochemokine that can be control by inflammation response itself and has been associated with obesity along other inflammatory diseases [33]. On the other hand, RvE1 is a lipid mediator of which we could explore from two different points of view: the source or the action. Most important, since this is a lipid mediator, it is logical to expect that in obese individuals with present a lipid pool higher lipid in general would present a lower level compared with healthy individuals [37,38].

In addition, most of the information available of RvE1 is associated with its mechanism of action and its pro-resolutive effects. RvE1 has been showed to modulate leukocytes, endothelial activation along other anti-inflammatory properties [38].

One of the concepts of the inflammation present in many chronic diseases such as atherosclerosis or even obesity is that the pro-resolute mediators are reduced, leading to the persistence of the pro-inflammatory mediator is and by this way promoting the persistence of the inflammation [37]. Since RvE1 known to modulate inflammation and comes in to play only when inflammation is present, we could

expect that the high of RvE1 could be trying to modulate the inflammation. Nevertheless, for some reason it is not enough.

For the best description of the participation of RvE1 and chemerin in the clinical scenario of obesity, it is important to take in consideration the following conceptual points:

in this study it was observe that the high levels of RvE1 were found in individuals with obesity, that these levels were 10-fold higher than chemerin levels, although the affinity of both for their receptor CMKLR1 is not equivalent [9,39]. This is evidence that suggests that resolution of the inflammatory process fails even in the subclinical setting.

On the other hand, in the context of obesity-adiposopathy *status*, the expression of CMKLR1 receptor was up-regulate in the hepatic metabolism by adiponectin levels [18]. This was in accordance with the results obtained in this study: high levels of RvE1 and chemerin and unbalance in the adiponectin levels, and their association with metabolic markers and pathological redistribution of adipose tissue content.

Then we explored the hypothetical combination of the oligomeric components of adiponectin with the HOMA indexes in the early identification of the clinical and metabolic alterations related to IR.

We analyzed whole and group with-obesity; preliminary we found a correlation of LMW-Adiponectin levels with IR indexes. Next, in

the clinical setting of adiposopathy *status* observed in the individuals included in this study, we used the ROC curves as a useful tool to evaluate the performance of the LMW-Adiponectin levels as a tool to discriminate the IR.

The main differences found were between obesity individuals with and without IR. LMW-Adiponectin is sufficient to distinguish people with IR from those without IR. Another important result was the ability of the HOMA-AD index to show the risk of IR, matching with the correlation with the adiposopathy *status* [40].

These results highlight the unbalance in the levels of oligomeric adiponectin components, the increase in LMW-Adiponectin while decreasing the HMW-Adiponectin, provided if they exceed the BMI > 30 kg/m². However, one limitation of the current study is that we cannot determine the progression of the disease to IR.

Since IR and adiposopathy are characterized by the deposition of ectopic adipose tissue with dysfunctional metabolic properties, and has been associated with adiponectin levels, in people with a wide range of adiposity [4,40]. The current study confirms that oligomeric adiponectin levels was as expected, lower in obese individuals and negatively correlated with IR.

At obesity-adiposopathy juncture, obesity was characterized by abnormal production of soluble mediators mainly by adipose tissue and activation of several pro-inflammatory signaling pathways. Such process resulting in the initiation of inflammation, in addition to the crosstalk between immune cells and metabolic organs.

Conclusion

Individuals with obesity that presented metabolic dysregulation and subclinical inflammatory profile, shown high levels of RvE1 and chemerin associated with their adiposity content, whereas the unbalance of adiponectin oligomers levels are parallel to IR, these facts together result in the ability to discriminate the presence of the absence of the pathogenic process of IR in individuals with obesity. On obesity-IR context, this is the first study to link the increased serum levels of three biomarkers (LMW-Adiponectin, RvE1 and chemerin) with adipose content, while a dysmetabolic response was observe.

We propose that LMW-adiponectin/HMW-Adiponectin and RvE1-chemerin relationships favors a specific *status* of adiposopathy in individuals with obesity. Such measurements could be a new way to early identify individuals with risk factors to insulin resistance.

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Author contributions

Perla Monserrat Madrigal-Ruiz, Fernanda-Isadora Corona-Meraz, and Rosa-Elena Navarro-Hernández: conceived the study and participated in its design and coordination. Mónica Vazquez-Del Mercado and Perla Monserrat Madrigal-Ruiz were responsible for the classification and clinical evaluation of the individuals included, performed of data base and participated in drafting the paper, and its coordination.

Milton-Omar Guzman-Ornelas, Griselda-Guadalupe Macias-López, Gustavo-Ignacio Diaz-Rubio and Fernanda-Isadora Corona-Meraz carried out the assays, performed of data base, and participated in drafting the paper. Milton-Omar Guzman-Ornelas, Marcelo-Heron Petri, and Rosa-Elena Navarro-Hernández performed statistical analysis and interpretation of data. Perla Monserrat Madrigal-Ruiz, Fernanda-Isadora Corona-Meraz, Marcelo-Heron Petri and Rosa-Elena Navarro-Hernández wrote and reviewed the final version of the manuscript. All authors: reviewed, read and approved the final version of the manuscript.

Disclosure

The authors declare that there is no conflicts of interest regarding the publication of this paper.

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