Progress in Nutrition 2019; Vol. 21, Supplement 1: 370-377 DOI: 10.23751/pn.v21i1-S.6738

Lipid profile in relation to inflammatory and insulin resistance markers and anthropometric indices in the apparently healthy abdominally obese

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Summary. *Background:* The present study aimed to investigate the association of lipid profile with anthropometric indices, Insulin resistance (IR), and inflammatory markers in apparently healthy abdominally obese persons, subdivided into insulin-resistant and non-insulin-resistant groups. *Methods:* In this cross-sectional study, 86 apparently healthy abdominally obese subjects were recruited, and divided into two groups based on their IR. Fasting blood samples were collected to determine serum metabolic features, and inflammatory markers (free fatty acids, lipopolysaccharide binding protein (LBP), interferon β, and Interleukin 1β). Abdominal obesity was defined as having waist circumference (WC)≥95cm. Anthropometric indices including BMI, WC, and WHR were assessed. *Results:* WC (p=0.020), Waist to hip ratio (p=0.010), HDL-C (p=0.005), and LDL-C (p=0.002) were significantly different between the two groups. WHR was significantly correlated with HDL-C (r=-0.315; p=0.002). There were significant differences in fasting insulin, HOMA-IR, and QUICKI (p<0.001 for all) between the IR and NIR groups. HOMA-IR was correlated with HDL-C (r=-0.25; p=0.019). Also, there was a significant correlation between QUICKI and FBS (r=-0.266; p=0.012). Other than serum LBP (p=0.038), there was no significant difference in inflammatory markers between the two groups. However, all inflammatory markers were significantly correlated with each other. *Conclusion:* This research demonstrates that WC, WHR, LDL-C, and LBP are higher and HDL-C is lower in the insulin resistant abdominally obese than non-insulin resistant abdominally obese. HOMA-IR was correlated with WC. There was a significant correlation of QUICKI with WC and HDL-C in the apparently healthy abdominally obese.

Key words: Lipid profile, insulin resistance, inflammatory markers, anthropometric indices, apparently healthy abdominally obese

Abbreviations

BP: Blood Pressure; BMI: Body Mass Index; FBS: Fasting Blood Sugar; FFAs: Free Fatty Acids; GIR: Glucose Infusion Rate; HDL-C: High Density Lipoprotein cholesterol; HOMA-IR: homeostasis model of insulin resistance; IR: Insulin resistance; INFβ: Interferon-β; IL1β: Interleukin-1-β; LBP: Lipoprotein Binding Protein; LDL-C: Low Density Lipoprotein cholesterol; LPS: Lipopolysaccharide; MetS: Metabolic Syndrome; MHAO: Metabolically Healthy Abdominally Obese; MUAO: Metabolically Unhealthy Abdominally Obese; NIR: Non-Insulin Resistance; QUICKI: Quantitative insulin sensitivity check index;T2DM: Type 2 Diabetes Mellitus; TC: Total Cholesterol ; WC: Waist Circumference; WHR: waist/hip ratio

Introduction

Obesity as a public health concern is associated with low-grade inflammation, dyslipidemia, and insulin resistance (IR), which are major risk factors for obesity-mediated diseases such as type 2 diabetes, cardiovascular disease, and premature death (1).

IR, as a primary metabolic disorder, plays a significant role in the development of dyslipidemia. Obesity-related dyslipidemia is characterized by increased levels of plasma free fatty acids (FFAs) and triglycerides, decreased levels of high-density lipoprotein cholesterol (HDL-C), and abnormal low-density lipoprotein cholesterol (LDL-C) composition. The most significant factor for obesity-related dyslipidemia is uncontrolled fatty acid release from adipose tissue (2, 3).

Adipocyte size is an essential factor which indicates the degree of adipose tissue contribution in dyslipidemia. Enlargement of adipocytes is associated with an increase in TG synthesis (4) and number of LDL-C and VLDL-C (5). Recently, it has become evident that the site of fat distribution beside the increase in fat mass is an important determinant of IR development and other obesity complications (6). The accumulation of central fat and presence of IR have both been associated with the dyslipidemia of metabolic syndrome (MetS) (7). Thus, increased waist/hip ratio (WHR) was found to be associated with small dense LDL-C particles, increased intraabdominal fat mass, or decreased insulin sensitivity (8).

IR and obesity-related inflammation are known as a low-grade chronic inflammatory state (9). Inflammation as a potential mechanism links adipose tissue expansion to cardiovascular and metabolic risk factor (10). The association between obesity and inflammation has been derived from overexpression of pro-inflammatory cytokines in obesity (11). Although the main mechanism accounted for inflammation in adipose tissue is still unknown, some factors like plasma FFAs are known to play an essential role (12). It was clarified that plasma FFAs are increased in obesity because of the lipolysis of adipocytes in inflamed adipose tissue (13).

Lipopolysaccharide (LPS) molecules, known as bacterial endotoxins, would trigger inflammation, with activation of immunity and cytokine release (14). Because of LPS short half-life (15) and no agreement on the measurement of its plasma level (16), lipopolysaccharide-binding protein (LBP) is introduced as a more reliable measurement (17). A study (18) on patients with MetS showed that LBP concentration was independently associated with abdominal obesity.

The association of dyslipidemia with inflammatory and IR markers has been extensively examined in several populations, but not in Tabriz people, whom the prevalence of obesity and associated co-morbidities has an increasing rate. Therefore, the present study was aimed to investigate the association of lipid profile with anthropometric indices, IR, and inflammatory markers (including FFAs, LBP, IL1β and INFβ) in apparently healthy abdominally obese persons, subdivided into insulin-resistant (IR) and non-insulin-resistant (NIR) groups.

Materials & Methods

Sampling

In this cross-sectional study, 86 apparently healthy abdominally obese participants were recruited through advertisement in health centers and governmental clinics from June to August 2015 in Tabriz University of Medical Science. Abdominal obesity was defined as waist circumference (WC)≥95cm, based on the definition of Iranian national committee of obesity (19). MetS was defined as the presence of <3 of the following metabolic abnormalities including abdominal obesity (WC≥95cm for both genders), high serum triglyceride (TG) concentration (≥150 mg/dl); low serum high density lipoprotein cholesterol (HDL-C) (<40 mg/dl for men and <50 mg/dl for women); elevated blood pressure (BP) (≥130/85 mmHg); and fasting blood sugar (FBS) (≥100 mg/dl) (19).

Apparently healthy subjects with abdominal obesity (WC≥95cm) and BMI between 25-35 kg/m^2 at the age range of 18 to 60 years were considered as inclusion criteria. Inflammatory or malignant disease, diabetes, cardiovascular disease, renal disease, hypo- or hyperthyroidism, severe mental disease, anticoagulant or hormonal therapy, hyperlipidemic and hyperglycemic drugs, oral contraceptives, anti-inflammatory drugs consumption, use of antioxidant supplements in the past 6 months or antibiotics in the past 3 months, β blockers, taking vitamin/mineral supplements, consecutive diarrhea for 3 days in past 3 months were regarded as exclusion criteria.

Gastrointestinal surgeries during the last year, irritable bowel syndrome, malabsorption, any weight-loss diet, energy intake out of the defined range (800-4000 kcal/day), sever exercise (>100min/week), alcohol consumption, TG>400mg/dl and being pregnant, lactating, or postmenopause were considered as excluded.

Laboratory measurements

After 10-12 h overnight fast, 5mL blood was obtained. Serum levels of FBS and lipid profile including TG, HDL-C, LDL-C, and total cholesterol were assessed. The rest of serum samples were stored in -70˚c for later measurement of interferon β (IFN β), FFAs, LBP, interleukin 1β (IL1β), and insulin. All the assays were conducted after centrifugation of blood samples at 3000 rpm for 5 minutes (20).

Quantitative insulin sensitivity check index (QUICKI), a simple marker for insulin sensitivity, and the homeostasis model of insulin resistance (HOMA-IR) were calculated as 1/(log fasting insulin + log fasting glucose in mg/dL) (21), and [fasting insulin (μIU/ml) × fasting glucose (mg/dl)/405], respectively (22) IR was defined as HOMA-IR value of ≥2.6 (23).

Anthropometric measurements

Weight was measured to the nearest 0.1 kg by Seca scale in light clothing without shoes. Height was measured to the nearest 0.1 cm, using a wall-mounted stadiometer. BMI was calculated as weight (kg) divided by the square of height in (m). Blood pressure (BP) was measured after a 10-min rest period, using mercury sphygmomanometer, twice with a 2-min interval by and the mean of the two measurements was recorded as the BP (24). WC was measured by an inelastic measuring tape to the nearest 0.1 cm between the rib and the iliac crest at the end of exhalation (25).

Dietary assessment

Dietary intake was measured using a 3-day food record (2 work days and 1 weekend). The obtained data were analyzed using *Nutritionist IV* software (Axxya Systems, Stafford, TX), modified for Iranian foods.

Statistical analysis and sample size estimation

Kolmogrov-Smirnov test was used to examine the normal distribution of variables. Data were expressed as mean± SD or median (25^{th}, 75^{th}), as appropriate. The independent samples t-test was applied for comparing the means (SD) of normally distributed variables, whereas the Mann–Whitney U test was used for values with skewed distribution. Chi-square test was performed for categorical variables. The correlations were examined using Pearson or Spearman correlation coefficient test between two variables, as appropriate. Level of significance was $p<0.05$. Statistical analyses were performed using SPSS ver. 17.0 for Windows (PASW Statistics; SPSS Inc., Chicago, IL, USA). The sample size was estimated to be 71 persons, according to a pervious study (26) based on serum HDL-C level, with 80% power and an α-error of 5%. Considering a drop-out rate of 20%, total sample size required was 86.

Ethical consideration

All of the participants signed informed consent form. The whole protocol of the study was approved by regional ethics committee of Tabriz University of Medical Sciences. The research was in accordance with the principles of the Declaration of Helsinki (Ethical code: TBZMED.REC.1394.982).

Results

The mean age for both groups was 36.70±7.44 years with a range of 20-50 years old. About seventy one percent of the participants had HOMAIR≥2.6 and constituted insulin-resistant group. General characteristic and anthropometric indices in all subjects, IR, and NIR groups are shown in Table 1. The mean of BMI for the IR and NIR groups was 31.7 and 30.6 kg/m^2, respectively. All participants in both groups were apparently healthy and abdominally obese (WC≥95cm). The IR and NIR groups did not differ in terms of age, BMI, SBP, and DBP; however, WC (p=0.020) and WHR (p=0.010) were significantly different between the two groups (Table 1). WHR was significantly correlated with HDL-C (r=-0.315; p=0.002) (Figure 1).

Except for serum HDL-C (p=0.005) and LDL-C (p=0.002), there was no significant differences in lipid profile between the IR and NIR groups (Table 2). There were significant differences in fasting insulin, HOMA-IR, and QUICKI (p<0.001 for all) be-

Table 1. General characteristic and anthropometric indices in NIR and IR groups

Variables	Total (n=86)	NIR group (n=25)	IR group (n=61)	*P* †
Age (years)	36.70±7.44	36.40±8.10	36.83±7.21	0.807
Weight (kg)	85.41±14.03	84.74±11.46	85.68±15.03	0.779
Height (m)	164.79±11.93	166.36±9.23	164.15±12.89	0.440
BMI (kg/m^2)	31.47±3.98	30.75±3.31	31.77±4.22	0.285
SBP (mmHg)	112.94±15.35	115.20±19.17	112±13.52	0.453
DBP (mmHg)	75.7±12.5	73.60±13.58	76.58±11.36	0.301
WC (cm)	105.04±7.42	102.16±5.86	106.022±7.71	**0.020***
HC (cm)	110.5±7.76	110.20±6.40	110.62±8.30	0.820
WHR	0.98±0.05	0.92±0.054	0.95±0.05	**0.010***
BF (%)	32.81±7.84	31.89±8.26	33.20±7.70	0.488
FM (kg)	27.88±7.54	26.80±6.35	28.32±7.98	0.400
FFM (kg)	57.63±12.31	58.19±11.83	57.40±12.60	0.790

† Independent samples t-test; *p<0.05

IR, Insulin Resistance; NIR, Non-Insulin Resistance; BMI, Body mass index; WC, Waist circumference ; HC, Hip circumference; WHR, Waist to hip ratio; BF: body fat; FM, Fat mass; FFM, Fat free mass; SBP, Systolic blood pressure; DBP, Diastolic blood pressure

Table 2. Metabolic features of the participants

Variables	Total (n=86)	NIR group (n=25)	IR group (n=61)	*p* †
FBS (mg/dl)	92.86±8.89	91.72±8.46	93.32±9.08	0.450
TG (mg/dl)	179.79±92.36	202.76±23.07	170.37±80.30	0.209
HDL-C (mg/dl)	42.186±8.35	46.04±7.71	40.60±8.14	**0.005***
LDL-C (mg/dl)	115.04±30.88	98.96±27.54	121.36±30	**0.002***
TC (mg/dl)	191.72±35.03	181.16±34.39	196.54±34.63	0.073
Fasting insulin (μU/ml)	17.60±1.09	6.24±1.76	22.26±8.28	**<0.001***
HOMAIR	4.05±0.25	1.41±0.41	5.13±1.99	**<0.001***
QUICKI	0.47±0.07	0.57±0.03	0.43±0.03	**<0.001***

†Independent samples t-test; *p<0.05

FBS, Fasting blood sugar; TG, Triglycerides; HDL-C, High-density lipoprotein cholesterol; LDL-C, Low-density lipoprotein cholesterol; QUICKI, Quantitative insulin sensitivity check index; HOMA-IR, homeostasis model of insulin resistance

tween the IR and NIR groups (Table 2). HOMA-IR was correlated with WC (r=0.21; p=0.042) (Figure 1). Also, there was a significant correlation of QUICKI with WC (r=-0.22; p=0.012) and HDL-C (r=0.25; p=0.019) (Figure 2). Other than serum LBP *(p=0.038)*, there was no significant difference in inflammatory markers between the two groups (Table 3). However, all inflammatory markers were significantly correlated with each other. INFβ had significant correlations with IL1β (r=0.660; p<0.001), FFAs (r=0.517; p<0.001), and LBP (r=0.610; p<0.001). IL1β was significantly correlated with FFAs (r=0.708; p<0.001) and LBP (r=0.631; p<0.001). A significant correlation was also

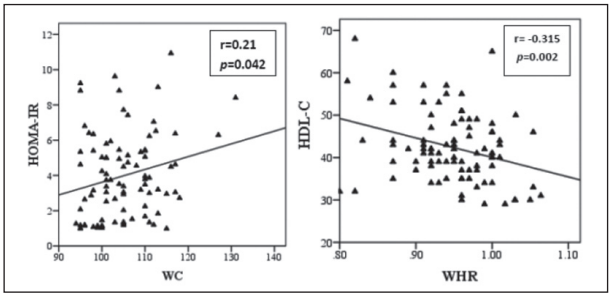

Figure 1. Spearman correlations between WC and HOMA-IR as well as between HDL-C and WHR. HDL-C: High Density Lipoprotein cholesterol; WC: Waist Circumference; WHR: waist/hip ratio; HOMA-IR: homeostasis model of insulin resistance

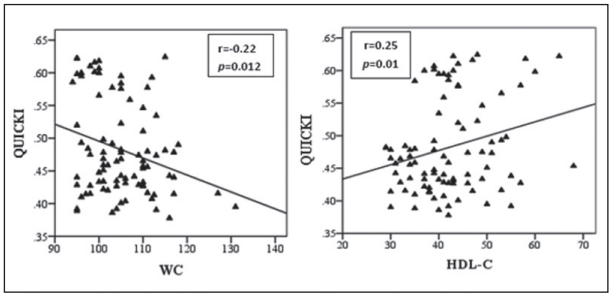

Figure 2. Pearson correlations between WC and QUICKI as well as between HDL-C and QUICKI. HDL-C: High Density Lipoprotein cholesterol; WC: Waist Circumference; QUICKI: Quantitative insulin sensitivity check index

observed between FFAs and LBP (r=0.729; p<0.001). However, there were no significant differences in dietary parameters between the two groups (Table 4).

Discussion

The aim of the present study was to investigate the relation of lipid profile with anthropometric indices, IR, and inflammatory markers in apparently healthy abdominally obese individuals. More than half of the participants were insulin resistant. Based on the previous research, abdominal obesity can lead to higher insulin concentration and the resultant hyperinsulinemia may encourage further obesity (27). Therefore, obesity and IR have synergistic effects and exacerbate each other (28).

No significant differences were observed in lipid profile between the IR and NIR groups, except for serum HDL-C and LDL-C. In line with this finding, in a cross-sectional research on Qatarian primary school obese students divided into two groups of overweight/not-overweight based on their waist circumference (WC), there were significant differences in HDL-C and LDL-C between the two groups (29). Another cross-sectional study on persons with/without MetS (30) indicated association of HDL-C and TG with IR status and MetS. In a research on 8411 participants from Korean genomic Rural Cohort study, TG/HDL-C ratio was correlated with WC and total cholesterol (TC), LDL-C, and TG (31). Another research on 60 morbidly obese people, divided into two subgroups based on glucose infusion rate (GIR), showed that

Table 3. Inflammatory markers between NIR and IR groups

Variables	Total (n=86)	NIR group (n=25)	IR group (n=61)	$P^{\dagger}$
LBP (nmol/l)	13.1 (10.3, 34.5)	12.1 (9.6, 23.2)	15.8 (12.6, 50.3)	**0.038***
INFβ (pg/dl)	751.0 (517.0,1080.2)	856.0 (608.0, 2057.0)	720.0 (517.5, 869.0)	0.078
IL1β (pg/ml)	722.4 (620.7, 1329.2)	762.4 (626.0, 2813.0)	717.0 (611.0, 1098.5)	0.264
FFAs (nmol/L)	1363.0 (1135.0, 3801.5)	1290.0 (1165.0, 5705.0)	1365.0 (1129.0, 2428.0)	0.658

† Mann-Whitney U test; *p<0.05: INFβ, interferon 1 β; LBP, Lipopolysaccharide binding protein;IL1β, Interleukin 1β; FFAs, Free fatty acids

Table 4. Dietary parameters of NIR and IR groups

Variable	NIR group (n=27)	IR group (n=61)	P
Energy (kcal/day)†	2056.05±694.86	2211.88±842.38	0.495 ξ
Dietary carbohydrates (g)†	300.85±105.12	340.57±140.27	0.219 ξ
Dietary protein (g)†	68.21±26.41	82.50±41.74	0.131 ξ
Dietary fat (g)†	61.79 (43.34-79.36)	55.04 (40.29-75.44)	0.297 ⁺
SFA (g)¥	12.74 (10.78-28.32)	14.86 (10.62-21.58)	0.956 ⁺
PUFA (g)¥	15.15 (9.83-22.36)	12.59 (9.43-20.28)	0.421 ⁺
MUFA (g)¥	17.96 (12.53-25.92)	16.66 (11.35-23.56)	0.253 ⁺
Cholesterol (mg)¥	164.5 (77-377.7)	257.8 (162.87-392.8)	0.154 ⁺
Dietary fiber (g)¥	14.32 (10.69-18.75)	14.37 (10.8-17.54)	0.794 ⁺

†Variables with normal numeric scales are reported as Mean (standard deviation).; ¥ Variables with non-normal numeric scales are reported as Median (25^{th}, 75^{th}).; ξ Independent Samples t- test; ⁺Mann-Whitney U test

other than HDL-C and TG, there was no significant difference in LDL-C and IL6 between the two groups (32). The difference in the outcome of the study could be due to small sample size. These results indicated that that not only there is a correlation between IR and lipid profile in obesity, but also IR may alter lipid profile in apparently healthy obese subjects, which is in line with our results (Table 2).

Our study also showed that among anthropometric indices, WC and WHR were significantly different between the two groups and WHR was correlated with HDL-C. This finding is in line with a study which examined effects of waist and hip circumferences on cardiovascular risk factors, a narrow hip circumference (adjusted for age, BMI, and waist circumference) was associated with low HDL-cholesterol and high glucose concentrations in men and high TG and insulin concentrations in men and women (33). Also, in another study on 907 women randomly selected from different geographic regions of Iran showed that WC is directly related to IR (34). Thus, changes in WC can be a sign of changes in HDL-C in people who are apparently healthy, independent of IR.

In the present research, QUICKI was significantly correlated with HDL-C and WC. Steinberger *et al.* (35) also reported that the degree of IR in obese adolescents may determine the levels of TG, LDL-C, and HDL-C. In line with our study, a research demonstrated that WC had significantly positive moderate correlations with fasting insulin and HOMA-IR (36).

Except for LBP, other inflammatory markers did not differ between the two groups in the present study. Our recent case-control study on 164 abdominally obese, divided into metabolically healthy abdominal obese (MHAO) and metabolically unhealthy abdominal obese (MUAO), indicated that levels of LBP and FFAs are more related to abdominal obesity than to the presence or absence of metabolic health (37). In a cross-sectional study, 93 age-matched middle-aged urban Gambian women were divided into three groups based on their BMI: lean, obese non-diabetic and obese diabetic. LPS levels were highest in the obese-diabetic group compared with the other two groups (38). Agwunobi *et al.* (39) were the first researchers to demonstrate, in humans, the impairment of insulin sensitivity 6-7h after the administration of low doses of LPS. Mehta et al. (40) also conducted a study in which healthy individuals with a BMI between 18 and 30 kg/m2 received intravenous LPS. The endotoxemia induced fast and transient increase in plasma TNF-α, IL-6, resistin, leptin, MCP-1, CRP, cortisol, and FFAs. It was also verified that the occurrence of endotoxemia induced systemic IR, but the function of pancreatic β-cells was not affected. Pussinen et al. (41) evaluated the relationship between endotoxemia and the incidence of T2DM in a cohort study involving 7169 individuals followed for 10 years. The authors concluded that the levels of LPS were positively associated with increased risk of T2DM and negatively correlated with HDL-C levels. Thus, it seems that a chronic exposure to slightly elevated levels of LPS may contribute to IR, and hence to the manifestation of chronic diseases. However, clinical studies have shown that the concentrations of circulating LPS and LBP (an endotoxemia marker) are higher in type 1 or 2 diabetic persons and in the obese (42), strengthening their link with IR and metabolic disorders.

The chronic exposure to slightly increased LPS levels in the blood is a risk factor for IR, since this endotoxin can induce an immune response and activate pathways leading to subclinical inflammation inhibiting several step of insulin signaling. Thus, endotoxemia-induced IR may contribute to weight gain and the development of T2DM. A population based study (43) including 559 overweight/obese and 500 normal weight showed that LBP levels were significantly higher in overweight/obese individuals than in normal weight individuals and elevated circulating LBP was associated with obesity, MetS, and T2DM in the apparently healthy Chinese. It can be concluded that LBP as a marker of endotoxaemia is associated with IR and WC.

The present work had some limitations like smaller sample size and its cross-sectional nature did not allow for a causal inference. But the strength of this study which to the best of our knowledge is the first to be conducted on Tabriz population and investigate the association of lipid profile with anthropometric indices, IR, and inflammatory markers in apparently healthy abdominally obese persons.

Conclusion

This research demonstrated that WC, WHR, LDL-C, and LBP were higher and HDL-C was lower in the insulin-resistant vs. non-insulin-resistant abdominally obese. HOMA-IR was correlated with WC. In addition, there was a significant correlation of QUICKI with WC and HDL-C in the apparently healthy abdominally obese.

Acknowledgment

Thanks to all participated in the study.

Funding

This study was financially supported by Nutrition Research Center, Tabriz University of Medical Sciences, Tabriz, Iran. The results of this paper were extracted from MSc. thesis of Mahsa Naghizadeh, registered at Tabriz University of Medical Sciences.

Authors' contribution

MSA and MN wrote the study protocol and study design. MSA and MN analyzed and interpreted the data. MN, PA, and NK helped with sampling. MSA and MN were involved in drafting the manuscript or revising it critically for content. All authors have given final approval of the version to be published.

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