Original Article

Association between complement component C3 and body composition: a possible obesity inflammatory biomarker for insulin resistance

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Background and Objectives: The C3 complement component (C3) is increasingly recognized as a cardiometabolic risk factor. We aimed to examine the role of C3 in insulin resistance (IR) and its association with adiposity. **Methods and Study Design:** Sixty-seven obese (18-35 years) participants were matched with normal weight participants from the University of Jordan. BMI, waist-hip ratio (WHpR), and waist-height ratio (WHtR) were calculated. Body percent fat mass (%FM) was determined using the bioelectrical impedance analysis. C3, insulin, and glucose serum concentrations were measured. IR was assessed by the homeostasis model assessment of IR (HOMA-IR). **Results:** Serum concentrations of C3 and IR were significantly higher in the obese group than that in the normal body weight, regardless of gender (women: 1.2±0.08 and men: 1.2±0.08 vs women: 0.88±0.07 and men: 0.94±0.05, $p<0.01$; women: 3.6±0.34 and men: 3.9±0.43 vs women: 1.7±0.12 and men: 2.0±0.24, respectively; $p<0.001$). After adjustment for the potential confounders, BMI, waist circumference, WHtR and %FM were correlated positively with C3 (r=0.44; 0.42; 0.47; 0.43, respectively; $p<0.001$), and with IR (r=0.67; 0.61; 0.59; 0.59, respectively; $p<0.001$). C3 was correlated with IR (r=0.35, $p<0.001$). In linear regression analysis, C3 was not associated with IR independent of BMI ($p>0.05$). **Conclusions:** C3 may be a marker of chronic inflammatory process independently underlying IR obese individuals regardless of gender, which may have a role in the progression of IR during obesity.

Key Words: ASP, BIA, HOMA-IR, proinflammatory, complement system

INTRODUCTION

Obesity is a global epidemic disease. It is an independent risk factor for type 2 diabetes mellitus (T2DM), cardiovascular diseases, and certain types of cancers. Obesity is recognized as a complex, multifaceted state of chronic low-grade systemic inflammation, that promotes the obesity-related cardiometabolic complications.[1,2] While adipose tissue (AT) plays a major role in energy storage, it also acts as an active endocrine tissue by expressing and secreting a range of multicellular bioactive proinflammatory adipokines and cytokines, including tumor necrosis factor-alpha (TNF-α), C-reactive protein (CRP), interleukins (IL), and anti-inflammatory factors such as adiponectin.[3] Evidence indicated that the association between obesity and insulin resistance (IR) has been well established, which may be a causal relationship. The major basis for this link is the ability of obesity to provoke IR, which is an essential aspect of the etiology of T2DM and obesity-related comorbidities.[4] Insulin is considered an essential regulator of nearly all aspects of adipocyte function, and adipocytes are one of the most highly insulin-responsive cells. AT amplifies the proinflammatory state by causing down streaming for insulin signaling pathways. This decreases insulin sensitivity, enhances hyperglycemia, and contributes to high compensatory hyperinsulinaemia during obesity.[5]

The complement system is a heat-labile component of the normal plasma made up of a large number of distinct plasma proteins, which react to opsonize pathogens and induce a series of inflammatory responses that help to fight with infection antibodies. The role of the complement system with IgM antibodies in patients with HIV-infected T-cells and patients with melanoma is well recognized.[6] Interestingly, the complement system is increasingly recognized as a cardiometabolic risk factor activated during obesity. The C3 complement component (C3) in particular, plays a critical role in the management of the complement system. Activation of any of the three pathways of the complement system (i.e. classical, alternative, and lectin pathways) leads to the cleavage by the convertase enzyme of the multifunctional protein C3.[7] C3 has been linked to the etiology of obesity, and to a wide range of obesity sequelae.[8] Moreover, C3 is associated with different anthropometric indicators among different age groups, such as BMI, waist circumference (WC), waist-

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Manuscript received 21 April 2016. Initial review completed 07 June 2016. Revision accepted 13 August 2016.
doi: 10.6133/apjcn.012017.02

hip ratio (WHpR), and waist-height ratio (WHtR).[7-9]

Understanding the role of the complement system in the augmentation of obesity-induced chronic AT inflammation and the progression of IR to T2DM may contribute to provide the profile of the immune response in obese individuals. No data about the association between C3 and body composition are available for Jordanian individuals. On these grounds, the objective of the present study was to investigate the association between C3 and body weight status determined by classical anthropometric measures, and the body composition determined by the bioelectrical impedance analysis (BIA), and its association with IR among obese Jordanian individuals aged 18-35 years. These findings would then be used to plan for appropriate public health and dietary interventions to prevent obesity and/or ameliorate immune-inflammatory profiles.

METHODS

Human participants

A case-controlled study was conducted between April 2015 and October 2015. A total of 67 (32 men and 35 women) obese (BMI ≥30 kg/m^2), and 67 normal weight (BMI=18.50-24.99 kg/m^2) age and gender matched students and employees (18-53 years) were recruited from all 19 health, scientific and humanities faculties, and all 27 administrative services units at the University of Jordan. Participants who consented to participate in the study were asked to fill in a health questionnaire. Participants with any chronic or acute illness or receiving any medical treatments were excluded from the study.[10] To eliminate the limitations associated with BMI, cases with % fat mass (%FM) <20 for men and <31 for women or controls with %FM ≥20 for men and ≥31 for women were excluded from the study.[11] The study protocol was approved by the Deanship of Academic Research at the University of Jordan (Ethical approval number 123/2014-2015). All measurements and data were used in a confidential manner.

Weight status assessment

In a follow-up session, weight, height, WC, and hip circumference (HC) were measured using standard procedures.[12] BMI, WHpR, and WHtR were calculated. Body composition was estimated using a calibrated BIA Bodystat®1500 MD unit (Body Stat Ltd., UK) for research purposes. Participants were asked to fast and avoid strenuous exercise for 8-12 hours prior to test, and to drink sufficient water the day before the test. During the test, they were asked to relax in a prone, anatomical position, and to remove any metal from their hands and legs.[11] Results were displayed instantly on the screen of the BIA device. %FM ≥20 for men and ≥31 for women was considered as having excess fat.[13]

Blood sampling

A 5 mL blood sample was collected from fasting (8-12 hours) participants. Blood samples were collected in serum separator tubes, allowed to clot at room temperature (25ºC), and then centrifuged at 3000 xg for 15 min (Labnet®, Hermle Z200A, Germany). Aliquots were stored at -20^{o}C until analyzed.

Biochemical analysis

Serum samples were defrosted. C3 serum concentrations were determined ELISA (MyBioSource®, Human C3 ELISA kit, CA. USA). Fasting insulin levels were determined by sandwich electrochemiluminescence immunoassay (ECLIA) (Roche Diagnostics®, Insulin, Switzerland). Fasting glucose levels were determined using the enzymatic colorimetric method (Human®, Glucose liquicolor, Germany). IR was determined by the homeostasis model assessment of IR (HOMA-IR).[14]

Statistical analysis

Statistical analyses were performed using SPSS for windows (IBM©, SPSS for windows version (19) 2010, Chicago). Results are presented as mean±standard error of the mean (SEM). Differences between the obese group and the control group were obtained using ANOVA. Partial correlations (r) were performed between different anthropometric, body composition, and biochemical variables for the full cohort, after the potential confounders were controlled for. The association between C3 and HOMA-IR were measured by multivariate linear regression analyses for the full cohort, in which HOMA-IR was entered as a dependent variable. The association of C3 with the risk of IR in obese as compared to controls was determined by multiple logistic regression and documented as OR with 95% CI. The cutoffs for different anthropometric indicators were defined as follows: WC >80 cm for women and >94 cm for men; WHpR ≥0.90 for women and ≥0.85 for men; and WHtR ≥0.50 for both genders.

RESULTS

Table 1 shows that weight, BMI, WC, WHpR, WHtR, and %FM were significantly (p<0.01) higher in the obese group than that in the normal body weight participants, regardless of gender. There was no significant difference between obese men and women with regard to age, BMI, HC, and WHtR (p>0.05).

Table 2 shows that C3 levels were significantly higher in the obese group (women: 1.2±0.08 and men: 1.3±0.08; p<0.01) than that among normal body weight counterparts (women: 0.88±0.07 and men: 0.94±0.05; p<0.01). Fasting insulin concentrations and HOMA-IR in the obese group were significantly (p<0.001) higher than that among the normal body weight group, regardless of gender. There was no significant difference between obese men and women for all tested biochemical variables (p>0.05), whereas WHtR was significantly different between normal body weight men and women (p<0.05).

Table 3 shows partial correlations (r) for the full cohort, after adjusting for the potential confounders. BMI, WC, WHtR, and %FM were positively and significantly correlated with C3. WHtR and BMI were the strongest indicators correlated with C3 (r=0.47 and r=0.44, respectively; p<0.001). BMI was the best indicator correlated with HOMA-IR (r=0.67, p<0.001).

Figure 1 illustrates the difference in mean C3 serum concentrations according to the percentage of the standard for the indicative cutoffs of WC, WHpR, and WHtR for

Table 1. Anthropometric and body composition characteristics of the participants[†]

Variables		Obese (n=67)	*p*-value[‡]	Normal (n=67)	*p*-value[‡]
Age (years)	Women (n=35)	25.4±1.0[a]	0.79	23.9±0.78[a]	0.91
	Men (n=32)	25.8±1.0[a]		23.8±0.75[a]	
Weight (kg)	Women (n=35)	84.2±2.2[a]	<0.001	57.3±1.0[b**]	<0.001
	Men (n=32)	102.9±3.0[a]		67.3±1.1[b**]	
Height (cm)	Women (n=35)	158.7±1.1[a]	<0.001	161.5±0.76[b]	<0.001
	Men (n=32)	172.8±0.72[a]		173.0±1.1[a]	
BMI (kg/m^2)	Women (n=35)	33.4±0.69[a]	0.36	21.9±0.31[b**]	0.20
	Men (n=32)	34.4±0.81[a]		22.5±0.32[b**]	
Waist circumference (cm)	Women (n=35)	95.5±1.3[a]	<0.001	73.1±0.79[b**]	<0.001
	Men (n=32)	107±2.0[a]		83.1±1.1[b**]	
Hip circumference (cm)	Women (n=35)	118±1.5[a]	0.57	98.2±0.82[b**]	0.09
	Men (n=32)	116.6±1.9[a]		95.9±1.0[b**]	
Waist-hip ratio	Women (n=35)	0.81±0.01[a]	<0.001	0.75±0.01[b**]	<0.001
	Men (n=32)	0.92±0.01[a]		0.87±0.02[b*]	
Waist-height ratio	Women (n=35)	0.60±0.01[a]	0.19	0.45±0.01[b**]	0.01
	Men (n=32)	0.62±0.01[a]		0.48±0.01[b**]	
% Fat mass	Women (n=35)	39.1±0.70[a]	<0.001	24.6±0.63[b**]	<0.001
	Men (n=32)	27.7±1.0[a]		12.9±0.69[b**]	
% Fat free mass	Women (n=35)	60.9±0.70[a]	<0.001	75.5±0.63[b**]	<0.001
	Men (n=32)	72.3±1.0[a]		87.1±0.69[b**]	

[†]Data are given as the mean ± SEM; $p \leq 0.05$ is considered statistically significant. Means within the same row with different superscript letters are significantly different.
[‡]*p*-value represents the difference between men and women within the same group.
[*]Data are significantly different at $p \leq 0.01$ level.
[**]Data are significantly different at $p \leq 0.001$ level.

Table 2. Biochemical characteristics of participants by gender among groups[†]

Variables		Obese (n=67)	*p*-value[‡]	Normal (n=67)	*p*-value[‡]
C3 (g/L)	Women (n= 35)	1.2±0.08[a]	0.35	0.88±0.07[b*]	0.47
	Men (n=32)	1.3±0.08[a]		0.94±0.05[b*]	
Fasting Glucose (mg/dL)	Women (n= 35)	87.7±1.5[a]	0.16	82.3±2.6[a]	0.06
	Men (n=32)	91.7±2.3[a]		88.5±1.7[b]	
Fasting Insulin (µIU/mL)	Women (n= 35)	16.3±1.3a	0.70	8.3± 0.47[b**]	0.58
	Men (n=32)	17.1±1.7[a]		8.9±0.84[b**]	
HOMA-IR	Women (n= 35)	3.6±0.34[a]	0.55	1.7±0.12[b**]	0.27

C3: complement 3; HOMA-IR: homeostasis model assessment of insulin resistance.
[†]Data are given as the mean ± SEM; $p \leq 0.05$ is considered statistically significant. Means within the same row with different superscript letters are significantly different.
[‡]*p*-value represents the difference between men and women within the same group.
[*]Data are significantly different at $p \leq 0.01$ level.
[**]Data are significantly different at $p \leq 0.001$ level.

Table 3. Correlation coefficients of tested biochemical variables with anthropometric and body composition indicators

Indicators	r (n=134)	
	C3 (g/L)[§]	HOMA-IR[‡]
BMI (kg/m^2)	0.44[**]	0.67[**]
Waist circumference (cm)	0.42[**]	0.61[**]
Waist-hip ratio	0.24[*]	0.26[*]
Waist-height ratio	0.47[**]	0.59[**]
% Fat mass	0.43[**]	0.59[**]
% Fat free mass	-0.43[**]	-0.59[**]

C3: complement 3; HOMA-IR: homeostasis model assessment of insulin resistance.
[‡]Values are gender-adjusted correlation coefficients.
[§]Values are smoking and gender-adjusted correlation coefficients.
[*]Correlation is statistically significant at 0.01 level.
[**]Correlation is statistically significant at 0.001 level.

all participants, which shows whether these indicators exceed the indicative cutoffs or not (i.e. above or below the 100%). C3 serum concentrations were significantly higher among individuals with high %FM of the standard for WC, WHpR, and WHtR, than individuals with a low percent of the standard for the full cohort.

Figure 2 shows the partial correlation between HOMA-IR, and C3 after the outliers were omitted and missing values were replaced by a series mean. After we controlled for gender and smoking, the r value was 0.316 ($p<0.001$).

To examine the effect of C3 on IR, we conducted linear regression models in which HOMA-IR was entered as a dependent factor, and C3 as an independent factor. The predicted changes in HOMA-IR for the full cohort per unit change of selected independent variable were documented as a β with its corresponding *p*-value and 95%

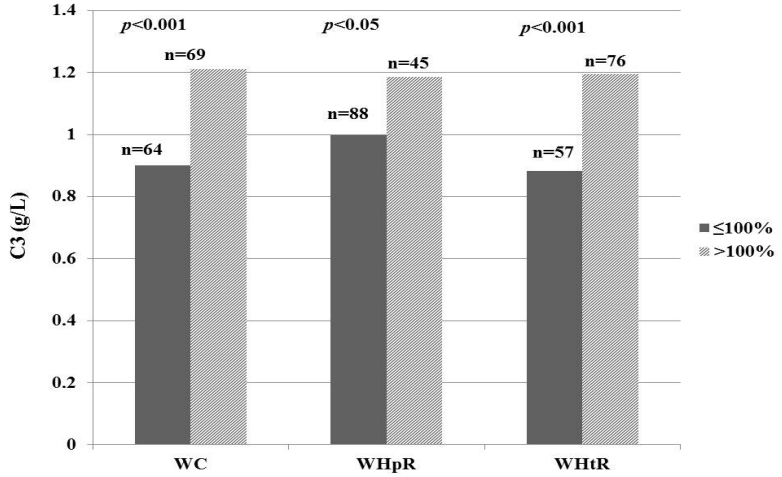

Figure 1. Differences in mean complement 3 (C3) serum levels according to the percent of indicative cutoffs of waist circumference (WC), waist-hip ratio (WHpR), and waist-height ratio (WHtR)

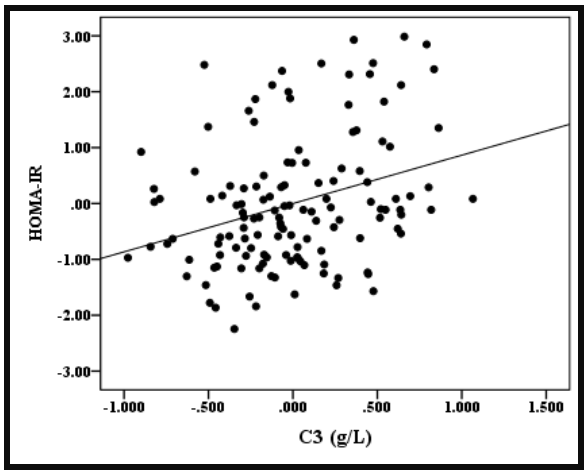

Figure 1. Partial correlation between homeostasis model assessment of insulin resistance (HOMA-IR) and complement 3 (C3)

Table 4. Association between HOMA-IR and C3 in the full cohort[†]

Predictors	β-coefficient	*p*-value	95% CI for β
C3 (g/L)	1.7	<0.001	0.930–2.407
Model 1[‡]	1.6	<0.001	0.805–2.323
Model 2[§]	0.28	NS	-0.401–0.963

β: unstandardized regression coefficient; C3: complement 3; HOMA-IR: homeostasis model assessment of insulin resistance.
[†]$p \leq 0.05$ is considered statistically significant.
[‡]Model 1: adjusted for age, gender and smoking.
[§]Model 2: adjusted as in model 1 plus BMI.

Table 5. Odd ratios of the obese participants with insulin resistance as compared to normal weight participants without insulin resistance[†]

Predictors (n cases/n controls)	OR	*p*-value	95% CI for OR
Crude complement 3	8.07	<0.001	2.71–24.0
Model 1[‡]	16.95	<0.001	4.45–64.66
Model 2[§]	0.388	NS	0.000–0.000

[†]$p \leq 0.05$ is considered statistically significant.
[‡]Model 1: adjusted for age, gender, and smoking.
[§]Model 2: adjusted as in model 1plus BMI.

CI (Table 4). C3 was no longer associated with HOMA-IR increment when BMI was entered into the model.

Table 5 represents the OR of obese participants with IR as compared to controls without IR for C3. The odds of IR among obese participants increased by 16.95-fold as C3 serum concentrations increased, as compared to normal body weight controls (95% CI: 4.45–64.66, $p<0.001$) regardless of age, gender, and smoking status. However, when we adjusted for the BMI, the *p*-value was higher than 0.05.

DISCUSSION

The global epidemic of obesity has increased in all age groups from 857 million in 1980 to reach 2.1 billion in 2013.[1] This study aimed to investigate the association between C3 and different anthropometric and body composition measures, and their association with IR among a group of obese adults as compared to normal weight counterparts.

Mean HOMA-IR was significantly higher in the obese group than that among normal weight participants ($p<0.001$), and was also correlated with WC, WHpR, WHtR, and %FM regardless of gender ($p<0.05$). These findings are consistent with other reports.[15-17] While BMI

showed the strongest association with HOMA-IR, WHpR showed the weakest. Tulloch-Reid *et al.* (2003)[18] reported that BMI was the best predictor of diabetes in men and women, regardless of age. Furthermore, findings demonstrated that WC and WHtR significantly correlated with HOMA-IR (p<0.001).[19,20] Hence, our findings support that obesity has the ability to engender IR.[3,4,10]

Our findings showed that mean C3 serum concentrations were significantly higher among the obese participants than that in the normal weight counterparts, regardless of gender (p<0.01). We also found a positive correlation between mean C3 serum concentrations and different anthropometric and body composition indicators, including WC, WHpR, WHtR, and %FM (p<0.01). The improbable activation of the complement system among obese individuals was investigated by different researchers with regard to obesity measures among different age groups and their results were in accordance with our findings.[7-9] Evidently, AT contains a considerable amount of C3 mRNA, factor B; and it ranks as the first among other tissues to contain factor D (or Adipsin) production. Thus, AT can produce all activating factors of the alternative pathway of the complement system.[21,22]

In accordance with the findings of an earlier report which indicated that elevated C3 is associated with T2DM and IR,[23] we found a positive correlation between IR and C3. Nevertheless, in the current study, we examined this association in the context of several confounders, including age, gender, smoking, and BMI, and demonstrated that one unit increment in C3 was associated with a 1.564 increase in HOMA-IR, regardless of gender, age, and smoking (p<0.001). However this association disappeared when BMI was entered into the third model. These results highlighted the synergistic role of C3 with other inflammatory biomarkers during obesity-induced IR. All alternative pathway factors are produced in the AT as aforementioned. C3 cleavage into C3a and C3b is enhanced by the C3 convertases. The former will form acylation-stimulating protein (ASP) (C3a-desArg), which binds to C5L2 in the AT and provides an insulin-like function. It enhances the metabolism of glucose, triglycerides production, and insulin secretion.[4,24,25] However, both fractions will bind to their receptors and act as potent chemoattractants in obese individuals.[8] In addition, elevated levels of different cytokines from AT may disrupt ASP signaling pathway, leading to elevated levels of ASP's precursor and therefore ASP resistance.[26] Thus, the association between increased %FM and elevated C3 serum concentrations, which in turn exacerbates IR induced by obesity, seems convincing.

This is the first study to provide data on the association between C3 and body composition in obese Jordanian adults. The main limitations of this study were as follows: First, ASP or other cleavage products of C3 were not measured, thus we could not provide a comprehensive profile of the complement system's role in the inflammatory condition associated with obesity. Second, lipid concentrations were not determined, which may affect the C3 serum concentrations, independent of obesity.[4] Third, surrogate indexes of liver function, such as aspartate transaminase and alanine transaminase were not examined to determine the source of C3.[8] Finally, the case-controlled design does not provide the direction of the association and therefore we cannot determine conclusions on the mechanism nor on causality.

Conclusion

Complement 3 serum concentrations were not only associated with anthropometric and body composition indices, but also with increased HOMA-IR among adult men and women. The association between HOMA-IR and C3 was determined by the BMI. The impact of the complement system component on IR in healthy obese individuals needs to be fully evaluated in order to provide an integral understanding of subclinical inflammation associated with obesity.

ACKNOWLEDGEMENTS

The authors would like to acknowledge all participants from the University of Jordan for their time and contribution.

AUTHOR DISCLOSURES

The authors have no conflicts of interest to declare in relation to this article. This work was supported by a grant from the Deanship of Academic Research at the University of Jordan, Jordan (Grant number123/2014-2015).

REFERENCES

1. Ng M, Fleming T, Robinson M, Thomson B, Graetz N, Margono C et al. Global, regional, and national prevalence of overweight and obesity in children and adults during 1980-2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet. 2014;384:766-81. doi: 10.1016/s0140-6736(14)60460-8.
2. Al-Domi HA. Genetic factors that act as an effect modifier for environmental risk factors of obesity. Dirasat, Agricultural Sciences. 2013;39:27-37.
3. Albakri A, Al-Domi H, Majdalani K, Nawaiseh H. Adipose tissue remodeling and its effect on insulin sensitivity in obese individuals: a critical review. Jordan Journal of Agricultural Sciences. 2014;10:215-24.
4. Wlazlo N, van Greevenbroek MM, Ferreira I, Jansen EJ, Feskens EJ, van der Kallen CJ, Schalkwijk CG, Bravenboer B, Stehouwer CD. Low-grade inflammation and insulin resistance independently explain substantial parts of the association between body fat and serum C3: the CODAM study. Metabolism. 2012;61:1787-96. doi: 10.1016/j.metabol.2012.05.015.
5. Suganami T, Ogawa Y. Adipose tissue macrophages: their role in adipose tissue remodeling. J Leukoc Biol. 2010;88:33-9. doi: 10.1189/jlb.0210072.
6. Sakamoto M, Fujisawa Y, Nishioka K. Physiologic role of the complement system in host defense, disease, and malnutrition. Nutrition. 1998;14:391-8.
7. Volp AC, Barbosa KB, Bressan J. Triacylglycerols and body fat mass are possible independent predictors of C3 in apparently healthy young Brazilian adults. Nutrition. 2012;28:544-50. doi: 10.1016/j.nut.2011.08.014.
8. Fiorentino TV, Hribal ML, Andreozzi F, Perticone M, Sciacqua A, Perticone F, Sesti G. Plasma complement C3 levels are associated with insulin secretion independently of adiposity measures in non-diabetic individuals. Nutr Metab Cardiovasc Dis. 2015;25:510-7. doi: 10.1016/j.numecd.2015.02.007.
9. Wamba PC, Mi J, Zhao XY, Zhang MX, Wen Y, Cheng H, Hou DQ, Cianflone K. Acylation stimulating protein but not

complement C3 associates with metabolic syndrome components in Chinese children and adolescents. Eur J Endocrinol. 2008;159:781-90. doi: 10.1530/eje-08-0467.
10. De Pergola G, Nitti A, Bartolomeo N, Gesuita A, Giagulli VA, Triggiani V, Guastamacchia E, Silvestris F. Possible role of hyperinsulinemia and insulin resistance in lower vitamin D levels in overweight and obese patients. Biomed Res Int. 2013; 2013:921348. doi: 10.1155/2013/921348.
11. Meeuwsen S, Horgan GW, Elia M. The relationship between BMI and percent body fat, measured by bioelectrical impedance, in a large adult sample is curvilinear and influenced by age and sex. Clin Nutr. 2010; 29:560-6. doi: 10.1016/j.clnu.2009.12.011.
12. WHO. Waist circumference and waist-hip ratio. Geneva: WHO Publications; 2011.
13. McArdle WD, Katch FI, Katch VL. Exercise physiology: energy, nutrition, and human performance. Baltimore, Maryland: Lippincott Williams and Wilkins; 2007.
14. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia. 1985;28:412-9.
15. Obeidat AA, Ahmad MN, Haddad FH, Azzeh FS. Evaluation of several anthropometric indices of obesity as predictors of metabolic syndrome in Jordanian adults. Nutr Hosp. 2015;32:667-77.
16. Gayoso-Diz P, Otero-Gonzalez A, Rodriguez-Alvarez MX, Gude F, Cadarso-Suarez C, Garcia F, De Francisco A. Insulin resistance index (HOMA-IR) levels in a general adult population: curves percentile by gender and age. The EPIRCE study. Diabetes Res Clin Pract. 2011;94:146-55. doi: 10.1016/j.diabres.2011.07.015.
17. Manios Y, Kourlaba G, Kafatos A, Cook TL, Spyridaki A, Fragiadakis GA. Associations of several anthropometric indices with insulin resistance in children: the children study. Acta Paediatr. 2008;97:494-9. doi: 10. 1111/j.1651-2227.2008. 00729.x.
18. Tulloch-Reid MK, Williams DE, Looker HC, Hanson RL, Knowler WC. Do measures of body fat distribution provide information on the risk of type 2 diabetes in addition to measures of general obesity? Comparison of anthropometric predictors of type 2 diabetes in Pima Indians. Diabetes Care. 2003;26:2556-61.
19. Carneiro IB, Sampaio HA, Carioca AA, Pinto FJ, Damasceno NR. Old and new anthropometric indices as insulin resistance predictors in adolescents. Arq Bras Endocrinol Metabol. 2014;58:838-43.
20. Mbanya VN, Kengne AP, Mbanya JC, Akhtar H. Body mass index, waist circumference, hip circumference, waist-hip-ratio and waist-height-ratio: which is the better discriminator of prevalent screen-detected diabetes in a Cameroonian population? Diabetes Res Clin Pract. 2015; 108:23-30. doi: 10.1016/j.diabres.2015.01.032.
21. Onat A, Can G, Rezvani R, Cianflone K. Complement C3 and cleavage products in cardiometabolic risk. Clin Chim Acta. 2011;412:1171-9. doi: 10.1016/j.cca.2011.03.005.
22. Phieler J, Chung KJ, Chatzigeorgiou A, Klotzsche-von Ameln A, Garcia-Martin R, Sprott D et al. The complement anaphylatoxin C5a receptor contributes to obese adipose tissue inflammation and insulin resistance. J Immunol. 2013; 191:4367-74. doi: 10.4049/jimmunol.1300038.
23. Carroll MV, Sim RB. Complement in health and disease. Adv Drug Deliv Rev. 2011;63:965-75. doi: 10.1016/j.addr. 2011.06.005.
24. Coelho M, Oliveira T, Fernandes R. Biochemistry of adipose tissue: an endocrine organ. AMS. 2013;2:191-200. doi: 10.5114/aoms.2013.33181.
25. Lim J, Iyer A, Suen JY, Seow V, Reid RC, Brown L, Fairlie DP. C5aR and C3aR antagonists each inhibit diet-induced obesity, metabolic dysfunction, and adipocyte and macrophage signaling. FASEB J. 2013;9:822-31. doi: 10. 1096/fj.12-220582.
26. Cianflone K, Xia Z, Chen LY. Critical review of acylation-stimulating protein physiology in humans and rodents. Biochim Biophys Acta. 2003;1609:127-43.