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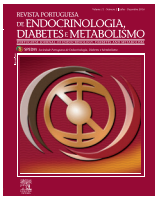

Artigo Original

Platelet to Lymphocyte Ratio and Homeostasis Model Assessment of Insulin Resistance in Pediatric Obesity and Overweight

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INFORMAÇÃO SOBRE O ARTIGO

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A B S T R A C T

Introduction: There is a complex interplay between obesity, inflammation and insulin resistance. We aimed to evaluate the relationship between inflammatory markers, as platelet-to-lymphocyte ratio (PLR) and neutrophil-to-lymphocyte ratio (NLR), and insulin resistance, measured by homeostasis model assessment of insulin resistance (HOMA-IR), in a sample of overweight and obese children and adolescents.
Methods: In this cross-sectional retrospective study, a total of 92 pediatric patients were enrolled (77 obese, 15 overweight) from our general pediatric outpatient clinic. All subjects had a complete blood cell count, glucose, insulin and lipid panel measurements performed in fasting blood samples.
Results: HOMA-IR was positively associated with PLR ($p < 0.001$) and NLR ($p < 0.05$). After adjustment for age, sex and body mass index, the association between HOMA-IR and PLR remained statistically significant.
Conclusion: The positive and independent association between PLR and HOMA-IR may stem from a pro-inflammatory status associated with obesity, and from the complex interplay between platelets, insulin signaling and inflammation. As PLR is an easily available inexpensive marker of inflammation, it is a potential biomarker of insulin resistance and severity of obesity and it could be useful in the follow-up of these patients in daily clinical practice.

Relação entre o Racio Plaqueta-Linfócito e o Modelo Homeostático de Insulinorresistência na Obesidade Pediátrica

Palavras-chave:
Adolescente
Contagem de Linfócitos
Contagem de Plaquetas
Criança
Excesso de Peso
Índice de Massa Corporal
Obesidade Pediátrica
Resistência à Insulina

R E S U M O

Introdução: Avaliar Existe uma relação complexa entre obesidade, inflamação e insulinorresistência. Este estudo pretendia avaliar a relação entre marcadores de inflamação, tais como os rácios plaqueta-linfócito (PLR) e neutrófilo-linfócito (NLR), e a insulinorresistência, medida pelo HOMA-IR (*homeostasis model assessment of insulin resistance*), numa amostra de crianças e adolescentes com obesidade e excesso de peso.
Métodos: Neste estudo transversal retrospectivo, foram avaliados 92 indivíduos em idade pediátrica (77 com obesidade, 15 com excesso de peso) seguidos na nossa consulta de Pediatria, com hemograma completo, glicose, insulina e perfil lipídico efectuados em jejum.
Resultados: O HOMA-IR correlacionou-se positivamente com o PLR ($p < 0,001$) e o NLR ($p < 0,05$). Após correção para idade, género e IMC, a associação entre o HOMA-IR e o PLR manteve-se estatisticamente significativa.
Conclusão: A associação positiva e independente entre o PLR e o HOMA-IR poderá dever-se a

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um estado pró-inflamatório associado à obesidade e à relação complexa entre plaquetas, insulina e inflamação. Assim, uma vez que o PLR é um marcador de inflamação acessível e de baixo custo, poderá revelar-se um potencial marcador de insulinorresistência e gravidade da obesidade, útil no seguimento destes doentes na prática clínica.

Introduction

Obesity is a serious public health problem worldwide. One third of children and adolescents in the United States are obese or overweight.[1] In Europe, one third of 11-year-olds is obese or overweight.[2] There is an increasing rate of hypertension, dyslipidemia, atherosclerosis, and prediabetes in children, associated with obesity.[3] Furthermore, children and adolescents with obesity are at risk for developing type 2 diabetes mellitus and metabolic syndrome, carrying this susceptibility into adulthood.[4]

There is a strong association between inflammation and obesity. One study using data from the Third National Health and Nutrition Examination Survey demonstrated a significant elevation in C-reactive protein level (CRP) in obese and overweight children.[5] Adipose tissue is a source of pro-inflammatory cytokines, especially interleukin-6 and tumor necrosis factor-alpha (TNF-alpha). Simultaneously, the increase in adiposity is associated with lower levels of adiponectin, an anti-inflammatory cytokine, contributing to a systemic inflammatory state.[6]

Insulin resistance (IR) has a multifactorial origin. Visceral obesity, low levels of adiponectin, high levels of free fatty acids, inflammation and genetics contribute to this entity.[7] In fact, IR is associated with low-grade inflammation, as is shown by the independent association between C-reactive protein and insulin sensitivity,[8] some components of the insulin resistance syndrome (IRS and by the overexpression of TNF-alpha in white adipose tissue in obese and insulin-resistant states.[9] Also, in a landmark study, obese mice lacking TNF-alpha function had lower levels of IR.[10] Moreover, several studies have shown a positive association between white blood cell count and type 2 diabetes.[11] Alongside, platelets are potential sites of IR, having insulin receptors, which is associated with impairment in the anti-aggregating action exerted by insulin.[12]

The homeostatic model assessment of insulin resistance (HOMA-IR) is a widely used, accessible, indirect method of quantifying the response of peripheral tissue to insulin.[13]

The neutrophil to lymphocyte ratio (NLR) and platelet to lymphocyte ratio (PLR) have been the subject of intense research and are emerging as accessible and cost-effective markers of inflammation.[14] They have been associated with patient survival in different types of cancer[14] and with cardiovascular and metabolic disorders.[15] In fact, recent studies showed a positive association between PLR and mortality in patients with non-ST segment elevation myocardial infarction[16] and severity of coronary atherosclerosis, alongside C-reactive protein.[17]

To the best of our knowledge, no study to date has evaluated the association between NLR and PLR and IR in children and adolescents with obesity or overweight. In this study, we aimed to assess the association between these inflammatory markers and HOMA-IR, in a sample of pediatric obese and overweight subjects, hypothesizing that higher NLR and PLR associate with higher HOMA-IR levels. We also aimed to assess the association between HOMA-IR and triglycerides to high density lipoprotein cholesterol (TG/HDL-C), reported to be closely related to IR in white adults[18,19] and children,[20-23] being proposed as an alternative to HOMA-IR.[24]

Methods

Subjects

In this retrospective cross-sectional study, obese and overweight patients, aged 5-17 years old, admitted to our general pediatric outpatient clinic, from 2010 to 2015, were identified from medical records. Only patients presenting a complete blood cell count, fasting glucose and insulin were considered. Individuals with hereditary diseases, diabetes mellitus, endocrine disorders, infectious or inflammatory diseases were excluded. Asthma was not an exclusion criterion, comprising a total of 14 individuals, although we considered this diagnosis as a potential confounding factor. Leukocytosis, leukopenia, thrombocytosis or thrombocytopenia were considered exclusion criteria. A total of 92 subjects were included in our study.

Laboratory analysis

Blood samples were collected via venipuncture after a 12-hour fast. Complete blood count was measured by flow cytometry using Unicel DxH 800 Cellular Analysis System (Beckman Coulter, Inc. California, USA).

Plasma glucose was measured by enzymatic assay (hexokinase method), using Cobas c501 analyzer (Roche Diagnostics, Mannheim, Germany). Plasma insulin was measured using Unicel DxC 600i immunoenzymatic assay analyser (Beckman Coulter, Inc. California, USA). Triglycerides, total cholesterol, low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C) were evaluated by enzymatic colorimetric assay, using Cobas c501 analyzer (Roche Diagnostics, Mannheim, Germany).

Clinical measurements

Obesity was defined as body mass index (BMI) greater than the 97th percentile for age and gender, and overweight as BMI between the 85 and 97th percentile, using WHO reference growth charts since there are no national BMI reference charts. HOMA-IR was calculated as fasting glucose (mg/dL) * fasting insulin (UI/L) / 405. NLR was calculated as neutrophils (x 10^9/L) / lymphocytes (x 10^9/L). PLR was calculated as platelets (x 10^9/L) / lymphocytes (x 10^9/L). Triglyceride to HDL-C ratio (Tg/HDL-C) was calculated as triglyceride (mg/dL) / HDL-C (mg/dL).

Statistical analysis

Statistical analysis was performed using R statistical software, version 3.2.2. Kolmogorov-Smirnov test was used to assess if the results were normally distributed. Clinical and laboratorial characteristics of patients were summarized using median, range and interquartile range for continuous variables, as these variables were not normally distributed. Spearman correlation analysis was used to explore the relationship of HOMA-IR with BMI, age, neutrophil and lymphocyte counts, NLR, PLR and Tg/HDL-C. Since the distribution of HOMA-IR was skewed, it was naturally log-transformed before the subsequent regression analysis. The association of HOMA-IR (as the dependent variable) with NLR and PLR (as independent variables) was explored with unadjusted and multivariable-adjusted models. Potential confounders included age, sex, BMI, Tg/HDL-C and diagnosis of asthma. The statistical significance threshold was set at $p < 0.05$.

Table 1. Summary of characteristics (n = 92)

Male / female, n (%)	49 (53) / 43 (47)
Age, years	11.5 (6-17); 6
BMI, kg/m^2	25.8 (19.6-41.9); 6.07
BMI Percentile	
P85-97 (overweight) n (%)	15 (16.3)
> P97 (obese) n (%)	77 (83.7)
BMI z-score	2.37 (1.23-4.28); 0,56
Asthma n (%)	14 (15%)
Fasting glucose, mg/dL	88 (63-110); 12.25
Fasting plasma insulin, IU/mL	9.01 (2.28-37.25); 5.39
HOMA-IR	2.06 (0.44-9.46); 1.12
Total cholesterol, mg/dL	157 (96-216); 40.5
HDL-C, mg/dL	52 (25-78); 15
LDL-C, mg/dL	88 (45.8-133); 35
Triglycerides, mg/dL	71 (25-211); 49.5
Tg/HDL-C	1.33 (0.47-7.03); 1.3
Erythrocytes, x10^9/L	4.82 (3.74-10.6); 0.39
Hemoglobin, x10^9/L	13.44 (10.6-16.2); 1.05
Leukocytes, x10^9/L	6.9 (4.2-11.5); 2.13
Neutrophils, x10^9/L	3.5 (1.5-7.4); 1.4
Lymphocytes, x10^9/L	2.5 (1-4.9); 0.73
Monocytes, x10^9/L	0.6 (0.3-1.3); 0.2
Eosinophils, x10^9/L	0.2 (0-2); 0.3
Basophils, x10^9/L	0 (0-0.1); 0.03
Platelets, x10^9/L	251 (145-430); 78.5
PLR	100 (42.77-193); 38.12
NLR	1.32 (0.38-4.5); 0.76

Data are given as median (range) and inter-quartile range or n and percentage.
BMI: body mass index; HOMA-IR: homeostatic model assessment of insulin resistance; HDL-C: high density lipoprotein cholesterol; LDL-C: low density lipoprotein cholesterol; Tg/HDL-C: triglycerides to high density lipoprotein cholesterol ratio; PLR: platelet to lymphocyte ratio; NLR: neutrophil to lymphocyte ratio.

Ethics statement

This study was approved by the ethics committee of our hospital. For the purpose of this study, no extra samples were collected, no changes to routine care of the patients were made and all data were collected retrospectively.

Results

The demographic, clinical and laboratorial characteristics of the patients are presented in Table 1. The median age of participants was 11.5 years (range 6-17); 53% were male. Seventy-seven (82.6%) patients were obese and 15 (17.4%) were overweight. The median BMI was 25.8 (range 19.6-41.9). The median HOMA-IR was 2.06 (range 0.44-9.46; IQR 1.12).

Spearman correlation analyses are shown in Table 2 and Table 3. Age, BMI, neutrophils, Tg/HDL-C, NLR and PLR were positively correlated with HOMA-IR. BMI was significantly positively correlated with neutrophils and NLR, but not with PLR.

In unadjusted linear regression models, NRL, PLR (Fig. 1) and Tg/HDL-C were positively associated with HOMA-IR (Table 4). These associations, except for NLR and neutrophils, remained statistically significant after adjusting for age, sex and BMI. After additionally adjusting for diagnosis of asthma, PLR and Tg/HDL-C remained positively associated with HOMA-IR. The relation between PLR and HOMA-IR is independent of Tg/HDL-C.

Discussion

PLR and HOMA-IR

In our study, PLR was significantly associated with HOMA-IR, independent of age, sex, BMI, asthma and Tg/HDL-C ratio. As adipose tissue is a source of pro-inflammatory markers,[6] one could argue that this association stems from the influence of BMI itself. However, there was no correlation between BMI and PLR (Table 3), although there was a significant correlation between BMI with neutrophils and NLR.

In a cross-sectional study in adults, increased PLR was significantly associated with the presence and severity of metabolic syndrome, alongside high levels of C-reactive protein.[17] Likewise, in a sample of children and adolescents, a higher platelet count was also associated with the presence of metabolic syndrome.[25] This association can be attributed to a pro-inflammatory status associated with obesity, in which platelets may play an important role.[12,26]

Neutrophiles, NLR and HOMA-IR

There was a positive correlation between neutrophils and HOMA-IR, and BMI.

Similarly, Lee C *et al* reported a positive association of granulocytes and HOMA-IR, independent of age, sex, BMI, ethnicity, smoking and family history of diabetes.[27] In a study of obese, female adolescents, neutrophils were positively associated with BMI, waist circumference and total adipose tissue.[28]

Although NLR was initially positively associated with HOMA-IR, this association was blurred after adjusting for age, sex and BMI. Similarly, in a cohort of nondiabetic adults, NLR was also initially positively associated with HOMA-IR, but was confounded by BMI[27] and in a sample of obese children, a higher NLR was found in the patient group compared to healthy children, although not statistically significant.[29]

Tg/HDL-C and HOMA-IR

We found a positive significant association between Tg/

Table 2. Spearman correlation analysis – HOMA-IR

	Age	BMI	Neut.	Lymph.	Mon.	Plat.	NLR	PLR	Tg/HDL
HOMA-IR	0.36**	0.42**	0.29*	-0.17	0.09	0.2	0.35**	0.35**	0.39**

Data are given as Rho coefficients; * $p < 0.05$; ** $p < 0.001$

Table 3. Spearman correlation analysis – BMI.

	Age	Neut.	Lymph.	Mon.	Plat.	NLR	PLR	Tg/HDL
BMI	0.75**	0.23*	-0.12	-0.01	-0.25	0.21*	-0.03	0.09

Data are given as Rho coefficients; * $p < 0.05$; ** $p < 0.001$

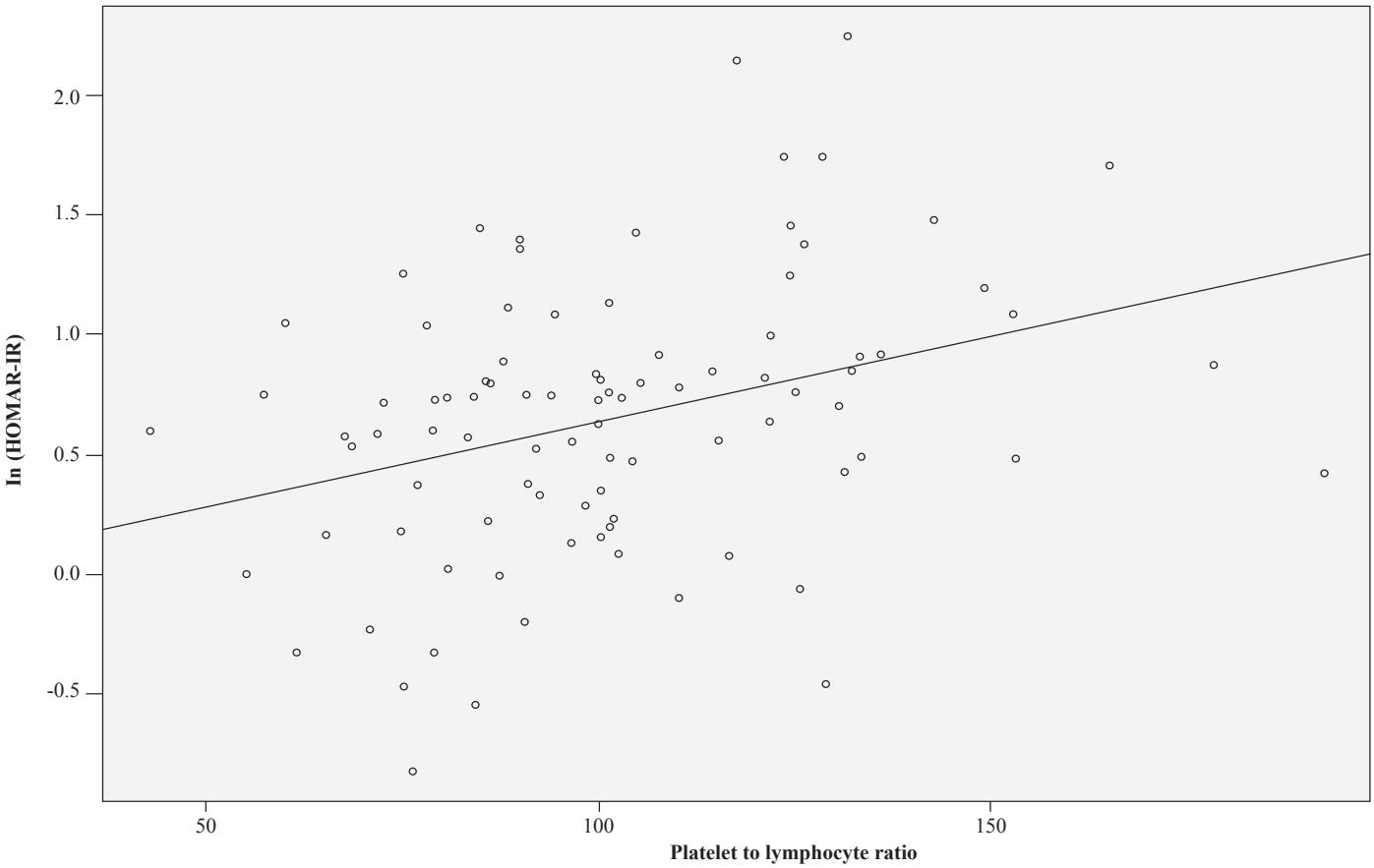

Figure 1. Unadjusted linear regression analysis showing a positive significant correlation between ln(HOMA-IR) and PLR (β = 0.007, $p < 0.001$)

Table 4. Estimated regression coefficients (95% confidence intervals) on the association between PLR, NLR, Neutrophils, Tg/HDL and HOMA-IR

		Ln(HOMA-IR)	
		Beta Coefficients (95% CI)	*p*-value
Platelet to lymphocyte ratio	**Unadjusted**	0.007(0.003, 0.011)	< 0.001
	Model 1	0.008 (0.004, 0.011)	< 0.001
	Model 2	0.007 (0.003, 0.011)	< 0.001
	Model 3	0.006 (0.002, 0.01)	0.0017
Neutrophil to lymphocyte ratio	**Unadjusted**	0.19 (0.03, 0.36)	< 0.05
	Model 1	0.11 (-0.04, 0.27)	0.16
	Model 2	0.06 (-0.10, 0.23)	0.45
	Model 3	0.05 (-0.09, 0.19)	0.49
Neutrophils	**Unadjusted**	0.1 (0.006, 0.198)	< 0.05
	Model 1	0.06 (-0.031, 0.151)	0.19
	Model 2	0.05 (-0.034, 0.144)	0.23
	Model 3	0.03 (-0.047, 0.115)	0.4
Triglycerides to HDL-C ratio	**Unadjusted**	0.19 (0.11, 0.27)	< 0.001
	Model 1	0.18 (0.09, 0.26)	< 0.001
	Model 2	0.17 (0.09, 0.24)	< 0.001

Model 1: adjusted for age, sex and body mass index; Model 2: Model 1 + asthma; Model 3: Model 2 + triglycerides to high density lipoprotein cholesterol ratio.

HDL-C and HOMA-IR, independent of age, sex, BMI and asthma. Similarly, several studies have found this association, both in adults and children.[20] Hirschler *et al* reported a significant association of Tg/HDL-C with HOMA-IR, independent of age, sex and BMI in a sample of Argentinian indigenous children.[21] Additionally, in other studies Tg/HDL-C was a significant predictor of atherosclerosis[22] and arterial stiffness[23] which relates to arterial stiffness in adults. We tested whether TG/HDL-C was an independent predictor of arterial stiffness in youth.\nMETHODS: Subjects 10 to 26 years old (mean 18.9 years, 39% male, 56% non-Caucasian, n = 893 and a better predictor of metabolic syndrome than HOMA-IR.[24]

Asthma

In our study, 15% of patients had asthma. This chronic inflammatory condition is associated with higher C-reactive protein levels[30] and NLR compared to healthy controls,[31] and could bias the relation between PLR and HOMA-IR. However, even after adjusting for asthma diagnosis, PLR remained significantly associated with HOMA-IR.

Limitations

Several limitations must be considered. The cross-sectional design of our study does not allow exploring causality and temporal relationship between the studied variables. The modest sample size, the absence of a control group and the use of single values for HOMA-IR and white blood cell subtypes instead of multiple values over time are other limitations. Although the regression analyses accounted age as a potential confounder, we did not consider pubertal stage, which is known to influence HOMA-IR. Furthermore, as the HOMA-IR cut-off for IR in children and adolescents is a matter of debate, we did not classify patients as insulin resistant or insulin sensitive, that would allow to measure the impact of PLR on the prediction of an insulin resistance state. Also, our study did not include potential confounders like age of onset and duration of obesity and family history of obesity, diabetes mellitus and cardiovascular disorders that might bias the association between obesity, inflammation and IR.

Conclusion

In conclusion, in our sample of children and adolescents, PLR was independently and positively associated with HOMA-IR. As far as we know, we described for the first time the association between PLR and IR. This association may stem from a pro-inflammatory status associated with obesity, and from the complex interplay between platelets, insulin signaling and inflammation. PLR has the potential to be an accessible and quick marker of IR and severity of obesity and it could be useful in the follow-up of these patients in daily clinical practice. Large prospective multicentric studies could further explain the association between inflammation, obesity and insulin resistance in younger patients.

Ethical Disclosures

Conflicts of Interest: The authors report no conflict of interest.

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Confidentiality of Data: The authors declare that they have followed the protocols of their work center on the publication of patient data.

Protection of Human and Animal Subjects: The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).

Responsabilidades Éticas

Conflitos de Interesse: Os autores declaram a inexistência de conflitos de interesse na realização do presente trabalho.

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Proteção de Pessoas e Animais: Os autores declaram que os procedimentos seguidos estavam de acordo com os regulamentos estabelecidos pelos responsáveis da Comissão de Investigação Clínica e Ética e de acordo com a Declaração de Helsínquia da Associação Médica Mundial.

Confidencialidade dos Dados: Os autores declaram ter seguido os protocolos do seu centro de trabalho acerca da publicação dos dados de doentes.

References

1. Ogden CL, Carroll MD, Kit BK, Flegal KM. Prevalence of childhood and adult obesity in the United States, 2011-2012. JAMA. 2014;311:806–14.
2. World Health Organization. Global Status Report on Noncommunicable Diseases 2014. Geneva: WHO; 2014.
3. Prendergast C, Gidding SS. Cardiovascular risk in children and adolescents with type 2 diabetes mellitus. Curr Diab Rep. 2014;14:1–9.
4. Lee JM. Why young adults hold the key to assessing the obesity epidemic in children. Arch Pediatr Adolesc Med. 2008;162:682–7.
5. Ford ES, Galuska DA, Gillespie C, Will JC, Giles WH, Dietz WH. C-reactive protein and body mass index in children: Findings from the Third National Health and Nutrition Examination Survey, 1988-1994. J Pediatr. 2001;138:486–92.
6. Freitas Lima LC, Braga VA, do Socorro de França Silva M, Cruz JC, Sousa Santos SH, et al. Adipokines, diabetes and atherosclerosis: an inflammatory association. Integr Physiol. 2015;6:304.
7. DeBoer MD. Obesity, systemic inflammation, and increased risk for cardiovascular disease and diabetes among adolescents: A need for screening tools to target interventions. Nutrition. 2013;29:379–86.
8. Festa A, D'Agostino R, Howard G, Mykkänen L, Tracy RP, Haffner SM. Chronic subclinical inflammation as part of the insulin resistance syndrome the insulin resistance atherosclerosis study (IRAS). Circulation. 2000;102:42–7.
9. Xu H, Barnes GT, Yang Q, Tan G, Yang D, Chou CJ, et al. Chronic inflammation in fat plays a crucial role in the development of obesity-related insulin resistance. J Clin Invest. 2003;112:1821–30.
10. Uysal KT, Wiesbrock SM, Marino MW, Hotamisligil GS. Protection from obesity-induced insulin resistance in mice lacking TNF-α function. Nature. 1997;389:610–4.
11. Gkrania-Klotsas E, Ye Z, Cooper AJ, Sharp SJ, Luben R, Biggs ML, et al. Differential White Blood Cell Count and Type 2 Diabetes: Systematic Review and Meta-Analysis of Cross-Sectional and Prospective Studies. PLoS One. 2010;5:e13405.
12. Santilli F, Simeone P, Liani R, Davì G. Platelets and diabetes mellitus. Prostaglandins Other Lipid Mediat. 2015;120:28–39.
13. Ascaso JF, Pardo S, Real JT, Lorente RI, Priego A, Carmena R. Diagnosing Insulin resistance by simple quantitative methods in subjects with normal glucose metabolism. Diabetes Care. 2003;26:3320–5.
14. Moore MM, Chua W, Charles KA, Clarke SJ. Inflammation and Cancer: causes and consequences. Clin Pharmacol Ther. 2010;87:504–8.
15. Bhat T, Teli S, Rijal J, Bhat H, Raza M, Khoueiry G, et al. Neutrophil to lymphocyte ratio and cardiovascular diseases: a review. Expert Rev Cardiovasc Ther. 2013;11:55–9.
16. Azab B, Shah N, Akerman M, McGinn JT Jr. Value of platelet/lymphocyte ratio as a predictor of all-cause mortality after non-ST-elevation myocardial infarction. J Thromb Thrombolysis. 2012;34:326–34.
17. Akboga MK, Canpolat U, Yayla C, Ozcan F, Ozeke O, Topaloglu S, et al. Association of platelet to lymphocyte ratio with inflammation and severity of coronary atherosclerosis in patients with stable coronary artery disease. Angiology. 2016;67:89–95.
18. McLaughlin T, Abbasi F, Cheal K, Chu J, Lamendola C, Reaven G. Use of metabolic markers to identify overweight individuals who are insulin resistant. Ann Intern Med. 2003;139:802–9.
19. Li C, Ford ES, Meng YX, Mokdad AH, Reaven GM. Does the association of the triglyceride to high-density lipoprotein cholesterol ratio with fasting serum insulin differ by race/ethnicity? Cardiovasc Diabetol. 2008;7:4.
20. Murguía-Romero M, Jiménez-Flores JR, Sigrist-Flores SC, Espinoza-Camacho MA, Jiménez-Morales M, Piña E, et al. Plasma triglyceride/HDL-cholesterol ratio, insulin resistance, and cardiometabolic risk in young adults. J Lipid Res. 2013;54:2795–9.
21. Hirschler V, Maccallini G, Sanchez M, Gonzalez C, Molinari C. Association between triglyceride to HDL-C ratio and insulin resistance in indigenous Argentinean children. Pediatr Diabetes. 2015;16:606–12.
22. Bittner V, Johnson BD, Zineh I, Rogers WJ, Vido D, Marroquin OC, et al. The TG/HDL cholesterol ratio predicts all-cause mortality in women with suspected myocardial ischemia a report from the Women's Ischemia Syndrome Evaluation (WISE). Am Heart J. 2009;157:548–55.
23. Urbina EM, Khoury PR, McCoy CE, Dolan LM, Daniels SR, Kimball TR. Triglyceride to HDL-C Ratio and Increased Arterial Stiffness in Children, Adolescents, and Young Adults. Pediatrics. 2013;131:e1082–90.
24. Liang J, Fu J, Jiang Y, Dong G, Wang X, Wu W. Triglycerides and high-density lipoprotein cholesterol ratio compared with homeostasis model assessment insulin

resistance indexes in screening for metabolic syndrome in the chinese obese children: a cross section study. BMC Pediatr. 2015;15:138.
25. Lim HJ, Seo MS, Shim JY, Kim KE, Shin YH, Lee YJ. The association between platelet count and metabolic syndrome in children and adolescents. Platelets. 2015;26:758–63.
26. Dan K, Gomi S, Inokuchi K, Ogata K, Yamada T, Ohki I, et al. Effects of interleukin-1 and tumor necrosis factor on megakaryocytopoiesis: mechanism of reactive thrombocytosis. Acta Haematol. 1995;93:67–72.
27. Lee CT, Harris SB, Retnakaran R, Gerstein HC, Perkins BA, Zinman B, et al. White blood cell subtypes, insulin resistance and β-cell dysfunction in high-risk individuals – the PROMISE cohort. Clin Endocrinol. 2014;81:536–41.
28. Kim JA, Park HS. White blood cell count and abdominal fat distribution in female obese adolescents. Metabolism. 2008;57:1375–9.
29. Nascimento H, Rocha S, Rego C, Mansilha HF, Quintanilha A, Santos-Silva A, et al. Leukocyte count versus c-reactive protein levels in obese Portuguese patients aged 6-12 years old. Open Biochem J. 2010;4:72–6.
30. Agassandian M, Shurin GV, Ma Y, Shurin MR. C-reactive protein and lung diseases. Int J Biochem Cell Biol. 2014;53:77–88.
31. Dogru M, Yesiltepe Mutlu RG. The evaluation of neutrophil-lymphocyte ratio in children with asthma. Allergol Immunopathol. 2016;44:292-6.