The relationship between hematologic variables and metabolic syndrome

Gholamhosein Sadri[1], Masoumeh Sadeghi[2*], Nizal Sarrafzadegan [3], Hamidreza Roohafza [4], Mehrdad Yazdani[5], Maryam Boshtam[6], Azam Sadeghi [7], Safoura Yazdekhasti[7]

Abstract

Introduction-The relation between hematologic variables and insulin resistance has been reported previously; however, there is still debate about the correlation between hematologic variables and the metabolic syndrome (MetS). This study aimed to evaluate the relationship between MetS and white blood cells (WBC) and red blood cells (RBC).

Method and Material-This cross-sectional study recruited 11974 participants over 19 years old who participated in the Isfahan Healthy Heart Program (IHHP) in Najafabad and Arak, Isfahan. Participants were selected using multi-stage random sampling. A questionnaire about demographic variables, including age, sex, and past medical history, was filled for each participant by a trained nurse, and the participants' blood pressure, height, weight, waist circumference, and other anthropometric variables were recorded by physicians using standard methods. After 12 hours fasting, laboratory parameters, including RBC, WBC, hemoglobin (Hb), and hematocrit, (Hct) together with such biochemical variables as glucose, triglyceride (TG), and HDL-cholesterol were measured. MetS was defined according to the ATP-III criteria. The data were entered in SPSS-11 and analyzed using the *t*-test and correlation analysis.

Result-From the 11974 participants, 6132 (51%) were female. Mean age was 35.6±3.8 years in the females and 35.9±32 years in the males. In general, 23.1% of the subjects had MetS: 35% in the females and 10.6% in the males ($p<0.05$). WBC and RBC were higher in the subjects with Mets. Regarding the correlation between the hematologic variables and the MetS components, the most significant correlations were seen between TG and WBC (r: 0.195, $p<0.001$) and HDL-C and RBC (r: -0.245, $p<0.001$).

Conclusion- According to our findings, high counts of RBC and WBC were observed in those with MetS. The predictive use of these parameters needs further longitudinal studies***(Iranian Heart Journal 2011; 12 (3):40-46*)**.

Keywords: RBC WBC Metabolic Syndrome

1.Assistant Professor of Pharmacy, Hypertension Research Center, Isfahan Cardiovascular Research Institute, Isfahan University of Medical Sciences, Isfahan, Iran.

2.Associated Professor of Cardiology, Cardiac Rehabilitation Research Center, Isfahan Cardiovascular Research Institute, Isfahan University of Medical Sciences, Isfahan, Iran.

3.Professor of Cardiology, Cardiovascular Research Center, Isfahan Cardiovascular Research Institute, Isfahan University of Medical Sciences, Isfahan, Iran.

4.Psychiatrist, Tobacco Control Department, Isfahan Cardiovascular Research Center, Isfahan Cardiovascular Research institute, Isfahan University of Medical Sciences. Isfahan, Iran.

5..MD, Cardiovascular Research Center, Isfahan Cardiovascular Research Institute, Isfahan University of Medical Sciences, Isfahan, Iran.

6.MSc in Physiology, Cardiovascular Research Center, Isfahan Cardiovascular Research Institute, Isfahan University of Medical Sciences, Isfahan, Iran.

7.BSc, Cardiovascular Research Center, Isfahan Cardiovascular Research Institute, Isfahan University of Medical Sciences, Isfahan, Iran.

The metabolic syndrome (MetS), a cluster of cardiovascular risk factors, including obesity, impaired glucose tolerance, decreased serum high-density lipoprotein cholesterol (HDL), and increased triglyceride (TG), is prevalent worldwide.[1-3]

MetS is estimated to affect 42% of Iranian women and 24% of Iranian men [4], 20% of adults in the US, 50% of Canadians, and 13.1% of Eskimos.[5-8] MetS has been associated with increased risk of cardiovascular disease in a large number of studies and is considered a key target in secondary prevention efforts.[8]

Some studies have described an association between leukocyte and erythrocyte counts and insulin tolerance.[9-13]– a key component of MetS.[1,2-6] Some epidemiological studies have associated increased serum lipid levels and/or hypertension with leukocyte and erythrocyte counts.[14-17] A small amount of data from China and Taiwan has also demonstrated a significant association between MetS and increased blood cell counts.[18] According to another study, the overall prevalence of MetS in central Iran is 21.9% .[19]

Given that leukocyte and erythrocyte count can have inflammatory roles, we sought to assess the association between leukocyte and erythrocyte counts and MetS components in the central part of Iran.

Materials and methods

This study recruited 12600 individuals aged over 19 years in the three Iranian cities of Isfahan, Najafabad, and Arak. Complete data were available in 11974 individuals aged 19 years.

The study was conducted over a one-year period, as part of the Isfahan Healthy Heart Program (IHHP), an interventional program for cardiovascular diseases prevention and health promotion, which lasted 5 years. Isfahan and Najafabad were cities of intervention and Arak served as control. Details of the IHHP have been extensively published previously.[20,21] Multi-stage sampling method was used. Based on the Isfahan-to-Najafabad population ratio of 70/30, we selected 4410 subjects from Isfahan and 1890 from Najafabad (sample size: 6300). The urban-to-rural population ratio in Isfahan, Najafabad, and Arak was 90/10, 60/40, and 67/33, respectively; hence, 3996 (90%) of the subjects in Isfahan were chosen from the city's urban areas and 441 (10%) from its villages. In Najafabad, we selected 1134 (60%) individuals from urban areas and 756 (40%) from rural areas. In Arak, 4221 (67%) individuals were chosen from urban areas and 2074 (33%) from villages.

Sampling was facilitated by the use of a clustered list of households compiled in 1993 for a nationwide polio immunization program. Fifteen random clusters were selected. The polio program clusters were of equal size, hence our clusters were also equal. In Isfahan, we used household health records kept at health centers to select samples from rural areas. In total, we selected 8 villages as clusters. These villages had different populations; therefore, the samples were selected in proportion to the number of households in every village. Equal numbers of men and women were selected, reflecting sex distribution in the population at the time of the study.

In Najafabad, urban and rural samples were selected from 7 urban and 7 rural health and treatment centers according to age distribution and size of the population in each cluster. In Arak, we used the list of households from the polio immunization program to select the required

samples from 10 urban clusters; rural samples were selected in 6 age groups from 13 villages, taking into account the population of every village and each age group. Initially, trained personnel conducted home interviews and obtained demographic information, including age, sex, and past medical and drug history using questionnaires. The subjects were then asked to attend a pre-designated health center after 12-14-hours of fasting. Trained general physicians measured height, weight, waist circumference, and hip circumference of lightly dressed subjects under standard conditions using a Seca 220 scale. Using a Diplomat Riester 0124CE standard sphygmomanometer, blood pressure was measured and recorded on both arms after 5 minutes of rest in sitting position. If the difference of readings exceeded 10 mmHg, the higher of the two readings would be recorded.[19] Blood samples were taken to measure HDL-C, TG, and fasting plasma glucose (FPG) using Pars Azmoon laboratory kits and an ELAN 2000 autoanalyzer. FPG was measured using the glucose oxidase method.

Leukocyte and erythrocyte counts were measured using a cell counter. All the samples were sent to the reference laboratory of Isfahan Cardiovascular Research Center, which is quality controlled by the Leuvin university laboratory in Belgium.

The US National Cholesterol Education Program Adult Treatment Panel III (NCEP) definition of MetS was used in their study. It consists of the following [9]:

1. Raised blood pressure: systolic BP ≥ 130 or diastolic BP ≥85 mm Hg

2. Raised triglycerides: ≥ 150 mg/dL

3. Reduced HDL cholesterol: < 40 mg/dL (1.03 mmol/L) in males, < 50 mg/dL (1.29 mmol/L) in females

4. Raised fasting plasma glucose :(FPG) ≥100 mg/dL

5. Central obesity: waist circumference ≥ 102 cm (male) or ≥ 88 cm (female)

Based on the components of MetS, we divided our study population into four groups: Group I met none of the above criteria, whereas groups II, III, and IV met 1, 2 and 3-5 criteria, respectively.

Patients with conditions that could alter blood cell counts such as renal, hepatic and pulmonary disease, infections and/or cancers, as well as those with leukocyte counts above 15000/ml or lower than 4000/ml and/or hemoglobin concentration greater than 16 g/dl and lower than 9 g/dl were excluded from the study.[23]

Statistical analysis: Data were processed in SPSS-11. We used the independent *t*-test to assess mean leukocyte and erythrocyte counts according to the MetS components. We used the Spearman correlation test to assess any relationship between leukocyte and erythrocyte counts and the MetS components. P values less than 0.05 were considered statistically significant.

Results

We studied 11974 individuals: 6132 women (51%) and 5842 men (49%) with mean ages of 35.6±3.8 years and 35.7±3.2 years, respectively. MetS was diagnosed in 35% of the women and 10.6% of the men, with an overall prevalence of 23.1%.

Table I shows the prevalence of each of the MetS components according to age group and sex.

Hypertriglyceridemia and low HDL-C were the most common forms of dyslipidemia in the men and women, respectively. The prevalence of the MetS components increased in both sexes with age.

Table I. Percentage of MetS components according to age and sex.

Age (years)	Number	Hypertension Number (%)	Increased waist circumference Number (%)	Increased FBS Number (%)	Hypertriglyceridemia Number (%)	Decreased HDL Number (%)
Men						
19-24years	220	13(5.7)	4(1.8)	1(0.4)	55(25.1)	80(36.2)
25-34 years	1742	110(6.3)	70(4.0)	12(0.7)	620(35.6)	599(34.4)
35-44 years	1483	132(8.8)	129(8.7)	38(2.6)	789(53.2)	566(38.2)
45-54 years	996	180(18.1)	179(18.0)	57(5.7)	623(62.6)	370(37.1)
55-64 years	624	194(30.9)	159(25.5)	72(11.5)	376(60.3)	206(33.1)
65<years	777	370(47.5)	161(20.7)	113(14.5)	405(52.2)	242(31.2)
Total	5842	999(17.1)	707(12.1)	293(5.0)	2868(49.1)	2063(35.3)
Women						
19-24years	176	5(2.7)	117(66.5)	1(0.6)	35(19.7)	81(45.9)
25-34 years	1716	77(4.5)	1073(62.6)	12(0.7)	419(24.4)	1007(58.7)
35-44 years	1755	149(8.5)	1130(64.4)	58(3.3)	681(38.8)	1381(78.7)
45-54 years	1103	259(23.5)	692(62.8)	94(8.5)	601(54.6)	955(86.6)
55-64 years	624	246(39.3)	305(57.0)	80(12.9)	417(66.8)	552(88.4)
65<years	758	385(50.8)	430(56.0)	130(17.3)	509(67.2)	666(87.9)
Total	6132	1121(18.3)	3797(61.9)	375(6.1)	2662(43.4)	2642(75.7)

Table II shows the mean leukocyte and erythrocyte counts according to the MetS components. It can be seen that mean leukocyte/erythrocyte counts are significantly higher in the subjects with blood pressure ≥130/85 mm Hg, FPG ≥110 mg/dL, waist

circumference >102 cm (male), 88 cm (female), triglyceride ≥ 150 mg/dL, and HDL-C <40 mg/dL (male), 50 mg/dL (female) (p<0.05).

Table II. Mean and standard deviation of leukocyte and erythrocyte counts according to MetS component

		Mean leukocyte count (per ml)	P	Mean erythrocyte count (per ml)	P
Blood pressure	Increased	6973±1517	<0.01	$4.97\times10^6 \pm 0.65\times10^6$	<0.01
	Normal	6170±1442		$4.73\times10^6 \pm 0.59\times10^6$	
FBS	Increased	7068±1254	<0.01	$4.84\times10^6 \pm 0.51\times10^6$	<0.01
	Normal	6607±1852		$4.63\times10^6 \pm 0.52\times10^6$	
Waist-to-hip ratio	Increased	6735±1454	<0.01	$4.82\times10^6 \pm 0.55\times10^6$	<0.01
	Normal	6324±1618		$4.61\times10^6 \pm 0.56\times10^6$	
TG	Increased	6911±1437	<0.01	$4.93\times10^6 \pm 0.54\times10^6$	<0.01
	Normal	6591±1045		$4.74\times10^6 \pm 0.56\times10^6$	
HDL-C	Increased	7091±1987	<0.01	$4.86\times10^6 \pm 0.73\times10^6$	<0.01
	Normal	6608±1942		$4.62\times10^6 \pm 0.55\times10^6$	

Values are based on NCEP criteria the MetS syndrome Table III shows the results of the correlation analysis via the Spearman test. The leukocyte and erythrocyte counts were found to correlate significantly with TG, FPG, central obesity, and HDL, but not with systolic/diastolic blood pressure (p<0.05). The strongest correlations were seen between erythrocyte counts and HDL and between leukocyte counts and TG

Table III. Correlation between leukocyte and erythrocyte counts and the MetS component

Variable	Leukocyte		Erythrocyte	
	Correlation coefficient (r)	P	Correlation coefficient (r)	P
Waist circumference	0.149	<0.001	0.218	<0.001
Systolic blood pressure	0.017	NS	0.017	NS
Diastolic blood pressure	0.008	NS	0.008	NS
FBS	0.078	<0.001	0.084	<0.001
TG	0.195	<0.001	0.168	<0.001
HDL-C	-0.184	<0.001	-0.245	<0.001

NS: No significant difference

Discussion

We found a significant correlation between leukocyte and erythrocyte counts and all of the MetS components, except hypertension. The prevalence of MetS in our study population was 35% in the women and 10.6% in the men. The prevalence of MetS increased with age. Also, the presence of any of the MetS components (except for hypertension) was accompanied by a significant rise in leukocyte and erythrocyte counts.

One study[5] found that the prevalence of MetS increased with age in Asia, Europe, Africa, and the Americas: MetS was found to be more prevalent in women. However, the relationship between MetS and hematological indicators has been scarcely addressed in the literature.

A study[23] found that the Taiwanese with increased erythrocyte and leukocyte counts were at higher risk of having MetS by 2 and 3 folds, respectively. Similar to our study, the authors of the latter study reported a significant correlation between all the MetS components (except hypertension) and leukocyte and erythrocyte counts. It must be noted however, that the prevalence of MetS in Taiwan is 9% in men and 5% in women, which is considerably lower than that reported in our study population[23] Studies have revealed isolated findings on the association between hematological indicators and some cardiovascular risk factors. However, as MetS consists of a constellation of risk factors, isolated findings are unable to establish a clear cut link between MetS and hematological indicators.

The increase in leukocyte and erythrocyte counts in MetS has been attributed to hyperinsulinemia and insulin resistance.[25] It is postulated that increased serum insulin increases immune system activity and increases inflammatory markers such as Tumour Necrosis Factor-A and Interleukin 6, leading to increased leukocyte counts.[25-27]

It has been posited by some authors that increased serum cortisol in MetS may be the cause of the associated rise in leukocytes counts too.[28] Some laboratory studies have demonstrated that increased serum insulin stimulates the bone marrow, resulting in the expansion of the erythroid cell line and the pursuant increase in erythrocyte numbers[29]; clinical studies have yet to confirm these findings.

Conclusion

Larger-scale studies on the association between MetS and hematological parameters, by taking account of serum insulin concentration and insulin resistance are warranted. The prevalence of MetS is relatively high (23% in our study population). Future studies into the association of hematological parameters and MetS may lead to the development of inexpensive diagnostic tests with potentially wide application in indentifying individuals at high risk of cardiovascular disease.

Acknowledgment

The Isfahan Healthy Heart Program (IHHP) is supported by a grant No. 31309304) from the Iranian Budget and Planning Organization, as well as the Deputy for Health of the Iranian Ministry of Health and Medical Education, Isfahan Cardiovascular Research Centre and Isfahan Provincial Health Center, both affiliated to Isfahan University of Medical Sciences. We thank the personnel of Isfahan and Arak Provincial Health offices for their cooperation.

References

1. Fonseca VA. The metabolic syndrome, hyperlipidemia, and insulin resistance. Clin Cornerstone. 2005;7(2-3):61-72. Review.

2. Kim E. Insulin resistance at the crossroads of metabolic syndrome: systemic analysis using microarrays. Biotechnol J. 2010 Sep;5(9):919-29. Review.

3. Heidari R, Sadeghi M, Talaei M, Rabiei K, Mohammadifard N, Sarrafzadegan N. Metabolic syndrome in menopausal transition: Isfahan Healthy Heart Program, a population based study. Diabetology & Metabolic Syndrome 2010, 2(E pub).

4. Sarrafzadegan N, Kelishadi R, Baghaei A, Hussein Sadri G, Malekafzali H,Mohammadifard N, Rabiei K, Bahonar A, Sadeghi M, O'Laughlin J. Metabolic syndrome: an emerging public health problem in Iranian women: Isfahan Healthy Heart Program. Int J Cardiol. 2008;131(1):90-6.

5. Eckle RH, Grundy SM, Zimmet PZ. The metabolic syndrome. Lancet 2005; 365(9468): 1415-28.

6. Park YW, Zhu S, Palanippan L, Heshka S, Carnethon MR, Heymsfield SB. The metabolic syndrome: prevalence and associated risk factors findings in the US population from the third national health and nutritional examination survey, Archives of Internal Medicine 2003: 163(4): 427-36.

7. Pollex RL, Khan H, Connelly PW, Young TK, Hegele RA. The metabolic syndrome in Inuit. Diabetes Care 2004; 27(6): 1517-9.

8. Wyszynski DF, Waterqorth DM, Barter PJ, Cohen J, Kesaneiemi YA, Mahley RW, et al. relation between atherogenic dyslipidemia and adult treatment program III definition of metabolic syndrome AM J Cardiol 2005; 95(2):194-8.

9. Expert panel on detection, evaluation and treatment of high blood cholesterol in adults. Executive summary of the third report of the national cholesterol education program (NCEP) expert panel on detection, evaluation and treatment of high blood cholesterol in adults (Adult Treatment Panel III). JAMA 2001;285: 2486-96.

10. Barbieri M, Ragno E, Benvenuti E, Zito GA, Ferrucci L, Paolisso G. New aspects of insulin resistance syndrome: impact on hematological parameters. Diabetologia 2001; 44(10):1232-7.

11. Piédrola G, Novo E, Escobar F, García-Robles R. White blood cell count and insulin resistance in patients with coronary artery disease. Ann Endocrinol (Paris). 2001;62(1 Pt 1):7-10.

12. Vivian CM, Ellinger; Ludmila T. Carlini; Rodrigo O, Moreira; Ricardo M.R. Meirelles. Relation between insulin resistance and hematological parameters in a Brazilian sample. Arq Bras Endocrinol Metab 2006; 50(1): 114-7.

13. Vozarova B, Weyer C, Lindsay R.S, Pratley R.E, Bogardus C, Tataranni P.A. High White Blood Cell Count Is Associated With a Worsening of Insulin Sensitivity and Predicts the Development of Type 2 Diabetes. Diabetes. 2002;51(2):455-61.

14. Munir TA, Afzal MN, Habib-ur-Rehman. Baseline leukocyte count and acute coronary syndrome: predictor of adverse cardiac events, long and short-term mortality and association with traditional risk factors, cardiac biomarkers and C-reactive protein. J Ayub Med Coll Abbottabad. 2009;21(3):46-50.

15. Kim DJ, Noh JH, Lee BW, Choi YH, Chung JH, Min YK, Lee MS, Lee MK, Kim KW. The associations of total and differential white blood cell counts with obesity, hypertension, dyslipidemia and glucose intolerance in a Korean population. J Korean Med Sci 2008;23(2):193-8.

16. Wen Y. High red blood cell distribution width is closely associated with risk of carotid artery atherosclerosis in patients with hypertension. Exp Clin Cardiol 2010;15(3):37-40.

17. Cicco G, Pirrelli A. Red blood cell (RBC) deformability, RBC aggregability and tissue oxygenation in hypertension. Clin Hemorheol Microcirc. 1999;21(3-4):169-77.

18. Nakanishi N, Suzuki K, Tatara K. White blood cell count and clustered features of metabolic syndrome in Japanese male office workers. Occup Med, 2002; 52(4): 213-8.

19. Gharipoor NI, Kelishadi R, Baghaie AM, Bosh tam Ni, Rabeie K. Prevalence of metabolic syndrome in An Iranian Adult population.

Advanced Research Yields in Atherosclerosis, 2005; 1(3): 188-92.

20. Sarraf-Zadegan N, Sadry G, Malek Afrali H, Baghaei NI, MohammadiFard N, Shahrokhy S. et al. Isfahan Healthy Heart Programme: a comprehensive integrated community-based programme for cardiovascular disease prevention and control. Design Methods and initial experince. Acta Cardiol 2003; 58(4): 309-20.

21. Sarrafzadegan N, Baghaei A, Sadri Gh, Kelishadi R, Malekafzali H, Boshtam M. Isfahan healthy heart program: Evaluation of comprehensive, community-based interventions for non-communicable disease prevention. Prevention and Control 2006; 2:73–84.

22. Saitoh S. [Guideline for the management of elderly hypertension]. Nihon Ronen Igakkai Zasshi. 2008 Nov;45(6):601-4. Japanese.

23. Wang YY, Lin SY, Liu PH, Cheung BM, Lai \\'A. Association between hematological parameters and metabolic syndrome components in a Chinese population. J Diabetes Complications 2004; 18(6): 322-7.

24. Pe´rez-Lo´pez FR, Larrad-Mur L, Kallen A, Chedraui P, Taylor HS. Gender Differences in Cardiovascular Disease: Hormonal and Biochemical Influences. Reproductive Sciences 2010;17(6): 511-531.

25. Toker S, Rogowski O, Melamed S, Shirom A, Shapira I, Berliner S, et al. Assosiation of components of the metabolic syndrome with the appearance of aggregated red blood cells in the peripheral blood. An unfavourable hemorheological finding. Diabetes Metab Res Rev 2005;21(2):197-202.

26. Lazenby MG, Crook MA. The innate immune system and diabetes mellitus: the relevance of periodontitis? A hypothesis. Clin Sci (Lond). 2010 Aug ;119(10):423-9.

27. Chuang CC, Martinez K, Xie G, Kennedy A, Bumrungpert A, Overman A, Jia W, McIntosh MK. Quercetin is equally or more effective than resveratrol in attenuating tumor necrosis factor-{alpha}-mediated inflammation and insulin resistance in primary human adipocytes. Am J Clin Nutr. 2010 Dec;92(6):1511-21. Epub 2010 :13.

28. Anagnostis P, Athyros VG, Tziomalos K, Karagiannis A, Mikhailidis DP. Clinical review: The pathogenetic role of cortisol in the metabolic syndrome: a hypothesis. J Clin Endocrinol Metab 2009;94(8):2692-701

29. Aiss A, Benhaddad A, Monnier JF, Fedou C. Insulin-like growth factor-binding protein and blood rehology. Clin of the immune system? Diabetologia. 1998; 41(10): 1241-8. Hemorheol Microcirc, 2002; 26(3): 209-17.