Correlation of Hematologic Factors to Carotid Intima-Media Thickness in Men and Women: a Study of 2767 Asymptomatic Subjects of Taiwan

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Abstract-

Purpose: A correlation between carotid intima-media thickness (CIMT) and blood cells has not been well documented. Studies of a possible relationship between blood cell components and left (Lt) and right (Rt) side CIMT in asymptomatic men and women in Taiwan have not been conducted previously. The study aims to correlate factors of complete blood cells (CBC) to CIMT for men and women.

Methods: Data collection from 2767 asymptomatic healthy checkup individuals, age 35-75, 1517 men and 1250 women, were separated into four groups: CIMTML (men's Lt), CIMTMR (men's Rt), CIMTWL (women's Lt), and CIMTWR (women's Rt) for analysis of CBC factors vs. CIMT. A cut-off point for each factor was examined for the existence of significant differences in CIMT for individuals among the four test groups who had abnormal CBC data.

Results: The regression equations of eight CBC factors vs. CIMT of four groups calculated as R2adj range were from 70.5% to 79.4%. Further comparison of CIMT in different groups by cut points of CBC factors showed significant differences in red blood cells (RBC) and platelets (PLT), but not in white blood cells (WBC).

Conclusion: Higher RBC, and lower mean corpuscular volume (MCV) and mean corpuscular hemoglobin (MCH) were associated with lower CIMT in asymptomatic men in Taiwan. Further studies to confirm these differences are warranted.

Key Words: carotid intima-media thickness, blood cell, atherosclerosis

Acta Neurol Taiwan 2012;21:158-164

INTRODUCTION

High resolution B-mode ultrasound examination on carotid artery atherosclerosis is widely applied in daily practice, especially for the neurologist[1,2], because of its convenience, noninvasiveness, and because of the well

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Received November 24, 2011. Revised February 29, 2012.
Accepted September 14, 2012.

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established association of carotid artery atherosclerosis with risk of thrombotic stroke[3,4].

Carotid intima-media thickness (CIMT) is the assessment most frequently used to predict thrombotic stroke because the thickness measurement is a continuous number that can be directly compared to other factors in a linear way[5]. It is well known that several factors influence CIMT (e.g, sex, age, blood pressure, serum lipids)[6] and that some of them vary according to differences in population and life style[7-10]. Thus, it may be beneficial for every country to establish its own CIMT data bank.

There have been a few reports concerning CIMT in Taiwan, one in hypertensive patients[11] and another in non-symptomatic subjects[6]. We have suggested that these studies should be performed by stratifying groups according to gender and according to separate measures of CIMT in left and right carotid arteries[12]. Blood cells are known to be involved in the genesis of atherosclerosis and have prognostic ability in regard to risk of stroke[13-16]. For example, white blood cell (WBC) levels are known to be associated with the inflammatory mechanism of atherosclerosis[17], monocyte levels are linked to carotid plaque formation[18] and platelet (PLT) and red blood cell (RBC) levels are known to be associated to the formation of plaque[19,20]. This study examined the association of blood cell levels with the presence or absence of left-right side increasing of CIMT in asymptomatic men and women in Taiwan.

METHODS

We analyzed CIMT and eight CBC factors of 2767 asymptomatic individuals (1517 men and 1250 women), age from 35-75, who came to Eonway Healthy Maintenance Center, Western Garden Medicare Group for a thorough health checkup, from Feb. 12, 2003 to Oct. 24, 2008.

CBC factors used for analysis of an association with CIMT were measured by XT-1800i automated analyzer (Sysmex Corp. Japan) which consisted of eight factors: WBC (10^3/uL), RBC (10^6/uL), hemoglobin (Hb) (g/dL), hematocrit (Hct) (%), MCV (fL), MCH (pg), mean corpuscular hemoglobin concentration (MCHC) (g/dL), and PLT (10^3/uL).

For CIMT (in mm), B-mode ultrasonography was performed with a Toshiba SSA 6600A system equipped with a high-resolution broadband transducer 7.5 MHz. All persons were examined by an experienced technologist using standard methods described previously[6,12]. Paired T-Test analysis of CIMT to 30 volunteer subjects repeated after 2 weeks showed no significant differences. The mean$\pm$SD of CIMT at first vs. 2 weeks later were 0.8250$\pm$0.158 mm and 0.838$\pm$0.155 mm with T = -1.35 and p = 0.187.

The four groups of individuals analyzed for CIMT were CIMTML (men/Lt carotid), CIMTMR (men/Rt carotid), CIMTWL (women/Lt carotid), and CIMTWR (women/Rt carotid).

The following cut points of upper and lower limit of each CBC factor were used for further comparisons of CIMT differences: WBC, 10×10^3/mL, RBC, 6.0×10^6/mL and 4.4×10^6/mL for men and 5.5×10^6/mL and 4.0×10^6/mL for women, Hb, 14 g/dL for men and 12 g/dL for women, Hct 50% and 39% for men and 44% and 36% for women, MCV, 70 fL, MCH, 34.6 pg and 25.4 pg for men and 25.4 pg for women, MCHC, 36 g/dL and 31 g/dL, PLT, 140×10^3/mL. Cut points of all factors except for MCV were selected by upper or lower limit of each factor. Some cut points of factors were excluded because of insufficient case numbers (No).

Regression equations were used to determine significant differences between all CBC factors and CIMT. A two sample t-test was used to compare differences of CIMT between groups separated by cut points. Minitab 15 software was used for all statistical analyses.

RESULTS

The basic statistical analyses are presented in Table 1 with all variables in men and women. There are significant differences between men and women in all eight CBC factors and in CIMT Lt and CIMT Rt.

The regression equation of eight CBC factors to CIMT and the statistical data for all four groups are: -4.96 - 0.0003 WBC + 0.0314 RBC + 0.142 Hgb - 0.0919

Table 1. Descriptive Statistic Data of All CBC Factors and CIMT in Men and Women

CBC	Men		Women		P-Value
Factors/units	Mean (SD)	95%CI	Mean (SD)	95%CI	
WBC/10^3/uL	6.507 (1.693)	(6.424, 6.589)	6.088 (1.572)	(6.004, 6.173)	0.000‡
RBC/10^6/uL	5.136 (1.400)	(5.068, 5.204)	4.505 (0.425)	(4.483, 4.528)	0.000‡
Hgb/g/dL	15.497 (1.228)	(15.437, 15.557)	13.291 (1.232)	(13.225, 13.358)	0.000‡
Hct/%	45.992 (3.464)	(45.823, 46.160)	40.352 (3.280)	(40.176, 40.529)	0.000‡
MCV/fL	90.584 (6.165)	(90.284, 90.884)	89.922 (6.794)	(89.557, 90.288)	0.006†
MCH/pg	30.533 (2.458)	(30.414, 30.653)	29.640 (2.755)	(29.491, 29.788)	0.000‡
MCHC/g/dL	33.685 (1.1542)	(33.629, 33.741)	32.919 (1.168)	(32.856, 32.982)	0.000‡
PLT/10^3/uL	221.94 (50.12)	(219.50, 224.38)	246.94 (70.61)	(243.14, 250.73)	0.000‡
CIMT Lt	0.788 (0.116)	(0.782, 0.794)	0.740 (0.099)	(0.735, 0.746)	0.000‡
CIMT Rt	0.781 (0.111)	(0.776, 0.787)	0.737 (0.101)	(0.731, 0.743)	0.000‡

†p<0.01, ‡p<0.001

Table 2. Mean and SD of CIMT between Two Sides of Cut Points of All CBC Factors in Men with P-value

Factors	Cut	Sample	Lt			Rt		
	Points	No	Mean	SD	P-Value	Mean	SD	P-Value
WBC/10^3/uL								
	≤10	1471	0.788	0.116	0.226	0.781	0.111	0.731
	>10	46	0.813	0.139		0.787	0.115	
RBC/10^6/uL								
	≤6.0	1455	0.79	0.117	0.000‡	0.783	0.112	0.000‡
	>6.0	62	0.743	0.087		0.737	0.081	
	≤4.4	69	0.814	0.119	0.066	0.810	0.114	0.034*
	>4.4	1448	0.787	0.116		0.780	0.111	
Hgb/g/dL								
	≤14	1391	0.797	0.326	0.287	0.784	0.223	0.184
	>14	126	0.813	0.129		0.866	0.671	
Hct/%	≤50	1374	0.790	0.119	0.024*	0.783	0.113	0.036*
	>50	143	0.771	0.093		0.766	0.086	
	≤39	37	0.830	0.124	0.048*	0.835	0.123	0.010*
	>39	1480	0.787	0.116		0.780	0.110	
MCV/fL	≤70	44	0.751	0.104	0.017*	0.950	1.210	0.432
	>70	1473	0.799	0.319		0.786	0.219	
MCH/pg								
	≤34.6	1498	0.788	0.117	0.886	0.782	0.111	0.123
	>34.6	19	0.784	0.107		0.752	0.077	
	≤25.4	67	0.748	0.089	0.000‡	0.744	0.083	0.000‡
	>25.4	1448	0.790	0.117		0.783	0.112	
MCHC/g/dL								
	≤36	1478	0.789	0.117	0.400	0.782	0.111	0.192
	>36	39	0.777	0.084		0.762	0.094	

Table 2. Mean and SD of CIMT between Two Sides of Cut Points of All CBC Factors in Men with P-value

Factors	Cut	Sample	Lt			Rt		
	Points	No	Mean	SD	P-Value	Mean	SD	P-Value
	≤31	32	0.775	0.092	0.413	0.772	0.085	0.535
	>31	1485	0.789	0.117		0.781	0.111	
PLT/10^3/uL								
	≤140	51	0.762	0.080	0.038*	0.763	0.093	0.196
	>140	1466	0.789	0.117		0.782	0.112	

*p<0.05, ‡p<0.001

Table 3. Mean and SD of CIMT between Two Sides of Cut Points of All CBC Factors in Women with P-value

Factors	Cut	Sample	Lt			Rt		
	Points	No	Mean	SD	P-Value	Mean	SD	P-Value
WBC/10^3/uL								
	≤10	1228	0.740	0.099	0.379	0.736	0.100	0.107
	>10	22	0.762	0.112		0.781	0.121	
RBC/10^6/uL								
	≤5.5	1217	0.740	0.099	0.879	0.737	0.100	0.541
	>5.5	33	0.737	0.101		0.750	0.122	
	≤4.0	96	0.724	0.109	0.130	0.717	0.112	0.066
	>4.0	1154	0.742	0.098		0.739	0.100	
Hgb/g/dL								
	≤12	1110	0.742	0.100	0.016*	0.739	0.102	0.006‡
	>12	140	0.722	0.092		0.711	0.114	
Hct/%								
	≤44	1098	0.738	0.098	0.061	0.735	0.100	0.122
	>44	152	0.755	0.106		0.749	0.106	
	≤36	101	0.721	0.099	0.043*	0.720	0.112	0.115
	>36	1149	0.742	0.099		0.738	0.100	
MCV/fL								
	≤70	41	0.722	0.099	0.236	0.728	0.018	0.634
	>70	1209	0.741	0.099		0.736	0.003	
MCH/pg								
	≤25.4	99	0.721	0.088	0.030*	0.718	0.098	0.053
	>25.4	1151	0.742	0.100		0.738	0.101	
MCHC/ g/dL								
	≤31	79	0.724	0.070	0.044*	0.723	0.087	0.172
	>31	1171	0.741	0.101		0.737	0.103	
PLT/10^3/uL								
	≤140	19	0.726	0.105	0.567	0.732	0.089	0.795
	>140	1231	0.740	0.099		0.737	0.101	

*p<0.05, ‡p<0.01

Table 4. Different Correlation of Hematologic Factors and PLT in Men and Women

Factors	Men			Women	
	Lt	Rt		Lt	Rt
RBC*	+++	+++	RBC*	-	-
Hgb*	-	-	Hgb*	+	++
Hct*	+	+	Hct†	+	-
MCV†	+	-	MCV†	-	-
MCH†	+++	+++	MCH†	-	-
MCHC†	+	-	MCHC†	+	-
PLT*	+	-	PLT*	-	-

*increase value of factors, †decrease value of factors, ‡-: no; +: mild; ++: moderate; +++: strong correlation

Hct + 0.141 MCV - 0.394 MCH + 0.209 MCHC - 0.000930 PLT, - 3.24 - 0.0122 WBC - 0.0011 RBC + 0.140 Hgb - 0.0802 Hct + 0.113 MCV - 0.317 MCH + 0.154 MCHC - 0.000732 PLT, 4.3 - 0.0228 WBC + 0.737 RBC + 1.28 Hgb - 0.473 Hct + 0.136 MCV - 0.290 MCH - 0.247 MCHC - 0.000598 PLT, and 2.4 - 0.0258 WBC + 0.723 RBC + 0.636 Hgb - 0.262 Hct + 0.065 MCV - 0.074 MCH - 0.186 MCHC - 0.000777 PLT in CIMTML, CIMTMR, CIMTWL, and CIMTWR, respectively. The models of these regression equations are able to explain 79.4%, 77.3%, 70.5%, and 72.3% of cases in CIMTML, CIMTMR, CIMTWL, and CIMTWR, accordingly.

Further analysis comparing CIMT of each factor separated by cut points showed significant differences of the following as factor, cut point, mean (SD) of CIMT (below and above cut point), *p*-value of men: RBC, 6.0 $\times 10^6$/uL, below, 0.790 (0.117), above, 0.743 (0.087), $p = .000$ of men's Lt and below, 0.783 (0.112), above, 0.737 (0.081), $p = .000$ of men's Rt; RBC, 4.4×10^6/ml, above, 0.780 (0.111), below, 0.810 (0.114), $p = 0.034$ of men's Rt; Hct, 50%, below, 0.790 (0.119), above, 0.771 (0.093), $p = .024$ of men's Lt and below, 0.783 (0.113), above, 0.776 (0.086) of men's Rt; Hct, 39%, below, 0.830 (0.124), above, 0.787 (0.116), $p = .048$ of men's Lt and below, 0.835 (0.123), above, 0.780 (0.110), $p = .010$ of men's Rt; MCV, 70 fl, below, 0.751 (0.104), above, 0.799 (0.319), $p = .017$ of men's Lt; MCH, 25.4 pg, below, 0.748 (0.089), above, 0.790 (0.117), $p = .000$ of men's Lt and below, 0.744 (0.083), above, 0.783 (0.112), $p = .000$ of men's Rt; PLT, 140×10^3/mL, below, 0.762 (0.080), above, 0.789 (0.117), $p = .038$ of men's Lt.

Further analysis comparing CIMT of each factor separated by cut points showed significant differences of the following as factor, cut point, mean (SD) of CIMT of below and above cut point, *p*-value of women: Hb, 12.0 g/dL, below, 0.742 (0.100), above, 0.722 (0.092), $p = .016$ of women's Lt and below, 0.739 (0.102), above, 0.711 (0.114), $p = .006$ for women's Rt; Hct, 36%, below, 0.721 (0.099), above, 0.742 (0.099), $p = .043$ of women's Lt; MCH, 25.4 pg, below, 0.721 (0.088), above, 0.742 (0.100), $p = .030$ of women's Lt; MCHC, 31.0 g/dL, below, 0.724 (0.070), above, 0.741 (0.101), $p = .044$ of women's Lt. For details see Table 2 and 3 for results of men and women.

DISCUSSION

The linear correlation of all factors of CBC to CIMT for all four groups is good, though not excellent, and to our knowledge, has never been shown before. We found that at some cut points of certain factors of CBC, there was no significant difference regarding CIMT. Those factors and their cut points of groups that showed lower CIMT when the factor's level was higher were: RBC, 6.0×10^6/mL of men's Lt and Rt; RBC, 4.4×10^6/mL of men's Rt; Hb, 12.0 g/dL of women's Lt and Rt; Hct, 50% of men's Lt and Rt; Hct, 39% of men's Lt and Rt. Those factors and their cut points of groups that showed higher CIMT when factor's level were higher were: Hct, 36% of women's Lt; MCV, 70 fL of men's Lt; MCH, 25.4 pg of men's Lt and Rt; MCH, 25.4 pg of women's Lt; MCHC, 31.0 g/dL of women's Lt; PLT, 140×10^3/mL of men's Lt.

Overall, WBC showed no difference in CIMT for all four groups in upper limit cut point of 10×10^3/mL, while PLT below the cut point of 140×10^3/mL was associated with a significantly lower CIMT in men's Lt. These results might be explained by other reports of significance in monocyte, a subgroup of WBC[17] and PLT corpuscular volume[16], but not whole WBC and PLT. However, one study showed that leukocytosis is associ-

ated with 2 years follow up of increasing CIMT[21].

For RBC's, multiple indexes as such as RBC, Hct, Hb, MCV, MCH, and MCHC, the most significant factors occurred over RBC above upper limit and MCH below lower limit in men's Lt and Rt (p = .000). The second important groups of factors were Hct below lower limit of men's Rt and Hb above upper limit of women's Rt. The Edinburgh Study showed that Hct was linearly related to CIMT in men but not in women, yet showed no difference when comparing Hct with four groups of CIMT separated by 0.65, 0.85 and 1.05[22]. Our data showed no linear correlation of Hct to CIMT, nor had we tested the way Lee et al[22] did with four stepwise groups of CIMT. However, our study showed significant differences of Hct to CIMT; the lower the Hct, the higher the CIMT was in men; and the lower the Hct, the lower CIMT was in women. Comparing our data to that of the Edinburgh Study, the correlation trend of Hct to CIMT is the same in women, but reversed in men. It is well known that men and women are different in many aspects of pathogenesis, risk factors and protective effects to atherosclerosis and cardiac and cerebral thrombosis[2,8,15,17,23,24]. Most of these differences in men and women are quantitative, but unlike the Hct in our series which showed a trend in the reverse direction.

The limitation of this study is that there are no associated factors concerning atherosclerosis such as hypertension, smoking, and hyperlipidemia, etc. for different groups to compare. This is due to lack of such electronic record of these factors in the past of our facility.

In conclusion, men and women are similar in regard to the correlation of CBC factors to CIMT in some degree, except for an opposite direction of Hct between men and women. For detailed comparisons see Table 4. Further studies with better design to clarify this phenomenon are highly recommended.

ACKNOWLEDGMENTS

We are very grateful to Prof. Rong-Chi Chen from En Chu Kong Hospital for discussion and suggestions for this manuscript.

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