Association between erythrocyte parameters and metabolic syndrome in urban Han Chinese: a longitudinal cohort study

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Abstract

Background: Although various cross-sectional studies have shown that erythrocyte parameters, including red blood cell (RBC), hemoglobin (Hb) and hematocrit (HCT), were linked with metabolic syndrome (MetS), few longitudinal studies have been used to confirm their relationship. The study, therefore, constructed a large-scale longitudinal cohort in urban Chinese population to highlight and confirm the association between erythrocyte parameters and MetS/its components.

Methods: A longitudinal cohort with 6,453 participants was established based on the routine health check-up systems to follow up MetS, and Generalized Estimating Equation (GEE) model was used to detect the association between erythrocyte parameters and MetS/its components (obesity, hyperglycemia, dyslipidemia, and hypertension).

Results: 287 MetS occurred over the four-year follow-up, leading to a total incidence density of 14.19 per 1,000 person-years (287/20218 person-years). Both RBC and Hb were strongly associated with MetS (RR/95% CI, P value; 3.016/1.525-5.967, 0.002 for RBC; 3.008/1.481-6.109, 0.002 for Hb), with their dose-response trends detected. All three erythrocyte parameters (RBC, Hb and HCT) were found to be associated with obesity, hypertension and dyslipidemia with similar dose-response trends respectively, while only Hb showed a significant association with hyperglycemia.

Conclusions: Elevated erythrocyte parameters were confirmed to be associated with MetS/its components in urban Chinese population, suggesting that erythrocyte parameters might be served as a potential predictor for risk of MetS.

Keywords: Metabolic syndrome (MetS), Erythrocyte parameters, Longitudinal cohort study, Generalized estimated equation (GEE)

Background

The metabolic syndrome (MetS) is characterized by obesity, hyperglycemia, dyslipidemia, hypertension and insulin resistance (IR) [1,2]. Various cross-sectional studies have demonstrated that erythrocyte parameters, including red blood cell (RBC), hemoglobin (Hb) and hematocrit (HCT), were associated with MetS [2-8]. These cross-sectional studies showed that elevated RBC was associated with MetS in Taiwan [2], Israel [3], Korea [4], Japan [5,6], Hb in Thailand [7] and Japan [6,8]. These positive associations were further detected in an Ethiopian cohort [9]. Furthermore, in a Japanese cohort [10], HCT was reported to be positively associated with insulin resistance, which is the basic pathogenesis for MetS. As most current results were reported from cross-sectional studies, and few from cohort studies, further longitudinal cohort studies are required to confirm the assumption in different populations.

The study, we established a longitudinal cohort with 6,453 participants based on the routine health check-up systems in urban Chinese population to follow up MetS, and each individual in this cohort was undergone at least three repeated health checks in the five years (January 2005 to January 2010). Furthermore, Generalized Estimating Equation (GEE) model, which could handle the repeat
measurement data with high autocorrelation in the framework of logistic regression model [11-14], was used to detect the association between erythrocyte parameters and MetS/its components (obesity, hyperglycemia, dyslipidemia, and hypertension).

Methods

Study population

A large scale longitudinal cohort was set up in 2005 on middle-to-upper class urban Han Chinese who attended routine health check-up at the Centers for Health Management of Shandong Provincial Hospital and Shandong Provincial Qianfoshan Hospital. Four groups of participants without cerebral infarction, cardiovascular disease, coronary artery bypass surgery, MetS and its single component in their first check-up at the year of 2005, 2006, 2007 and 2008 were included in the baseline of our longitudinal cohort study respectively. Figure 1 showed the total of 6453 participants having at least three repeated health check-up within five years (January 2005 to January 2010), and the samples of repeated surveys each year.

All individuals in the longitudinal cohort underwent a general health questionnaire, anthropometric measurements, and laboratory tests. The general health questionnaire covered the current status of smoking, alcohol intake, diet, sleeping quality and physical activity. Anthropometric measurements involved height, weight, and blood pressure. Both height and weight were measured with light clothing without shoes. Body mass index (BMI) was calculated as weight/height² (kg/m²) as an evidence of obesity. Blood pressure was measured using Omron HEM-907 by the cuff-oscillometric method on the right arm in sitting position after a 5-min rest, and the mean systolic and diastolic blood pressure values of two measurements were recorded respectively. While the participant was fasting, a venous blood sample was taken for laboratory test. Laboratory tests included RBC, Hb, HCT, white blood count (WBC), platelet distribution width (PDW), mean platelet volume (MPV), thrombocytocrit (PCT), glucose, total cholesterol (CHOL), low-density lipoprotein (LDL), high-density lipoprotein (HDL), triglycerides (TG), gamma-glutamyl transpeptidase (GGT), serum albumin (ALB), serum globulins (GLO), blood urea nitrogen (BUN), and serum creatinine (SCR), etc. This study was approved by the Ethics Committee of School of Public Health, Shandong University, and all participants were given informed written consent.

Definition of the metabolic syndrome

Considering the target population was Chinese with their specific physiological characteristics, Diabetes Branch of the Chinese Medical Association (CDS) [15] was used as the MetS diagnostic criteria, which is very popular for the Chinese population in clinical practice. MetS was defined as presence of three or more of the following four medical conditions: 1) overweight or obesity, i.e. BMI ≥25.0 Kg/m²; 2) hypertension, i.e. systolic blood pressure (SBC) ≥140 mmHg, or diastolic blood pressure (DBP) ≥90 mmHg, or previously diagnosed; 3) dyslipidemia, i.e., fasting TG ≥1.7 mmol/L, or fasting HDL <0.9 mmol/L; 4) hyperglycemia, i.e. fasting blood-glucose (FPG) ≥6.1 mmol/L, or 2 h Post-meal Glucose (PG) ≥7.8 mmol/L, or previously diagnosed.

Statistical analysis

To account for missing values, multiple imputation was performed. Since imputation method was depended on

![Figure 1 The samples of repeated surveys at each year.](http://www.biomedcentral.com/1471-2458/13/989)
the patterns of the missing data and the types of the imputed variables, without loss of generality, the Markov chain Monte Carlo (MCMC) method was chosen according to MI Procedure of SAS 9.1.3 [16]. Most variables had less than 2% missing observations before imputation except diet, drinking, smoking, quality of sleep and physical activity having less than 10% missing values. The original continuous erythrocyte parameters were categorized into 4 levels (Q1-Q4) using the 3 quartiles of P25, P50 and P75 as critical values, with ≤ P25 for Q1, >P25 and ≤ P50 for Q2, >P50 and ≤ P75 for Q3, and > P75 for Q4 respectively. Summary statistics were used to illustrate the distribution characteristics for variables of interest at each repeated surveys, and student’s t test for continuous variables and chi-square test for categorical variables were used to detect the statistical significances compared with the first survey (baseline).

As GEE model could handle the repeat measurement data with high autocorrelation in the framework of logistic regression model [11-14], it was used to detect the association between erythrocyte parameters and MetS/its components. Simple GEE model was firstly used to select variables associated with MetS/its components, then variables which were significant at the level of 0.05 in the simple GEE analysis entered the multiple GEE model to adjust the potential confounding. The ‘Logit’ link function was chosen in GEE analysis, with significance level 0.05. All the statistical analyses were performed on SAS 9.1.3.

Results

Table 1 summarized the characteristics of erythrocyte parameters levels and other potential confounding factors of the participants at each repeated survey, which showed that most factors were generally higher than that in the first survey (baseline). A total of 294 cases of MetS occurred over the four-year follow-up, leading to a total incidence density of 14.19 per 1,000 person-years (287/20218 person-years). During the follow up, 3 participants were diagnosed as cerebral infarction (person-years), 141 participants were diagnosed as cardiovascular disease (person-years) and no-one underwent coronary artery bypass surgery (see Additional file 1: Table S20).

Table 2 showed the selected variables associated with MetS at α = 0.05 level. It indicated that each of the 3 erythrocyte parameters (RBC, Hb, and HTC) with 9 potential confounding factors, including gender, age, GGT, GLO, BUN, WBC, diet, drinking and smoking might be linked with MetS. Also, each of the 3 erythrocyte parameters might be linked with the four components of MetS with their specific potential confounding factors respectively (see Additional file 2: Table S1, Additional file 3: Table S2, Additional file 4: Table S3 and Additional file 5: Table S4 for details).

Table 3 illustrated the summarized results of the association analyses between erythrocyte parameters and MetS/its components after adjusting potential confounding factors by multiple GEE model. (Confounding variables were not shown, detailed information seeing Additional file 6: Table S5, Additional file 7: Tables S6, Additional file 8: Table S7, Additional file 9: Table S8, Additional file 10: Table S9, Additional file 11: Table S10, Additional file 12: Table S11, Additional file 13: Table S12, Additional file 14: Table S13, Additional file 15: Table S14, Additional file 16: Table S15, Additional file 17: Table S16, Additional file 18: Table S17, Additional file 19: Table S18 and Additional file 20: Table S19.). It revealed that the top quartiles (Q4) of RBC and Hb were strongly associated with MetS (RR/95%CI, P value; 3.016/1.525-5.967, 0.002 for RBC; 3.008/1.481-6.109, 0.002 for Hb) using Q1 as reference level. Although no significant for Q2 and Q3, trends of increased of RR were observed from Q2 to Q4, indicating that there were dose–response trends between the 2 erythrocyte parameters and MetS. In addition, all three erythrocyte parameters (RBC, Hb and HCT) were found to be associated with obesity, hypertension and dyslipidemia with similar dose–response trends respectively, while only Hb showed a significant association with hyperglycemia.

Discussions

This study mainly attempted to confirm the association between erythrocyte parameters and MetS/its components using the longitudinal cohort. Although the longitudinal cohort study was based on routine health check-up in urban Han Chinese population from middle to upper socioeconomic strata, the positive associations between erythrocyte parameters and MetS/its components were observed, which were also detected in other two cohort study [9].

RBC had been reported to be associated with MetS in various populations by cross-sectional studies [2-6] and in Ethiopia by a cohort studies [9]. At present study, we not only confirmed that RBC was associated with MetS and its 3 single components (dyslipidemia, obesity and hypertension), but also observed the dose–response trends (seeing Table 3 or Additional file 7: Table S6, Additional file 8: Tables S7 and Additional file 9: Table S8). These results highlighted the positive association between RBC and MetS. In pathogenesis, this linkage might be explained by the insulin resistance(IR) mechanisms in the development of MetS, because insulin and insulin growth factors I and II supporting erythropoiesis in both vitro [17-21] and vivo [22-24] had been detected in laboratory studies.

As another important erythrocyte parameter, Hb also had been reported to be associated with MetS in Thailand [7] and Japan [6] by Cross-sectional studies,
as well as in Ethiopia [9] by a cohort study. This positive association was also detected in our longitudinal cohort study with a potential dose–response trend between them (seeing Table 3 or Additional file 11: Table S10, Additional file 12: Table S11, Additional file 13: Table S12, Additional file 14: Table S13 and Additional file 15: Table S14). The possible mechanism might be supported by the following pathogenesis. Hb is a well recognized carrier and buffer of nitric oxide (NO), and various compounds of Hb with NO can affect Hb-oxygen affinity of the whole blood [25]. Disturbed NO synthesis may exert an adverse effect on endothelial dysfunction through the L-arginine-

### Table 1 Distribution of erythrocyte parameters and other potential confounding factors

| Variables | The 1st survey (N = 6453) | The 2nd survey (N = 5300) | The 3rd survey (N = 5732) | The 4th surveys (N = 4542) | The 5th survey (N = 3346) |
|-----------|---------------------------|---------------------------|---------------------------|---------------------------|---------------------------|
| age | 38.563 ± 11.444 | 39.798 ± 11.572 | 40.619 ± 11.406 | 42.413 ± 11.495 | 43.317 ± 11.352 |
| sex | | | | | |
| male | 2688 | 2196 | 2415 | 1861 | 1351 |
| female | 3765 | 3104 | 3317 | 2681 | 1995 |
| RBC | 4.769 ± 0.456 | 4.705 ± 0.454 | 4.698 ± 0.454 | 4.678 ± 0.463 | 4.7 ± 0.432 |
| Hb | 142.454 ± 14.885 | 142.845 ± 15.27 | 141.73 ± 15.169 | 142.569 ± 15.381 | 142.115 ± 16.465 |
| HCT | 42.888 ± 3.905 | 42.408 ± 3.951 | 42.015 ± 3.889 | 42.191 ± 3.964 | 41.846 ± 3.869 |
| GGT | 18.004 ± 16.393 | 20.016 ± 20.032 | 19.383 ± 16.419 | 21.08 ± 20.193 | 21.336 ± 20.323 |
| ALB | 46.575 ± 2.427 | 45.789 ± 2.784 | 45.362 ± 2.742 | 45.128 ± 2.69 | 44.991 ± 2.436 |
| GLO | 27.016 ± 3.838 | 27.133 ± 3.973 | 28.253 ± 3.972 | 29.128 ± 4.046 | 30.314 ± 3.826 |
| BUN | 4.746 ± 1.197 | 4.698 ± 1.175 | 4.664 ± 1.154 | 4.772 ± 1.204 | 4.812 ± 1.145 |
| S-Cr | 76.943 ± 13.736 | 77.897 ± 13.842 | 77.502 ± 14.072 | 78.587 ± 14.694 | 77.012 ± 12.743 |
| WBC | 6.167 ± 1.466 | 6.069 ± 1.483 | 6.054 ± 1.479 | 6.142 ± 1.501 | 6.182 ± 1.489 |
| PDW | 12.346 ± 1.712 | 12.323 ± 1.722 | 12.226 ± 1.671 | 12.164 ± 1.669 | 12.088 ± 1.63 |
| MPV | 10.454 ± 0.811 | 10.448 ± 0.946 | 10.42 ± 0.803 | 10.398 ± 0.802 | 10.428 ± 0.796 |
| PCT | 0.247 ± 0.089 | 0.257 ± 0.320 | 0.254 ± 0.266 | 0.249 ± 0.055 | 0.245 ± 0.054 |
| Diet | | | | | |
| Vegetarian | 3454 | 2194 | 2098 | 1906 | 1214 |
| normal | 1863 | 792 | 750 | 550 | 463 |
| meat-based | 1118 | 2283 | 2866 | 2064 | 1653 |
| sea food | 18 | 31 | 18 | 22 | 16 |
| Drinking | | | | | |
| no | 3698 | 2959 | 3333 | 2731 | 1977 |
| yes | 2755 | 2341 | 2399 | 1811 | 1369 |
| Smoking | | | | | |
| no | 5274 | 4323 | 4678 | 3726 | 2718 |
| yes | 1179 | 977 | 1054 | 816 | 628 |
| Sleep | | | | | |
| ≥fair | 6270 | 5173 | 5557 | 4373 | 3250 |
| <fair | 183 | 127 | 175 | 169 | 96 |
| Exercise | | | | | |
| never/seldom | 4694 | 3902 | 4262 | 3469 | 2477 |
| often | 1759 | 1398 | 1465 | 1073 | 869 |

*P < 0.05 compared with the first survey (baseline); The abbreviations of the variables: RBC = red blood cell; Hb = Hemoglobin; HCT = Hematocrit; GGT = gamma-glutamyl tranpeptidase; ALB = serum albumin; GLO = serum globulins; BUN = blood urea nitrogen; S-Cr = serum creatinine; WBC = white blood cell; MPV = mean platelet volume; PDW = Platelet distribution width; PCT = Thrombocytocrit; Diet: 0: Vegetarian, 1: normal, 2: meat-based 3: sea food (the major kinds of food used to have); Drinking: 0: never, 1: seldom, 2: often, wine, 3: often beer, 4: often, Chinese spirits, 5: often, mixed all kinds; Smoking: 0: never, 1: seldom, 2: quit, 3: 1-4/d, 4: 5 -15/d, 5: >15/d; Quality of sleep: 0: excellent, 1: well, 2: fair 3: poor, 4: very poor (evaluated by themselves); Physical activity 0: never, 1: seldom (1–2 times a week), 2: often or everyday (more than 3 times a week).
NO pathway [26]. Furthermore, endothelial dysfunction was reported to be associated with MetS [27,28]. All these evidences expect the association between Hb and MetS/its components in population level.

Elevated HCT could increase blood viscosity and peripheral resistance to blood flow, and further contribute to IR [29-31]. Therefore, the association between HCT and MetS/its components should be observed in population level. In this paper, HCT associating with obesity, hypertension and dyslipidemia were all detected in urban Han Chinese population (seeing Table 3 or Additional file 17: Table S16, Additional file 18: Table S17, Additional file 19: Table S18), while no statistical significant association between HCT and MetS/ hyperglycemia was found (seeing Table 3, Additional file 16: Table S15 or Additional file 20: Table S19). Similar results were also observed in Ethiopia [9] and Japan [9] by cohort studies, as well as in Thailand [7] and Japan [9,11] by Cross-sectional studies.

Several limitations of this study must be considered. a) Selection bias might exist due to the samples just from routine health check-up population for middle-to-upper class urban Han Chinese. b) Owing to the absence of waist circumference measurement, the diagnostic criteria of MetS was just based on China Diabetes Federation, rather than international standard criteria.

### Table 2 The association analyses result from simple GEE model (MetS as dependent variable)

| Quartiles | red blood cell | hemoglobin | hematocrit | gender | age | GGT | ALB | GLO | BUN | S-Cr | WBC | PDW | MPV | PCT | Diet | Drinking | Smoking | Sleep | Exercise |
|-----------|---------------|------------|------------|--------|-----|-----|-----|-----|-----|------|-----|-----|-----|-----|------|---------|---------|-------|---------|
|           | Estimate      | ERR        | Z          | P > | RR  | Lower 95% confidence limits | Upper 95% confidence limits |
| Q4        | 1.284         | 0.244      | 5.271      | <0.001 | 3.612 | 2.241 | 5.824 |
| Q3        | 0.602         | 0.261      | 2.308      | 0.021 | 1.825 | 1.095 | 3.042 |
| Q2        | 0.050         | 0.292      | 0.170      | 0.865 | 1.051 | 0.593 | 1.864 |
| Q1        | ref           | ref        | ref        | ref   | ref  | ref  | ref  |
| Q4        | 1.271         | 0.209      | 6.078      | <0.001 | 3.564 | 2.366 | 5.370 |
| Q3        | 0.492         | 0.232      | 2.118      | 0.034 | 1.635 | 1.037 | 2.577 |
| Q2        | 0.251         | 0.240      | 1.045      | 0.296 | 1.285 | 0.803 | 2.056 |
| Q1        | ref           | ref        | ref        | ref   | ref  | ref  | ref  |
| Q4        | 1.005         | 0.210      | 4.776      | <0.001 | 2.732 | 1.809 | 4.127 |
| Q3        | 0.406         | 0.234      | 1.736      | 0.083 | 1.500 | 0.949 | 2.371 |
| Q2        | 0.123         | 0.249      | 0.496      | 0.620 | 1.131 | 0.694 | 1.844 |
| Q1        | ref           | ref        | ref        | ref   | ref  | ref  | ref  |
| gender    | −0.946        | 0.157      | −6.034     | <0.001 | 0.388 | 0.286 | 0.528 |
| age       | 0.410         | 0.039      | 10.596     | <0.001 | 1.507 | 1.397 | 1.625 |
| GGT       | 0.012         | 0.002      | 7.235      | <0.001 | 1.012 | 1.009 | 1.016 |
| ALB       | −0.050        | 0.025      | −1.981     | 0.048 | 0.951 | 0.906 | 0.999 |
| GLO       | 0.072         | 0.015      | 4.863      | <0.001 | 1.074 | 1.044 | 1.106 |
| BUN       | 0.177         | 0.049      | 3.599      | <0.001 | 1.193 | 1.084 | 1.314 |
| S-Cr      | 0.010         | 0.006      | 1.668      | 0.095 | 1.010 | 0.998 | 1.022 |
| WBC       | 0.284         | 0.031      | 9.061      | <0.001 | 1.328 | 1.249 | 1.412 |
| PDW       | 0.005         | 0.042      | 0.119      | 0.905 | 1.005 | 0.926 | 1.091 |
| MPV       | −0.093        | 0.094      | −0.983     | 0.326 | 0.912 | 0.758 | 1.096 |
| PCT       | −0.588        | 1.229      | −0.478     | 0.632 | 0.555 | 0.050 | 6.176 |
| Diet      | 0.223         | 0.073      | 3.049      | 0.002 | 1.250 | 1.083 | 1.442 |
| Drinking  | 0.173         | 0.046      | 3.796      | 0.001 | 1.189 | 1.087 | 1.300 |
| Smoking   | 0.143         | 0.044      | 3.246      | 0.001 | 1.153 | 1.058 | 1.257 |
| Sleep     | 0.109         | 0.076      | 1.432      | 0.152 | 1.115 | 0.961 | 1.294 |
| Exercise  | −0.013        | 0.159      | −0.080     | 0.937 | 0.987 | 0.723 | 1.348 |
Table 3 The summary results of the association analyses between erythrocyte parameters and MetS/its components after adjusting potential factors by multiple GEE model

| Parameters     | MetS   | Obesity | Hyperglycemia | Hypertension | Dyslipidemia |
|---------------|--------|---------|---------------|--------------|--------------|
|               | Estimate | P > | Z | RR | Estimate | P > | Z | RR | Estimate | P > | Z | RR | Estimate | P > | Z | RR |
| Red blood cell| Q4     | 1.104  | 0.002 | 3.016 | 0.474  | <0.001 | 1.606 | 0.215  | 0.202  | 1.239 | 0.484  | 0.001 | 1.622 | 0.431  | <0.001 | 1.539 |
|               | Q3     | 0.523  | 0.081 | 1.688 | 0.364  | 0.001  | 1.439 | 0.075  | 0.606  | 1.078 | 0.271  | 0.042  | 1.312 | 0.251  | 0.002  | 1.285 |
|               | Q2     | −0.039 | 0.895 | 0.961 | 0.006  | 0.955  | 1.006 | 0.068  | 0.605  | 1.071 | 0.113  | 0.389  | 1.120 | 0.123  | 0.103  | 1.131 |
|               | Q1     | ref    | ref    | ref    | ref    | ref    | ref    | ref    | ref    | ref    | ref    | ref    | ref    | ref    | ref    | ref    |
| Hemoglobin    | Q4     | 1.101  | 0.002 | 3.008 | 0.693  | <0.001 | 2.000 | 0.654  | 0.001  | 1.923 | 0.749  | <0.001 | 2.114 | 0.536  | <0.001 | 1.709 |
|               | Q3     | 0.454  | 0.144 | 1.575 | 0.447  | <0.001 | 1.564 | 0.519  | 0.001  | 1.680 | 0.390  | 0.006  | 1.477 | 0.254  | 0.003  | 1.289 |
|               | Q2     | 0.340  | 0.162 | 1.405 | 0.387  | <0.001 | 1.473 | 0.307  | 0.025  | 1.359 | 0.273  | 0.035  | 1.314 | 0.082  | 0.251  | 1.086 |
|               | Q1     | ref    | ref    | ref    | ref    | ref    | ref    | ref    | ref    | ref    | ref    | ref    | ref    | ref    | ref    | ref    |
| Hemocrite     | Q4     | 0.583  | 0.079 | 1.792 | 0.362  | 0.009  | 1.436 | 0.028  | 0.874  | 1.029 | 0.368  | 0.021  | 1.445 | 0.257  | 0.009  | 1.293 |
|               | Q3     | 0.214  | 0.479 | 1.238 | 0.297  | 0.013  | 1.346 | 0.151  | 0.320  | 1.163 | 0.324  | 0.018  | 1.383 | 0.195  | 0.018  | 1.215 |
|               | Q2     | 0.034  | 0.892 | 1.035 | 0.220  | 0.028  | 1.246 | 0.014  | 0.915  | 1.014 | 0.149  | 0.250  | 1.161 | 0.003  | 0.969  | 1.003 |
|               | Q1     | ref    | ref    | ref    | ref    | ref    | ref    | ref    | ref    | ref    | ref    | ref    | ref    | ref    | ref    | ref    |
c) The medication history and menstrual history of participants might be significant confounding factors, but they were absent in our database. d) Hematological parameter categories were based on a single assessment of blood, which may cause a misclassification bias. It is, therefore, desired to conduct a perfect longitudinal cohort study in general population for further highlighting the association between erythrocyte parameters and MetS.

Conclusion
In conclusion, elevated erythrocyte parameters were confirmed to be associated with MetS/its components in urban Chinese population, suggesting that erythrocyte parameters might be a potential predictor for risk of MetS.

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Competing interests
There is no conflict of interest for any of the authors. All authors had access to the data and were involved in drafting the article and revising it critically for important intellectual content.

References
1. Grundy SM, Brewer HB, Cleeman JI, Smith SC, Lenfant C, Conference P: Definition of metabolic syndrome - Report of the National Heart, Lung, and Blood Institute/American Heart Association Conference on Scientific Issues Related to Definition. Circ 2004; 109(3):433–438.
2. Wang Y-Y, Lin S-Y, Liu P-H, Cheung BMH, Lai W-A: Association between hematological parameters and metabolic syndrome components in a Chinese population. J Diabetes Complications 2004; 18(6):322–327.
3. Mardi T, Toker S, Melamed S, Shiron A, Zeltzer D, Shapira I, Berliner S, Rogowski O: Increased erythropoiesis and subclinical inflammation as part of the metabolic syndrome. Diabetes Res Clin Pract 2005; 69(3):249–255.
4. Kim JA, Choi YS, Hong JI, Kim SH, Jung HH, Kim SM: Association of metabolic syndrome with white blood cell subtype and red blood cells (Retracted Article. See vol 53, pg 871, 2006). Endocr J 2006; 53(1):133–139.
5. Kotani K, Sakane N, Kurozawa Y: Increased Red Blood Cells in Patients with Metabolic Syndrome. Endocr J 2006; 53:713–714.
6. Kawamoto R, Tabara Y, Kohara K, Miki T, Kusunoki T, Abe M, Kato K: Hematological parameters are associated with metabolic syndrome in Japanese community-dwelling persons. Endocrine 2013; 43(2):334–341.
7. Lohsoonthorn V, Jamjarasrungsi W, Williams MA: Association of hematological parameters with clustered components of metabolic syndrome among professional and office workers in Bangkok, Thailand. Diabetes Metab Clin Res 2007; 1(3):143–149.
8. Sugimoto H, Tomoda F, Kojke T, Kimura H, Kurosaki H, Masutani T, Inoue H: Blood Rhetology and Platelet Function in Untreated Early-Stage Essential Hypertensives Complicated with Metabolic Syndrome. Int J Hypertens 2012; 2012:1–5.
9. Nebeck K, Gelay B, Lemma S, Berhane Y, Bekele T, Khalil A, Haddis Y, Williams MA: Hematological parameters and metabolic syndrome: Findings from an occupational cohort in Ethiopia. Diabetes Metab Clin Res Rev 2012; 6(1):22–27.
10. Tabara Y, Igarashi M, Saito I, Nishida W, Kohara K, Sakurai S, Kawamura R, Okada Y, Hikumoto S, Onuma H, et al: association of hematological parameters with insulin resistance, insulin sensitivity, and asymptomatic cerebrovascular damage: The J-SHIP Toon Health Study. Clin Hemorheol Microcirc 2012. Epub ahead of print.
11. Rochon J: Application of GEE procedures for sample size calculations in repeated-measures experiments. Stat Med 1998; 17(16):1631–1638.
12. Lee JH, Herzog TA, Meade CD, Webb MS, Brandon TH: The use of GEE for analyzing longitudinal binomial data: A primer using data from a tobacco intervention. Addict Behav 2007; 32(1):187–193.
13. Lin KC, Chen Y-J, Shyr Y: A nonparametric smoothing method for assessing GEE models with longitudinal binary data. Stat Med 2008; 27(22):4428–4439.
14. Hubbard AE, Ahern J, Fleischer NL, Van der Laan M, Lippman SA, Jewell N, Bruckner T, Satirano WA: To GEE or Not to GEE Comparing Population Average and Mixed Models for Estimating the Associations Between Neighborhood Risk Factors and Health. Epidemiol 2010, 21(4):467–474.

15. Lu Y-h, Lu J-m, Wang S-y, Li C, Liu L-y, Zheng R-p, Tian H, Wang X-l, Yang L-j, Zhang Y-q, et al. Comparison of the diagnostic criteria of metabolic syndrome by International Diabetes Federation and that by Chinese Medical Association Diabetes Branch. Zhonghua yi xue za zhi 2006, 86(6):386–389.

16. Schafer J. Multiple imputation: a primer. Stat Methods Med Res 1999, 8:3–15.

17. Bersch N, Groopman JE, Golde DW: Natural and biosynthetic insulin stimulates the growth of human erythrocyt progenitors in vitro. J Clin Endocrinol Metab 1982, 55(3):1209–1211.

18. Dainiak N, Kreczko S: Interactions of insulin, insulinlike growth factor II, and platelet-derived growth factor in erythropoietic culture. J Clin Invest 1985, 76(3):1237–1242.

19. Sawada K, Krantz SB, Desypris EN, Koury ST, Sawyer ST. Human colony-forming units-erythroid do not require accessory cells, but do require direct interaction with insulin-like growth factor I and/or insulin for erythroid development. J Clin Invest 1989, 83(5):1701–1709.

20. Ratajczak J, Zhang Q, Pertusini E, Wojczyk BS, Wasik MA, Ratajczak MZ. The role of insulin (INS) and insulin-like growth factor-I (IGF-I) in regulating human erythropoiesis. Studies in vitro under serum-free conditions - comparison to other cytokines and growth factors. Leuk 1996, 12(3):371–381.

21. Miyagawa S, Kobayashi M, Kondi S, Sato T, Ueda K. Insulin and insulin-like growth factor I support the proliferation of erythroid progenitor cells in bone marrow through the sharing of receptors. Br J Haematol 2000, 109(3):355–362.

22. Widness JA, Susa JB, Garcia JF, Singer DB, Sehgal P, Oh W, Schwartz R, Schwartz HC. Increased erythropoiesis and elevated erythropoietin in infants born to diabetic mothers and in hyperinsulinemic rhesus fetuses. J Clin Invest 1981, 67(3):637–642.

23. Stonestreet BS, Goldstein M, Oh W, Widness JA. Effects of prolonged hyperinsulinaemia on erythropoiesis in fetal sheep. Am J Physiol 1989, 257(5 Pt 2):R1199–R204.

24. Petakov M, Biljanovic-Paunovic L, Jovicic G, Stojanovic N, Todorovic V, Jelkmann W. The influence of acute sterile inflammation on erythropoiesis in rats. Exp Hematol 1998, 26(3):222–227.

25. Zinchuk VW, Pronko TP, Lis MA. Blood oxygen transport and endothelial dysfunction in patients with arterial hypertension. Clin Physiol Funct Imaging 2004, 24(4):205–211.

26. Kelm M, Rath J. Endothelial dysfunction in human coronary circulation: relevance of the L-arginine-NO pathway. Basic Res Cardiol 2001, 96(2):107–127.

27. Singel DJ, Stamler JS. Chemical physiology of blood flow regulation by red blood cells: The role of nitric oxide and S-nitrosohemoglobin. Annu Rev Physiol 2005, 67:99–145.

28. Wei Y, Liu G, Yang J, Zheng R, Jiang L, Bao P. The association between metabolic syndrome and vascular endothelial dysfunction in adolescents. Exp Ther Med 2013, 6(6):1663–1666.

29. Facchini FS, Carantonini M, Jeppesen J, Reaven GM. Hematocrit and hemoglobin are independently related to insulin resistance and compensatory hyperinsulinaemia in healthy, non-obese men and women. Metabolism 1998, 47(7):831–835.

30. Nakano N, Suzuki K, Tatura K. Haematocrit and risk of development of Type 2 diabetes mellitus in middle-aged Japanese men. Diabetic Med 2004, 21(5):476–482.

31. Tamariz LJ, Young JH, Pankow JS, Yeh H-C, Schmidt MI, Astor B, Biancati FL. Blood Viscosity and Hematocrit as Risk Factors for Type 2 Diabetes Mellitus. Am J Epidemiol 2008, 168(10):1153–1160.