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Original Article

Effect of basal metabolic rate on serum homocysteine level in Chinese population

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Abstract: Background: Elevated plasma level of homocysteine (Hcy) have been found to be associated with an increased risk of ischemic stroke and cardiovascular disease (CVD). However, the impact of basal metabolic rate (BMR) on Hcy has not been recognized yet. The aim of this study was to estimate the relationship between BMR and the homocysteine level in Chinese general population. Methods: Adults were recruited from six communities in Jiangxi Province using a stratified multistage random sampling method. Patients were divided into two groups according to their basic Hcy levels: the hyperhomocysteine (HHcy, Hcy>15 μmol/L) group, and the normal homocysteine group. The data were obtained through on-site health examinations and face-to-face interviews. Results: 1413 subjects (mean age 53.59±13.53 years) were included in final analysis. The prevalence of HHcy was 26.04% (40.45% in male and 18.13% in female) in this population. HHcy patients were older, higher BMI, visceral adiposity index, BMR, and more likely to have a history of heart failure, hypertension compared to the group with concentrations below 15 μmol/L. Multivariate logistic regression analysis identified that age (odds ratio (OR)=9.045, 95% confidence interval (CI) [4.920, 16.631], *P<0.001*), gender (OR=0.393, 95% CI [1.416, 6.703], *P*<0.001), basal metabolic rate (BMR) (OR=5.003, 95% CI [1.416, 6.703], *P=0.005*) were independently correlated with HHcy. Conclusions: Increased BMR is associated with Hcy levels in general population, and elderly adults with lower BMR appeared to have higher incidence rate of HHcy.

Keywords: Basal metabolic rate, homocysteinaemia, hyperhomocysteinaemia, general population

Introduction

Hyperhomocysteinaemia (HHcy) is a serious clinical and public health challenge. It is estimated that HHcy affects 180 million adults, nearly 75% of the hypertensive population in China [1]. HHcy has been found as an important and independent risk factor of the CVD adverse events. Hcy levels were associated with pathogenesis and progression of coronary atherosclerosis in hypertensive patients [2]. In diabetes mellitus patients, above 14 μmol/L, each additional unit of Hcy concentration was associated with increased diabetic retinopathy and renal failure [3]. HHcy is also an independent risk factor of stroke, peripheral vascular disease and venous thrombosis in general population [4].

Hcy is an intermediate metabolite of methionine [2, 3]. Metabolic enzymes deficiency, and its co-factors such as folicand B vitamins deficiency, could lead to the increase of Hcy levels [5]. Other risk factors including smoke status, age, gender, physical activity are also directly associated with plasma Hcy concentration [6]. Several mechanisms have been proposed to link the damage caused by Hcy. Hcy could induce endothelial cell apoptosis, decrease endothelium thrombotic resistance, affect the bioavailability of the vasodilator [7].

Basal metabolic rate (BMR) is accounting forat least 60% of total energy expenditure in most general population [9]. The BMR measurement is influenced by gender, age, body mass, hormonal, height, which are features also discovered in HHcy [10]. BMR has recently been reported to be associated with pulmonary function indicators in overweight healthy subjects, and increased BMR may result from an increased fat-free mass in type 2 diabetes

patients [11, 12]. We sought to evaluate the effect of basal metabolic rate on serum homocysteine level in Chinese general population.

Subjects and methods

Study population

A cross-sectional epidemiological study was conductedin Jiangxi province from June 1st, 2013-June 1st, 2014. Design details and practice of the program have been described in elsewhere [13]. In the present study, we included subjects aged over 15 years and older. Subjects who were with acute or chronic illnesses such as cancer and severe renal and liver diseases were excluded. All participants have signed informed consents. The protocol of this study was approved by the Ethics Committee of the Second Affiliated Hospital of Nanchang University.

Data collection procedures

Well-trained professional research staff have participated in the study according to the standard operating procedures, which includs basic information questionnaire, anthropometric measurements, and blood pressure measurement.

Basic questionnaire

All the participants received a face to face standard questionnaire to fulfill information about demographic characteristics (such as gender, age), personal disease history, lifestyle such assmoking, alcohol. Current smoking referred to having smoking one cigarette or more per day for over 6 months before investigation. We obtained alcohol drinking status of subjects by asking whether they drink or have at least consumed alcohol once every week.

Anthropometric and body composition measurements

The height, waist and weight of each participant were measured using standardized protocol. Participant should took off shoes using a fixed measurement tape to measure height. The weight was measured on an electronic platform scale. Waist circumference was measured using a cloth tape directly on the participant's skin. Body weight/body fat was measured by instrument (V body HBF-371, Omron, Kyoto, Japan). The fat loss monitor displays the calculated value of body fat percentage using the bioelectrical impedance method and indicates BMR, body fat percentage (BFP), visceral adiposity index (VAI). Subjects step off the measurement platform, press the set button, and fill in the gender, height, and age. BMI was calculated as weight (kg)/height (m^2) [14].

Blood pressure

Each participant should had been sitting for 10 minutes before blood pressure measurement. Well trained staffsused unified automatic pressure monitor (Omron, Kyoto, Japan), and rigorously followed the standard operating procedure. With an interval of 2 min rest, each participant was measured three times on the same arm. And final systolic blood pressure (SBP), diastolic blood pressure (DBP), pulse pressure (PP), and heart rate (HR) were computed as the average of triplicate measurements for statistical analyses. Hypertension was defined as SBP>140 mmhg or DBP>90 mmhg or already having taken antihypertensive drug [15].

Laboratory measurements

We collected overnight fasting venous blood samples to measure Hcy, total cholesterol (TC), triglyceride (TG), non-high density lipoprotein (NHDL), high-density lipoprotein (HDL) cholesterol, and low-density lipoprotein (LDL) cholesterol by using an auto-analyzer (Olympus Au-2700). All biochemical measurements were conducted at the central chemistry laboratory in the second affiliated hospital of Nanchang university.

Statistical analysis

Normal distribution of all variables were conducted, distributed variables were expressed as mean ± standard deviation (*SD*). Skewed distribution variables were given as median value, upper and lower quartiles (interquartile range) and all were ln-transformed before analysis. Categorical variables were presented as relative frequencies (%). The study adults were stratified into two groups according to the extent of the Hcy level as described above. For comparing continuous data between two different groups, we used unpaired t-tested and Chi square (X^2) for categorical data. To determine the effect of different clinical risk factors on

Table 1. Characteristics of the study population

Variables	All (n=1413)		*P* value
	HHcy n=368	Normal homocysteine n=1045	
Gender (female)	167 (45.3%)	754 (72.20%)	0.000
Age (years)	62.00 (51.25, 70.00)	51.00 (44.00, 60.00)	0.000
BMI (kg/m^2)	22.62 (20.40, 25.52)	22.63 (20.48, 25.06)	0.110
HR (beats/min)	78.00 (69.00, 84.00)	50.00 (44.00, 58.00)	0.651
DBP (mmHg)	74.00 (68.00, 82.00)	72.00 (67.00, 79.00)	0.032
SBP (mmHg)	129.50 (119.00, 144.00)	123.00 (115.00, 135.00)	0.000
PP (mmHg)	72.00 (67.00, 79.00)	54.50 (46.00, 66.00)	0.000
TG (mg/dl)	97.90 (72.66, 143.53)	92.14 (67.33, 140.43)	0.167
HDL-C (mg/dl)	41.15 (37.25, 50.70)	44.51 (39.09, 51.47)	0.099
LDL-C (mg/dl)	67.92 (55.44, 81.95)	67.73 (56.12, 80.11)	0.862
CHOL (mg/dl)	158.67 (136.32, 181.31)	157.12 (137.39, 179.38)	0.869
NHDL (mg/dl)	112.42 (97.23, 130.41)	113.00 (98.30, 129.26)	0.384
Smoking [n (%)]	103 (28.0%)	154 (14.8%)	0.000
Alcohol Drinking [n (%)]	121 (32.9%)	231 (22.1%)	0.000
Waist (cm)	79.60 (72.00, 88.00)	79.60 (72.00, 88.00)	0.002
BMR (Kcal)	1297.50 (1140.00, 1464.00)	1195.00 (1091.50, 1347.00)	0.001
Body fat percentage	26.70 (21.33, 33.50)	28.50 (23.50, 33.15)	0.847
Visceral adiposity index	7.00 (4.40, 11.00)	6.00 (4.00, 9.00)	0.000
History of Hypertension [n (%)]	115 (31.2%)	180 (17.2%)	0.000
History of HF [n (%)]	65 (17.7%)	209 (20%)	0.490
Medications [n (%)]			0.140
Beta-blockers	38 (10.8%)	117 (11.2%)	
ACE-Is or ARBs	30 (8.2%)	81 (7.8%)	
Calcium-channel Blockers	32 (8.8%)	85 (8.2%)	
Statins	17 (4.7%)	52 (5.0%)	
Diuretics	28 (7.8%)	73 (7.0%)	
Antiplatelet agents	12 (3.3%)	41 (4.0%)	

Abbreviations: BMI, body mass index; HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; PP, pulse pressure; TG, triglyceride; CHOL, cholesterol; LDL, low-density lipoprotein; HDL, high-density lipoprotein; NHDL, non-high density lipoprotein; BMR, Basal metabolic rate; HF, heart failure; ACE-Is, angiotensin-converting enzyme inhibitors; ARBs, angiotensin II receptor blockers; Continuous variables, the mean ± SD or median (interquartile range); Dichotomous variables, NO (%).

Hcy levels, mulitvariate logistic regression analysis was performed. To deeply assess the relationships between BMR, age and homocysteine, baseline BMR were divided into 4 categories, and cox-proportional hazard models were used [6]. *P* value<0.05 was considered to be statistically significant. All data analyses were performed using Empower (R) (www.Empowerstats.com, X&Y Solutions, Inc, Boston, MA).

Results

We invited 1494 subjects to participate in our studyfrom six communities in Nanchang. Due to unwilling to join, data missing, or sufferedacute or chronic illnesses, 81 participants were excluded. 1413 subjects (mean age 53.59±13.53 years old) were included in final analysis. HHcy was defined by the plasma Hcy level>15 mol/L [7]. According to Hcy level, participants were divided into control group and HHcy group.

Table 1 shows the basic clinical characteristics of all subjects. The prevalence of HHcy was 26.04% (40.45% in men and 18.13% in women). There were no significant differences in BMI, LDL, TG, TC, HR, and NHDL levels between groups. Compared with control group, HHcy subjects were older, and had higher SBP, DBP,

Table 2. Univarable and forward-wald logistic regression analysis of the clinical factors for Hyperhomocysteinemia

Variables	Univariate		Multivariate	
	β 95% CI	*P* value	β 95% CI	*P* value
Age	10.178 (5.945, 17.425)	0.000	8.664 (4.700, 15.971)	0.000
BMI	1.643 (0.947, 2.851)	0.077	Not selected	
HR	0.859 (0.410, 1.802)	0.689	Not selected	
DBP	2.409 (1.002, 5.795)	0.050	0.436 (0.015, 13.090)	0.632
SBP	13.881 (5.721, 33.678)	0.000	1.409 (0.003, 12.549)	0.912
PP	4.090 (2.515, 6.650)	0.000	1.235 (0.108, 14.055)	0.865
TG	1.186 (0.968, 1.454)	0.101	Not selected	
Ln HDL-C	0.588 (0.342, 1.010)	0.054	Not selected	
Ln LDL-C	0.973 (0.638, 1.485)	0.900	NS	
Ln CHOL	0.791 (0.605, 1.935)	0.791	NS	
Ln NHDL	0.766 (0.427, 1.375)	0.372	Not selected	
Gender (female)	0.321 (0.251, 0.411)	0.000	0.387 (0.277, 0.540)	0.000
Smoking [n (%)]	1.899 (1.493, 2.415)	0.000	1.049 (0.782, 1.407)	0.750
Alcohol use [n (%)]	1.270 (0.969, 1.663)	0.083	NS	
Ln Waist	1.360 (0.817, 2.263)	0.237	Not selected	
Ln BMR	5.003 (2.603, 9.617)	0.000	3.050 (1.406, 6.617)	0.005
Ln BFP	0.823 (0.615, 1.102)	0.192	NS	
Ln VAI	1.466 (1.215, 1.770)	0.000	0.923 (0.729, 1.167)	0.502
History of hypertension [n (%)]	2.184 (1.663, 2.869)	0.000	1.419 (0.901, 0.2233)	0.131

Abbreviations: BMI, body mass index; HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; PP, pulse pressure; TG, triglyceride; CHOL, cholesterol; LDL, low-density lipoprotein; HDL, high-density lipoprotein; NHDL, non-high density lipoprotein; BMR, Basal metabolic rate; BFP, Body fat percentage; VAI, visceral adiposity index; NS, not selected.

Table 3. Regression analysis of age and homocysteine level according to the quartile of basal metabolic rate

Variable	Total		1st quartile		2st quartile		3st quartile		4st quartile	
	β (95% CI)	P	β (95% CI)	P	β (95% CI)	P	β (95% CI)	P	β (95% CI)	P
Age										
Model 1	10.8 (5.9, 19.8)	<0.001	36.5 (8.4, 158.6)	<0.001	13.4 (3.4, 54.0	<0.001	8.9 (2.4, 32.9)	0.001	4.6 (1.8, 11.5)	0.001
Model 2	10.6 (5.6, 20.0)	<0.001	34.9 (7.3, 166.6)	<0.001	12.8 (2.7, 60.0)	0.001	7.7 (2.0, 30.0)	0.003	5.2 (1.9, 13.9)	0.001

Model 1 adjusted for sex, smoke status. Model 2 adjusted for model 1 plus SBP, PP, history of hypertension, visceral adiposity index. All variables were received base ln-transformed.

and PP (all *P<0.05,* **Table 1**) levels. And HHcy were more likely to be men, havinga higher prevalence of smoker, or alcohol consumers, and history of hypertension (all *P<0.001,* **Table 1**). In the aspect of body composition measurements, HHcy group had bigger waist circumference, higher basal metabolic rate, and visceral adiposity index (all *P<0.001,* **Table 1**).

Table 2 shows the result of logistic regression analysis on clinical characteristic of HHcy rate in general population. Univariate logistic regression analysis showed that age (Odds ratio [OR]=10.178, 95% confidence interval [CI]: 5.945-17.425, *P<0.001*); SBP (OR=13.881, 95% CI: 5.721-33.678, *P<0.001*); PP (OR= 4.090, 95% CI: 2.515-6.650, *P<0.001*); gender (female) (OR=0.321, 95% CI: 0.251-0.411, *P<0.001*); current smoking (OR=1.899, 95% CI: 1.493-2.415, *P<0.001*); BMR (OR=5.003, 95% CI: 2.603-9.617, *P<0.001*); Vai (OR=1.466, 95% CI: 1.215-1.77, *P<0.001*); history of hypertension (OR=2.184, 95% CI: 1.663-2.869, *P<0.001*) correlated with Hcy levels. Further multivariate logistic regression analysis identified that age (OR=9.045, 95% CI: 4.920-16.631, *P<0.001*), gender (female) (OR=0.393, 95% CI: 1.416-6.703, *P<0.001*), BMR (OR=

5.003, 95% CI: 1.416-6.703, *P=0.005*) were independently correlated with Hcy.

On **Table 3**, two models were constructed to estimate the effect of age, BMR and homocysteine levelusing cox regression. Model 1 was adjusted for sex (men or women), current smoke, and current alcohol use. Model 2 was adjusted for the same variables as Model 1 plus the following risks: SBP, DBP, PP, hypertension, and VAI.

According to BMR four quartiles (Q1-Q4), we found that in different BMR quartiles of model 1, the association between ageand homocysteine also changed. In Q1, the beta was 36.5 (*P <0.001*); in Q4, the beta was 4.6 (*P<0.001*). And in the multivariate model 2, the change was still significant.

Discussion

There is limited research to evaluate the relationship between BMR and homocysteine levels in general population. In the present study, HHcy group exhibited significantly higher BMR level than control group. BMR was related to Hcy levels after adjusting for age, sex, SBP, DBP, PP, smoking, history of hypertension, and visceral adiposity index. In the first BMR quartile group, we saw older participants and higher HHcy rate. With the development of BMR, the effect of age on HHcy was weaker.

In the present study, the mean Hcy concentration was 14.58±7.29 μmol/L. The prevalence of HHcy was 26.04% in our study, from a middle-southern city of China. Higher than Western countries, the prevalence of HHcy which may due tolow nutritional factor intake and higher prevalence of MTHFR 677TT mutation in China [16]. Liu [17] reported the HHcy rate was 88.9% in northern Chinese populations, significantly higher than our research. The difference between northern and southern population maybe related to geographical variations, different lifestyles such as fruit, vegetables, and seafood with high folate content intake [18].

Previous population-based studies have demonstrated that Hcy concentrations between men and women were different, which was confirmed in our study. Gender was an independent risk factor of HHcy [19]. Totally 368 subjects were diagnosed with HHcy, and had two-fold higher incidence of men than women. The mean increased degree of Hcy was also significantly higher in men. This difference could be explained by the fact that men were characterized with larger muscle mass and greater creatine phosphate synthesis,while estrogen levels also adversely effectsthe Hcy formation [20].

It has been reported that ageis positively associated with increased serum concentration homocysteine [21]. In our study, it also has an independent influence on incident of HHcy (OR=9.045, 95% CI: 4.920-16.631, *P<0.001*). That could be explained by the finding that old participants were in a state of organ dysfunction, especially digestive and metabolic function. Reduced secretion of digestive juice, digestive enzyme, and less physical activity all contributed to low nutrition absorption and utilization [22]. Life style of eating and cooking also inhibited the nutrition absorption [23]. That means normal old population should beawareof folate, and vitamin B intake, especially for male.

Basal metabolic rate is an expression of resting metabolism [24]. BMR has recently gained attention due to its relations to obesity in women, and pulmonary function in chronic obstructive pulmonary patients [25]. Lee [26] identified genetic factors associated with the increase of BMR in obese Korean women, providinga new insight to the prevention and possible treatments of obesity. There are few studies about BMR as a determinant of HHcy; the present study showed that higher BMR was associated with higher Hcy levels. The exact mechanism why higher BMR level increase Hcy is still unknown. One of the possible reasons is that higher BMR level can increase methyl flux which is necessary for Hcy formation [27]. Another reason is that higher BMR always accompanies with higher methylated compounds demand, such as DNA, epinephrine, carnitine, and creatine, which along with Hcy are the products of transmethylation reactions [28]. More interestingly, we found that in thelower BMR group, the effect of age on Hcy level is stronger. Generally speaking, we should pay more attention to the high BMR group population, and old men with low BMR also need to be concerned.

Different predication equations have been widely used to estimate BMR such as Harris and Benedic, in different ethnic groups and on different purposes [29]. However, several authors have found that these equations overestimate or underestimate the BMR level [28, 29]. The Omron fat loss monitor with scale will provide specific body fat percentage and body weight by the bioelectrical impedance method. Muscles, blood vessels and bones are body tissues having a high water content that conduct electricity easily [30]. Body fat is the tissue that has little electrical conductivity. The body fat percentage are no more 10% than traditional measurements. Compared with body mass index which lacks information on the body composition, BMR may serve as a complementary tool to assess the possibly underlying metabolism behind persons' body composition.

There are some limitations of our study. First, the present study is only a small scale cross-sectional study, which necessitates further future study to identify the BMR used for HHcy patients. Second, we only included some confounding variables, but nomuch more other risk factors such as vitamin B6, diet, physical exercise, and gene mutation.

In summary, the study showed that the relation between age, gender and Hcy levels were statistically significant. We firstly evaluated the effect of basal metabolic rate on the prevalence of HHcy in Chinese general population. Furthermore, aged man with low BMR should beawareof BMR control especially. If normal generation could change their lifestyles, including physical activity levels, their Hcy levels and risk of stroke would be reduced.

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Disclosure of conflict of interest

None.

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