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ORIGINAL CONTRIBUTIONS

Metabolic Features of Individuals with Obesity Referred for Bariatric and Metabolic Surgery: a Cohort Study

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Abstract

Background The concept of metabolic obesity phenotypes has been proposed, but its relevance to metabolic features is unclear.

Purpose To determine a new definition of metabolic obesity phenotype, investigate the characteristics of expressing clustered normal and abnormal metabolic parameters, and analyze factors associated with metabolic abnormalities.

Materials and Methods Characteristics of 600 patients were analyzed. The definition of metabolic obesity phenotype includes elevated blood pressure, glucose, lipid, and uric acid levels and abnormal lipoprotein levels. Independent sample *t* test and a general linear model with repeated measures were applied to investigate the differences in metabolic parameters.

Results A total of 108 (18.0%) participants were obese yet metabolically healthy, whereas 492 (82.0%) were obese and metabolically unhealthy. Body weight at baseline was significantly higher in metabolically unhealthy phenotype ($P < 0.001$). For non-phasic oral glucose tolerance test (OGTT) curve shape, 100% glucose, 100% C-peptide, and 95.8% insulin curves were found in the metabolically unhealthy group. Men had an increased risk for elevated lipid level than women (OR = 1.83, 1.21–2.77). Individuals with class II/III obesity had an increased risk for elevated blood pressure, glucose, and UA levels than did those with class I obesity (OR = 2.22, 1.43–3.44; OR = 1.73, 1.11–2.68; OR = 3.61, 2.29–5.69, respectively).

Conclusions Approximately one-fifth of individuals with obesity had a metabolically healthy phenotype, and nearly one-third of individuals with class III obesity had this phenotype. Non-phasic OGTT curve shape is a meaningful predictive factor of metabolically unhealthy phenotype before bariatric surgery. Male sex and class II/III obesity are risk factors associated with specific metabolic abnormalities.

Keywords Metabolic phenotype · Obesity · Bariatric and metabolic surgery

Mengyi Li and Yang Liu contributed equally to this work.

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Introduction

The inexorable increase in obesity in both men and women in China and worldwide has risen to unacceptable levels with resultant hazardous health implications, affecting approximately 90 million Chinese or 16.3% of the global obese population in men and 12.4% of that in women [1]. Obesity, as a disease, is associated with type 2 diabetes mellitus (T2DM), cardiovascular disease (CVD), obstructive sleep apnea-hypopnea syndrome (OSAHS), polycystic ovary syndrome (PCOS), hepatobiliary disease, gout and osteoarthritis, kidney disease, and some cancers, among other conditions, as well as a shortened life span [2–5]. Based on the understanding of the pathophysiology of obesity, the medical diagnostic term "adiposity-based chronic disease" (ABCD) emerged [6], which indicates that adipose tissue can become dysfunctional in obesity and contribute to systemic metabolic disease [7].

Variation in metabolic status has been observed among individuals with obesity [8–16]. In 2008, a classification of metabolic obesity phenotypes (metabolically healthy obesity and metabolically unhealthy obesity) was proposed by Wildman et al., which focused on cardiometabolic risk factors [9]. Despite the various definitions of metabolic phenotypes since then, current definitions are mainly based on risks of arteriosclerotic cardiovascular disease (ASCVD) or T2DM: for instance, including metabolic syndrome (MeS), Adult Treatment Panel III [ATP III] criteria [10, 17–21], insulin resistance (IR) [22–26], or CRP [27, 28].

Obesity is a complex, chronic, systemic metabolic disease, mainly involving interactions among glycometabolism, lipid metabolism, and purine metabolism, which result in serious complications. Therefore, in our study, we focused on the abovementioned metabolic abnormalities as well as proposed and adopted a new metabolic obesity phenotype definition based on the present obesity research population. Our study aims were as follows: (i) to determine the definitions of metabolic obesity phenotypes based on metabolic components; (ii) to investigate the demographic, metabolic, and comorbidity characteristics of expressing clustered normal and abnormal metabolic parameters; and (iii) to analyze the factors associated with metabolic abnormalities. To the best of our knowledge, this is the first study based on metabolic phenotypes in Chinese individuals with obesity before bariatric surgery. Our study would increase the understanding of metabolic features fundamental to obesity, which might provide opportunities for demonstrating the underlying mechanisms of the pathophysiology of this systemic metabolic disease.

Materials and Methods

Study Design and Patients

This was a cross-sectional study that analyzed the metabolic features of individuals with obesity. Eligible participants in this study were those aged 18–65 years, with a diagnosis of obesity according to the World Health Organization (WHO) criteria for obesity in Asian populations [29], with metabolic parameter data available, and those who were preparing for bariatric and metabolic surgery for the first time in our hospital. Study individuals were categorized into the following groups according to metabolic obesity phenotypes: metabolically healthy group and metabolically unhealthy group. Anthropometric measurements included sex, age, height, body weight, body mass index (BMI), and seated blood pressure levels. Actual height and body weight were measured before surgery. Seated systolic (SBP) and diastolic blood pressures (DBP) were measured using a mercury sphygmomanometer according to the European Society of Cardiology (ESC) and the European Society of Hypertension (ESH)'s recommendations [30]. A blood sample was taken under fasting conditions to measure HbA_{1c}, 3-horal glucose tolerance test (OGTT), C-peptide, and insulin levels to accompany OGTT, uric acid, thyroid function, and lipid profile, including total cholesterol (TC), triglyceride (TG), high-density lipoprotein (HDL), and low-density lipoprotein (LDL). Additionally, the following comorbidity statuses were also recorded: history of arteriosclerotic cardiovascular disease (ASCVD) as stated by the patients and diagnosis of PCOS and OSAHS by clinical assessment before surgery. All laboratory tests were performed in the laboratory of our hospital. All related clinical data were obtained from our database, named "Beijing Friendship Hospital Metabolic Surgery Database (BFH-MSD)" (ClinicalTrials.gov ID: NCT03520699), which was approved by the Ethics Committees of Beijing Friendship Hospital (No. 2017-P2-131-02). Informed consent was obtained from all participants included in this database.

OGTT

After a 10-h overnight fast, all patients underwent a standard 75-g OGTT with venous blood sampling. Following the collection of the baseline blood sample (time 0), patients ingested 75-g glucose, and blood was obtained at 30, 60, 120, and 180 min from glucose intake (0 min) to determine plasma glucose (PG), serum insulin, and C-peptide concentrations.

Criteria

The glucose curves showed values matching the American Diabetes Association 2003 criteria for normal glucose

tolerance (NGT), impaired glucose tolerance (IGT), impaired fasting glucose (IFG), and T2DM [31]. The diagnosis of diabetes was defined as fasting plasma glucose (FPG) ≥ 7.0 mmol/l or 2-h PG ≥ 11.1 mmol/l during OGTT. IGT was defined as FPG < 7.0 mmol/l and 2-h PG concentration of 7.8–11.1 mmol/l following a 75-g oral glucose load. IFG was defined as FPG level of 6.1–6.9 mmol/l. All glycemic values represent venous plasma.

According to the WHO criteria, obesity in Asian populations can be classified into the following three levels: class I obesity (BMI 27.5–32.5 kg/m^2), class II obesity (BMI 32.5–37.5 kg/m^2), and class III obesity (BMI ≥ 37.5 kg/m^2).

Metabolic Obesity Phenotype Definitions

There is the absence of an established definition of the metabolic obesity phenotypes. In our study, metabolic obesity phenotypes were defined on the basis of obesity (BMI ≥ 27.5 kg/m^2), with combination of the following five metabolic abnormalities: elevated blood pressure level, elevated glucose and lipid levels, abnormal lipoprotein level, and elevated uric acid level. The phenotype of metabolically healthy is defined by 0 or 1 of the five metabolic abnormalities, whereas that of metabolically unhealthy is defined by two or more of the five metabolic abnormalities (Fig. 1).

Calculations

Insulin resistance was calculated by the homeostasis model assessment of insulin resistance (HOMA-IR), which is fasting insulin (FINS, uIU/ml) × FPG (mmol/l)/22.5. β cell function was calculated by homeostasis model assessment of β cell (HOMA-β), which is 20 × FINS/(FPG-3.5) [32]. Early-phase insulin secretion was calculated as the ratio between the incremental plasma insulin and glucose concentrations during the first 30 min of OGTT ($^{\triangle}I_{0-30}/^{\triangle}G_{0-30}$) [33]. Total insulin secretion was calculated as the ratio between the incremental areas under the insulin and glucose curves during OGTT [$^{\triangle}$G (AUC)/$^{\triangle}$I (AUC)]. Areas under the glucose and insulin curves (AUCs) were calculated by trapezoidal integration with 0 as baseline.

Shape phenotypes of the OGTT response curves (i.e., monophasic or biphasic) were classified according to previous studies [34–38]. A monophasic response was characterized by a gradual increase in plasma glucose concentrations until a peak was reached followed by a subsequent decrease until 180 min (i.e., one peak). A

A Metabolic abnormalities considered:

1. Elevated blood pressure: Systolic/diastolic blood pressure ≥ 130/85 mmHg or antihypertensive medication use

2. Elevated glucose level: Fasting glucose level ≥ 5.6 mmol/L or diagnostic criteria for definition of IFG, IGT, or T2DM or antihypertensive medication use

3. Elevated lipid level: Fasting triglyceride level (TG) ≥ 1.70 mmol/L or fasting total cholesterol level (TC) ≥ 5.18 mmol/L

4. Abnormal lipoprotein level: HDL-C level < 1.0 mmol/L in men, HDL-C level < 1.3 mmol/L in women or LDL-C ≥ 3.37 mmol/L

5. Elevated uric acid level: UA level > 420 μmol/L in men or > 360 μmol/L in women or lipid-lowering medication use

B Criteria for metabolic obesity phenotypes:

Obese, metabolically healthy: BMI ≥ 27.5 kg/m^2 and <2 metabolic abnormalities

Obese, metabolically unhealthy: BMI ≥ 27.5 kg/m^2 and ≥2 metabolic abnormalities

Fig. 1 Definition of metabolic obesity phenotypes. **a** Metabolic abnormalities considered; **b** criteria for metabolic obesity phenotypes. BMI indicates body mass index (calculated as weight in kilograms divided by height in meters squared); HDL-C, high-density lipoprotein cholesterol. To convert to millimoles per liter, multiply by 0.0259 for HDL-C, by 0.0113 for triglycerides, and by 0.0555 for glucose

biphasic response was characterized by a gradual increase in glucose, followed by a ≥0.25-mmol/l decrease at a subsequent time point (i.e., two peaks), with a glucose threshold of 0.25 mmol/l as described by Tschritter et al. [34] to minimize glucose concentration fluctuations that may be caused by the glucose analysis method rather than physiology reasons. A non-phasic response was characterized by a gradual increase in plasma glucose concentrations without decrease until 180 min (i.e., no peak). Similar criteria were used for the shape phenotypes of insulin and C-peptide curves.

Statistical Analysis

Statistical analyses were performed with SPSS 21.0 software (SPSS, Inc., Chicago, IL). Data were presented as mean (SD) for quantitative data and median (maximum, minimum) for qualitative data. For normally distributed quantitative data, independent sample *t* test was used to test the differences in demographic, metabolic, and comorbidity parameters. For non-normal distributions, non-parametric tests were applied. Qualitative data were analyzed using Chi-squared test. To analyze the changes in plasma glucose, C-peptide, and insulin levels with time in OGTT, a general linear model analysis with repeated measures was performed. All tests were two-tailed, and the level of significance was set at $P < 0.05$.

Results

Study Population Characteristics

From August 2016 to August 2018, 600 patients were recruited to participate in this study. For each metabolic abnormality, there was a significant difference between metabolically healthy and unhealthy obesity phenotype groups (Table S1 in the Supplementary Appendix; $P < 0.001$, respectively).

Among the study individuals, 18.0% (108 patients) were obese yet metabolically healthy (0 or 1 metabolic abnormalities), whereas 82.0% (492 patients) were obese and metabolically unhealthy (≥2 metabolic abnormalities) (Table 1). Although the proportions of female patients in both groups were higher than that of male patients, 92.3% of the male patients were in the metabolically unhealthy group (Table 1; $P = 0.004$). The metabolically unhealthy group was significantly heavier and had higher BMI level than the metabolically healthy group (Table 1; both $P < 0.001$). Regarding obesity classification, 67.0%, 79.4%, and 89.9% of individuals with class I, II, and III obesity, respectively, were in the metabolically unhealthy group (Table 1; $P < 0.001$). Mean SBP and DBP levels were significantly higher in the metabolically unhealthy group (Table 1; $P < 0.001$).

Metabolic Characteristics

Glucose Metabolism

In terms of the glucose regulation status, 87.1% of metabolically healthy individuals had NGT, whereas 100% of IFG, 93.8% of IGT, and 97.7% of T2DM individuals were in the metabolically unhealthy group (Table 2; $P < 0.001$). Mean HbA_{1c} level was significantly higher in the metabolically unhealthy group (Table 2; $P < 0.001$), whereas the duration of diabetes was not statistically different between the groups. Regarding glucose variables in OGTT, mean FPG levels, and 0.5-, 1-, 2-, and 3-h postprandial PG levels were all significantly higher in the metabolically unhealthy group (Table 2; $P < 0.001$). The overall proportion of glucose curve shapes was not significantly different between groups (Table 2, Fig. 2a–c; $P = 0.491$). Of note, 100% of non-phasic individuals were in the metabolically unhealthy group. Mean AUC of glucose level increased significantly in the metabolically unhealthy group than in the metabolically healthy group (Table 2; $P < 0.001$).

In terms of C-peptide variables in OGTT, mean fasting C-peptide levels and 2- and 3-h postprandial C-peptide levels were significantly higher in the metabolically unhealthy group (Table 2; all $P < 0.001$); but for the 0.5- and 1-h postprandial C-peptide levels, the differences did not reach statistical significance. There was no significant difference in the maximal C-peptide level between groups (Table 2; $P = 0.076$). However, the metabolically unhealthy group had longer C-peptide time to peak (Table 2; $P < 0.001$). The overall proportion of C-peptide curve shapes was significantly different between groups (Table 2, Fig. 2d–f; $P = 0.003$). Of note, 100% of non-phasic individuals were in the metabolically unhealthy group. Mean AUC of C-peptide level increased significantly in the metabolically unhealthy group than in the metabolically healthy group (Table 2; $P = 0.001$), whereas the mean ratio of C-peptide (maximum/fasting level) decreased significantly in the metabolically unhealthy group (Table 2; $P < 0.001$).

In terms of the corresponding insulin variables in OGTT, mean fasting insulin level and 2- and 3-h postprandial insulin levels were significantly higher in the metabolically unhealthy group (Table 2; all $P < 0.05$), but for the 0.5- and 1-h postprandial insulin levels, the differences did not reach statistical significance. There was no significant difference in maximal insulin level between groups (Table 2; $P = 0.797$). However, the metabolically unhealthy group had longer insulin time to peak (Table 2; $P < 0.001$). The overall proportion of insulin curve shapes was not significantly different between groups (Table 2, Fig. 2g–i; $P = 0.205$). Of note, 95.8% of non-phasic individuals were in the metabolically unhealthy group. Mean

Table 1 Demographic characteristics in different metabolic obesity phenotypes

	Obese, metabolically healthy	Obese, metabolically unhealthy	*P* value
Number of cases	108	492	
Male, *n* (%)	11(10.2)	132(26.8)	
Female, *n* (%)	97(89.8)	360(73.2)	0.004[*b]
Age (years old)	30.2 (8.34)	32.7(8.73)	0.004[*a]
History of smoking			
No, *n* (%)	66(82.5)	350(81.4)	0.815[b]
Yes, *n* (%)	14(17.5)	80(18.6)	
History of drinking			
No, *n* (%)	73(91.3)	366(85.1)	0.146[b]
Yes, *n* (%)	7(8.8)	64(14.9)	
Height (m)	1.65(0.1)	1.68(0.1)	0.018[*a]
Body weight (kg)	98.4(21.3)	110.0(23.5)	< 0.001[*a]
Excess weight (kg)	29.9(18.4)	39.7(20.3)	< 0.001[*a]
BMI (kg/m^2)	35.8(6.3)	39.0(6.8)	< 0.001[*a]
Obesity classification			
Class I	38(35.2)	77(15.7)	
Class II	41(38.0)	158(32.1)	
Class III	29(26.8)	257(52.2)	< 0.001[*b]
SBP (mmHg)	121.1(10.0)	130.7(15.1)	< 0.001[*a]
DBP (mmHg)	76.0(6.6)	81.0(10.0)	< 0.001[*a]

Data are *n* (%), mean (SD), or median (minimum, maximum)

[a] Nonparametric tests (Mann-Whitney test)

[b] Pearson Chi-squared test. [*] $P < 0.05$. Excess weight = initial weight-ideal weight (in which "ideal weight" is defined by the weight corresponding to a BMI of 25 kg/m^2)

SBP systolic blood pressure, *DBP* diastolic blood pressure. History of smoking: including current and former smokers. History of drinking: including current and former drinkers

AUC of insulin level did not increase significantly in the metabolically unhealthy group than in the metabolically healthy group (Table 2; $P = 0.066$), whereas the mean ratio of insulin (maximum/fasting level) decreased significantly in the metabolically unhealthy group (Table 2; $P < 0.001$).

Regarding insulin secretion, the mean early-phase secretion level increased significantly from metabolically healthy to metabolically unhealthy (Table 2; $P < 0.001$), whereas the mean total secretion level did not reach statistical significance. Although an official cut-off value to gauge HOMA-IR has not been published in China, the mean HOMA-IR level was significantly increased in the metabolically unhealthy group (Table 2; $P < 0.001$). Furthermore, the mean HOMA-β cell level decreased significantly in the metabolically unhealthy group than in the metabolically healthy group (Table 2; $P < 0.05$).

Lipid Metabolism

The mean TC, TG, HDL-C, and LDL-C levels were all significantly higher in the metabolically unhealthy group (Table 2; $P < 0.001$). Moreover, the mean TG and LDL-C levels in the metabolically unhealthy group were slightly above the reference range in central laboratory.

Uric Acid Levels

There was a significant difference in UA levels between the groups (Table 2; $P < 0.001$). Additionally, the mean UA level in the metabolically unhealthy group was above the reference range in the central laboratory.

Thyroid Metabolism

There were no significant differences in free triiodothyronine (FT3), free tetraiodothyronine (FT4), and thyroid-stimulating hormone (TSH) levels between the metabolically unhealthy and healthy groups (Table 2; all $P > 0.05$).

Comorbidity Characteristics

The overall proportions of patients with arteriosclerotic cardiovascular disease (ASCVD) and PCOS were not significantly different between the groups (Table 3; both $P > 0.05$).

Table 2 Metabolic characteristics in different metabolic obesity phenotypes

	Obese, metabolically healthy $n = 108$	Obese, metabolically unhealthy $n = 492$	P value
Glucose regulation status			
NGT, n (%)	88(87.1)	124(25.9)	
IFG, n (%)	0(0)	22(4.6)	
IGT, n (%)	8(7.9)	121(25.3)	
T2DM, n (%)	5(5.0)	211(44.1)	< 0.001[*b]
Duration of diabetes (years)	3.4(6.2)	3.3(3.7)	0.100[a]
HbA_{1c} (%)	5.4(0.6)	6.6(1.7)	< 0.001[*a]
Glucose variables			
Fasting plasma glucose (mmol/l)	4.6(0.8)	6.4(3.1)	< 0.001[*a]
Plasma glucose at 30 min (mmol/l)	8.7(1.9)	11.4(4.0)	< 0.001[*a]
Plasma glucose at 60 min (mmol/l)	10.8(3.4)	13.1(4.9)	< 0.001[*a]
Plasma glucose at 120 min (mmol/l)	9.1(2.6)	11.5(5.6)	< 0.001[*a]
Plasma glucose at 180 min (mmol/l)	5.0(2.0)	8.6(5.0)	< 0.001[*a]
Shape of glucose curves			
Nonphasic, n (%) Monophasic, n (%)	0(0) 92(92.0)	4(0.8) 440(93.2)	0.491[b]
Biphasic, n (%)	8(8.0)	28(5.9)	
AUC of glucose level	21.4(5.4)	33.0(13.7)	< 0.001[*a]
C-peptide variables			
Fasting C-peptide (ng/ml)	3.2(1.5)	4.2(1.8)	< 0.001[*a]
C-peptide at 30 min (ng/ml)	8.1(3.8)	8.0(3.8)	0.797[a]
C-peptide at 60 min (ng/ml)	10.2(4.3)	10.2(4.4)	0.651[a]
C-peptide at 120 min (ng/ml)	8.6(3.8)	10.5(4.4)	< 0.001[*a]
C-peptide at 180 min (ng/ml)	5.0(2.4)	7.6(3.4)	< 0.001[*a]
C-peptide max (ng/ml)	11.0(4.2)	11.7(4.7)	0.076[a]
C-peptide time to peak (h)	1.2(0.5)	1.7(0.7)	< 0.001[*a]
Shape of C-peptide curves			
Nonphasic, n (%) Monophasic, n (%)	0(0) 89(89.0)	49(10.3) 387(81.6)	0.003[*b]
Biphasic, n (%)	11(11.0)	38(8.0)	
AUC of C-peptide level	23.7(8.8)	27.0(10.1)	0.001[*a]
Ratio of C-peptide max/fasting	3.9(1.8)	3.1(1.4)	< 0.001[*a]
Insulin variables			
Fasting plasma insulin (uIU/ml)	26.6(33.1)	31.1(24.9)	< 0.001[*a]
Plasma insulin at 30 min (uIU/ml)	110.6(76.1)	100.4(78.1)	0.134[a]
Plasma insulin at 60 min (uIU/ml)	136.0(98.9)	134.7(93.5)	0.981[a]
Plasma insulin at 120 min (uIU/ml)	96.0(84.8)	125.8(101.3)	0.002[*a]
Plasma insulin at 180 min (uIU/ml)	35.1(36.9)	67.7(63.8)	< 0.001[*a]
Insulin max (ng/ml)	156.0(95.5)	162.0(110.8)	0.797[a]
Insulin time to peak (h)	1.0(0.5)	1.5(0.7)	< 0.001[*a]
Shape of insulin curves			
Nonphasic, n (%) Monophasic, n (%)	1(1.0) 87(86.1)	23(4.9) 388(81.9)	0.205[b]
Biphasic, n (%)	13(12.9)	63(13.3)	
AUC of insulin level	277.5(182.0)	318.0(209.2)	0.066[a]
Ratio of insulin max/fasting	9.5(8.7)	7.6(11.7)	0.001[*a]
Insulin secretion			
Early-phase insulin secretion	21.8(18.5)	13.7(51.5)	< 0.001[*a]
Total insulin secretion	0.1(0.1)	0.2(0.4)	0.051[a]

Table 2 (continued)

	Obese, metabolically healthy $n = 108$	Obese, metabolically unhealthy $n = 492$	P value
Insulin resistance			
HOMA-IR	5.7(7.5)	8.8(7.9)	$< 0.001^{*a}$
β cell function			
HOMA-β cell	498.8(1642.6)	379.8(657.5)	0.023^{*a}
Serum lipid			
TC (mmol/l)	4.3(0.7)	5.1(1.0)	$< 0.001^{*a}$
TG (mmol/l)	1.2(0.5)	2.5(2.0)	$< 0.001^{*a}$
HDL-C (mmol/l)	1.1(0.3)	1.2(3.3)	$< 0.001^{*a}$
LDL-C (mmol/l)	2.4(0.4)	3.3(9.4)	$< 0.001^{*a}$
Uric acid (umol/l)	358.7(88.9)	426.5(96.5)	$< 0.001^{*a}$
Thyroid function			
FT3 (pg/ml)	3.6(0.5)	3.6(0.5)	0.111^{a}
FT4 (pg/ml)	0.9(0.2)	0.9(0.6)	0.254^{a}
TSH (uIU/ml)	3.3(2.3)	3.4(2.4)	0.753^{a}

Data are n (%), mean (SD) or median (minimum, maximum)

[a] Nonparametric tests (Mann-Whitney test)

[b] Pearson Chi-squared test. * $P < 0.05$

The overall proportion of patients with OSAHS was significantly different between groups (Table 3; $P = 0.004$). There was no significant difference in the mean microalbumin to urine creatinine ratio (ACR) levels between groups (Table 3; $P = 0.010$).

Prevalence Analysis

Regarding the statistical difference in the proportion of sex between groups, we estimated the prevalence of each metabolic abnormality stratified by sex (Table 4). For elevated blood pressure level, elevated lipid level, and abnormal lipoprotein level, the prevalence in men was significantly higher than that in women (Table 4, Fig. S1; OR = 1.52, 1.04–2.23; OR = 1.83, 1.21–2.77; OR = 1.69, 1.08–2.65, respectively). After adjusting for age and obesity classification, there were no statistical differences in the prevalence in terms of elevated blood pressure and abnormal lipoprotein levels (aOR = 1.31, 0.88–1.94; aOR = 1.56, 0.98–2.48, respectively).

Regarding the statistical difference in the proportion of the obesity classification between groups, we estimated the prevalence of each metabolic abnormality stratified by obese classification (Table 4). For elevated glucose and uric acid levels, the prevalence of class II obesity was significantly higher than that of class I obesity (Table 4, Fig. S2; OR = 1.87, 1.17–2.99; OR = 1.89, 1.19–3.01, respectively). For elevated blood pressure, glucose, and uric acid levels, the prevalence of class III obesity was significantly higher than that of class I obesity (Table 4, Fig. S2; OR = 2.22, 1.43–3.44; OR = 1.73, 1.11–2.68; OR = 3.61, 2.29–5.69, respectively).

Discussion

Given the perspectives of obesity, a key consensus concept proposed that the diagnosis based solely on BMI lacked the information needed for effective interaction and was a barrier to the development of acceptable and rational approach to medical care [7, 40]. Therefore, in addition to BMI, metabolic features give a deep insight to reflect “obesity”. Not only that, there exists differences in weight loss among populations after bariatric surgery even those with similar BMI levels and receiving the same surgical procedures. Thus, it is necessary to provide new thoughts for the future research in this area. The results of the proportion of metabolic abnormalities in the different metabolic obesity groups showed that the definition in our study made a significant distinction between the two phenotypes, which laid the foundation for the following analysis.

Demographic Characteristics in Metabolic Obesity Phenotype

The reason for the interesting sex distribution may be relevant to the specific research population. The result presented that the higher proportion of women has a significant advantage, similar to the data of the 2018 International Federation for the Surgery of Obesity and Metabolic Disorder (IFSO) global registry, which reported that the proportion of women among the patients undergoing bariatric surgery worldwide was 73.7%. Of note, 92.3% of the male population belongs to the

metabolically unhealthy group, indicating that metabolic abnormalities might be a major determinant for surgical treatment in men. Moreover, men have an increased risk for elevated lipid level than women. As for the obesity classification, which is not included in the definition, our results showed an existing correlation with metabolic obesity phenotypes. Of note, 26.9% patients with class III obesity belonged to the metabolic obesity healthy phenotype group. This, therefore, reminds us the limitation in using BMI alone as an indicator of metabolic status in individuals with obesity. Furthermore,individuals with class II/III obesity have an increased risk for elevated blood pressure, glucose, and UA levels than those with class I obesity. This may be due to the fact that fat distribution is a known determinant of metabolic risk, which varies with BMI levels. In the future, we will pay attention to the visceral and abdominal subcutaneous fat of this cohort to investigate whether fat and its distribution are a favorable or nonfunctional fat depot for metabolism in individuals with obesity.

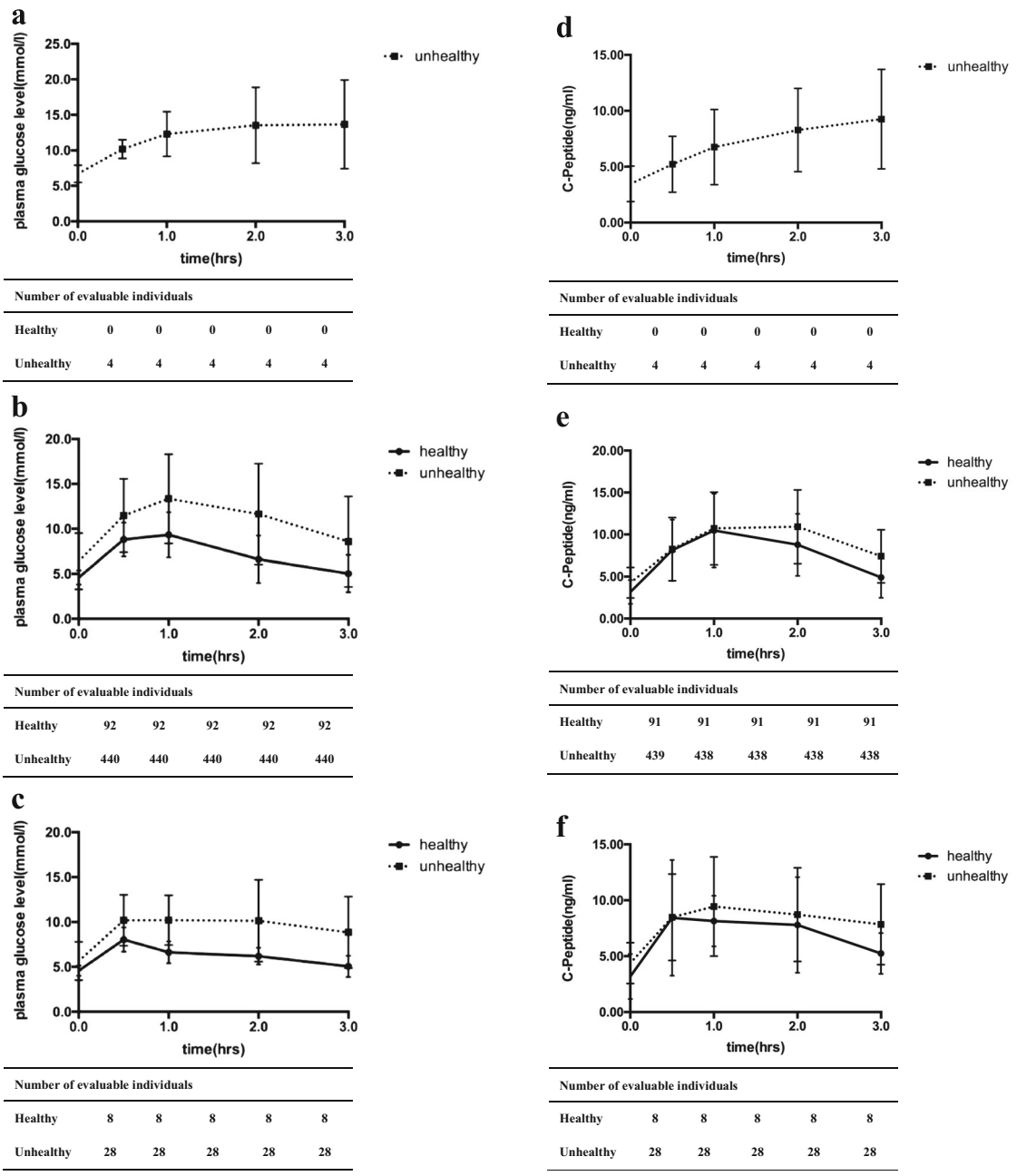

Fig. 2 Shape phenotypes of the OGTT response curves. Glucose curve during the OGTT (mean ± SD) in the non-phasic (**a**), monophasic (**b**), biphasic (**c**); corresponding C-peptide (**d**–**f**) and insulin (**g**–**i**) curves are also reported. Obese with metabolically healthy phenotype (solid lines) and obese with metabolically unhealthy phenotype (dashed lines)

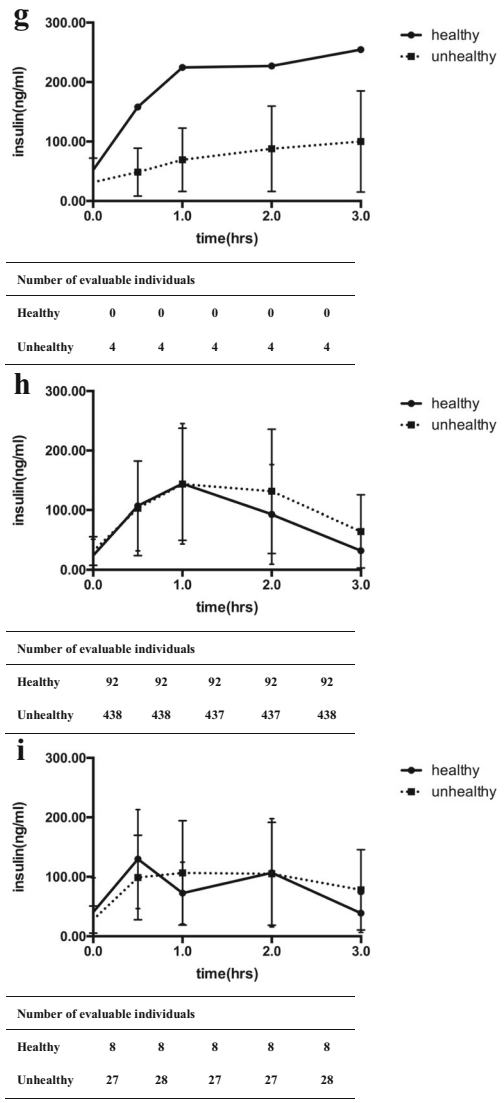

Fig. 2 (continued)

The Shape of OGTT in Obese, Metabolically Unhealthy Phenotype

Plasma glucose concentration during 75-g OGTTs is currently used for the diagnosis of diabetes [31]. Although the hyperinsulinemic-euglycemic clamp is considered to be the respective gold standard method of insulin sensitivity [41], OGTT was recognized as a relatively feasible and valid assessment of the parameters of glucose homeostasis, mainly insulin sensitivity and β cell function [42]. Until now, less attention has been devoted to investigating the information contained in a 3-h OGTT related to the concentration time course of the OGTT variables in individuals with obesity.

The metabolically obesity healthy phenotype appears to be a transient state that progresses over time to an unhealthy phenotype. Thus, a substantial number of subjects with impaired β cell function and insulin resistance are at a greater risk for developing T2DM. Several recent studies in adults use glucose curve shapes during OGTT to identify metabolic dysregulation and the potential risk for future T2DM [34, 36, 38]. In our study, we investigated the characteristics of the shape of the glucose, C-peptide, and insulin curves between the different metabolic obesity phenotypes. Interestingly, we found that, among the individuals with obesity, (i) OGTT curves can also be characterized by a high variability, i.e., non-phasic, monophasic, and biphasic shapes; (ii) glucose curve shape tends to be mirrored by similar C-peptide and insulin curve shapes; and (iii) non-phasic shape indicating worse glucose tolerance is strongly associated with metabolic obesity unhealthy phenotype. Our results appear to be consistent with previous studies [34, 38]. These data support the potential for rapid progression to overt T2DM [43].

Comorbidity Characteristics Between Metabolic Obesity Phenotypes

Before bariatric surgery, we recorded the clinical history data of ASCVD, PCOS, and OSAHS. As a result, we did not find any statistical differences in the overall proportions of ASCVD or PCOS between the two phenotype groups. However, the proportions of individuals with ASCVD and PCOS who were metabolically unhealthy were 95.5% and 84.6%, respectively. Moreover, the proportion of individuals with OSAHS who were metabolically unhealthy and diagnosed with mild, moderate, and severe OSAHS was 90.1%, 89.5%, and 93.7%, respectively. Statistical results suggest a relatively low incidence of ASCVD or PCOS in the study populations, but metabolically unhealthy phenotype accounts for a relatively high percentage of positively diagnosed patients. These results have further strengthened the pathogenesis correlations between ASCVD or PCOS and obesity with metabolic abnormalities. Additionally, the mean ACR level in the metabolically unhealthy group was between 30 and 300 mg/g suggesting microalbuminuria, which might indicate the early phase of hypertensive nephropathy or diabetic nephropathy, which is found in metabolically unhealthy populations.

Limitations

First, the main limitation was the study population selection. Although the study was focused on obesity, the results need to be assessed more carefully in the context of this condition in a larger population. Investigation with a larger cohort is definitely necessary, but the fact that we could already identify statistically significant differences in this study was encouraging. Furthermore, based on the cohort in the present study, we will perform further research on

Table 3 Comorbidity characteristics in different obesity metabolic phenotypes

	Obese, metabolically healthy $n = 108$	Obese, metabolically unhealthy $n = 492$	P value
Comorbidity			
ASCVD, *n* (%)			
No, *n* (%)	74(98.7)	380(94.8)	0.139 [b]
Yes, *n* (%)	1(1.3)	21(5.2)	
PCOS, *n* (%)			
No, *n* (%)	63(77.8)	320(76.4)	
Yes, *n* (%)	18(22.2)	99(23.6)	0.784 [b]
OSAHS, *n* (%)			
No, *n* (%)	33(64.7)	121(38.2)	
Mild, *n* (%)	8(15.7)	73(23.0)	
Moderate, *n* (%)	4(7.8)	34(10.7)	
Sever, *n* (%)	6(11.8)	89(28.1)	0.004*[b]
ACR (mg/g)	17.1(38.8)	51.4(190.6)	0.010*[a]

Data are *n* (%), mean (SD), or median (minimum, maximum)

[a] Nonparametric tests (Mann-Whitney test)

[b] Pearson Chi-squared test. * $P < 0.05$

ASCVD arteriosclerotic cardiovascular disease, including acute coronary syndromes, history of myocardial infarction, stable or unstable angina, coronary or other arterial revascularization, stroke, TIA, or peripheral arterial disease presumed to be of atherosclerotic origin [39], *PCOS* polycystic ovary syndrome, *OSAHS* obstructive sleep apnea-hypopnea syndrome, *ACR* microalbumin to urine creatinine ratio

the correlations between postoperative weight loss and metabolic obesity phenotypes, providing persuasive evidence for surgical selection. Second, some clinical data were missing during data collection. Although standardization and streamlined clinical data acquisition were performed according to the case report forms of our database, some data were missing due to the lack of compliance of some patients, such as duration of diabetes, history of smoking, and drinking. Additionally, further investigations of the effects on adipose tissue are still needed to evaluate a wider range of metabolic abnormalities.

Conclusion

Demographic, metabolic, and comorbidity characteristics differ between individuals with obesity classified as metabolically healthy and those classified as metabolically unhealthy. According to our new definition, approximately one-fifth of individuals with obesity can be classified as having a metabolically healthy phenotype, and nearly one-third of the individuals with class III obesity have this phenotype. Interestingly, non-phasic OGTT curve shape might be a meaningful predictive factor of the metabolically unhealthy

Table 4 Univariate logistic regression analysis of factors associated with metabolic abnormalities

Metabolic abnormalities.	Sex			Obese classification							
	Female *n* (%)	Male *n* (%)	OR	95%CI	Class I *n* (%)	Class II *n* (%)	OR	95%CI	Class III *n* (%)	OR	95%CI
1. Elevated blood pressure	224(72.5)	85(27.5)	1.52*	(1.04, 2.23)	47(15.2)	89(28.8)	1.17	(0.74, 1.86)	173(56.0)	2.22*	(1.43, 3.44)
2. Elevated glucose level	287(74.5)	98(25.5)	1.29	(0.86, 1.93)	61(15.8)	135(35.1)	1.87*	(1.17, 2.99)	189(49.1)	1.73*	(1.11, 2.68)
3. Elevated lipid level	275(72.4)	105(27.6)	1.83*	(1.21, 2.77)	70(18.4)	128(33.7)	1.16	(0.72, 1.86)	182(47.9)	1.13	(0.72, 1.76)
4. Abnormal lipoprotein level	76(67.9)	36(32.1)	1.69*	(1.08, 2.65)	17(15.2)	31(27.7)	1.06	(0.56, 2.02)	64(57.1)	1.66	(0.93, 2.98)
5. Elevated uric acid level	293(74.7)	99(25.3)	1.26	(0.84,1.89)	53(13.5)	123(31.4)	1.89*	(1.19, 3.01)	216(55.1)	3.61*	(2.29, 5.69)

For sex: female is reference. For obese classification: class I is reference.* $P < 0.05$

phenotype before bariatric surgery. Moreover, male sex and class II/III obesity could be risk factors associated with specific metabolic abnormalities. Further research in this area is indicated to further explore the relevance of metabolic phenotypes and features and their application to disease prevention, identification, diagnosis, and treatment and access to care for patients classified as metabolically unhealthy.

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Compliance with Ethical Standards

Conflict of Interests The authors declare that they have no conflict of interest.

Statement of Informed Consent Informed consent was obtained from all individual participants included in this study.

Statement of Human and Animal Rights This study was performed in accordance with the principles of the Declaration of Helsinki and was approved by the Ethics Committees of Beijing Friendship Hospital, Capital Medical University.

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