

Obesity phenotypes and their adipocyte dysfunction among the attendants at outpatient department

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Abstract

The present study was aimed to find out the frequency of obesity phenotypes and to correlate adipocyte dysfunction with different obesity phenotypes. A total of 1,507 apparently healthy adults attending the outpatient department were grouped into three based on body mass index which were then further categorized into six groups according to metabolically unhealthy or healthy phenotypes by the presence or absence of metabolic syndrome. Of them, metabolically obese normal weight, overweight, healthy obese and unhealthy obese groups were included as obesity phenotypes. Then by purposive sampling, leptin and adiponectin concentration of 184 subjects with different phenotypes were measured to find out the adipocyte dysfunction. Metabolically obese overweight followed by metabolically unhealthy obese were more prevalent i.e., 24.9% and 19.5%. All obesity phenotypes except metabolically obese normal weight were significantly documented with adipocyte dysfunction ($p < 0.05$).

Introduction

Obesity as well as overweight play as risk factors in the development of many chronic diseases like hypertension, type 2 diabetes, cardiovascular and respiratory diseases, and some cancers. Body mass index (BMI) determines the overweight (BMI 25-29.9 kg/m²) and obesity (BMI ≥ 30 kg/m²). However, BMI-based classification of obesity is not dependable because of its incapability to measure the body fat and adipocyte dysfunction directly.^{1,3} Even a normal weight person (BMI 18.5-24.9) may have adipocyte dysfunction and may present with metabolic syndrome.⁴ Such people are known as metabolically obese normal weight. Similarly a person with overweight or obesity may be metabolically healthy without adipocyte dysfunction,⁴ known as, metabolically healthy overweight and metabolically healthy obese. This gives rise of an actual need for accurate classification of obesity in question.

The term metabolic obesity has been floated to resolve this issue. Pajunen et al. (2011) and Goday et al. (2016) mentioned about metabolically healthy and metabolically unhealthy phenotypes in different BMI group (normal weight, overweight, obese).^{6,7} They used the components of metabolic syndrome (waist circumference, serum triglyceride, HDL-C, fasting blood sugar, blood pressure) for this classification. Individual having ≥ 3 components abnormal is regarded as metabolically unhealthy and individual having 0-2 components

abnormal is regarded as metabolically healthy. So, finally six metabolic phenotypes are identified as metabolically healthy normal weight, metabolically obese normal weight, metabolically healthy overweight, metabolically obese overweight, metabolically healthy obese and metabolically unhealthy obese.

Out of six metabolic phenotypes, metabolically obese normal weight, metabolically obese overweight, metabolically healthy obese and metabolically unhealthy obese are categorized as obesity phenotypes. Metabolic obesity, in fact, tends to speak out metabolically unhealthy state. Molecular pathophysiology behind the metabolic unhealthy state is ascribed to adipocyte dysfunction.

Metabolic disorders in obesity are usually associated with hypertrophy and hyperplasia of adipocytes, lead to inflammation of adipose tissue, and ultimately result in adipocyte dysfunction.⁴

Leptin and adiponectin are the hormones secreted by adipocytes. Leptin acts as proinflammatory;^{9,10} whereas adiponectin acts as anti-atherogenic^{11,12} and anti-inflammatory mediator. During adipocyte dysfunction, leptin resistance increases and adiponectin gene expression decreases;¹³ which leads to increase leptin concentration, decrease adiponectin concentration, that are responsible for obesity related comorbidities.⁸

Different methods are proposed to classify the



obesity phenotypes but yet to achieve consensus. Any criteria used to categorize obesity phenotypes need to be supported by the evidence of adipocyte dysfunction which is still unsettled. The current study was aimed to find out the frequency of obesity phenotypes among the adult attendants using metabolic syndrome criteria for categorization and to correlate adipocyte dysfunction with these phenotypes.

Materials and Methods

This study was conducted from March 2016 to February 2017. By non-probability sampling, a total of 1,507 study subjects of both sex, aged between 20 to 60 years were selected from the apparently healthy adult attendants from the outpatient department of Bangabandhu Sheikh Mujib Medical University. The subjects with BMI less than 18.5 kg/m², pregnancy, previous history of stroke, ischemic heart disease, chronic liver disease, chronic kidney disease and malignancy were excluded. Initial evaluation by history taking and clinical examination was performed and blood pressure, height, weight and waist circumference were recorded in a preformed data sheet.

With all aseptic precaution, fasting blood samples were collected from each study subject. Fasting plasma glucose was measured using hexokinase method (CI 4100 ARCHITECT, USA) whereas serum HDL-C was measured using enzymatic color test (Beckman Coulter Inc., USA) and serum triglyceride was measured using enzymatic glycerol phosphate oxidase method (Beckman Coulter Inc., USA).

The study subjects were grouped into three body mass index classes (normal weight, overweight and obese providing BMI 18.5-24.9, 25-29.9 and ≥ 30 kg/m² respectively) and also further categorized into metabolically unhealthy or healthy phenotypes by presence or absence of metabolic syndrome respectively. According to the modified NCEP ATP III criteria,¹⁴ metabolic syndrome was considered to be present if three or more of the following five criteria were metabolic syndrome: central obesity i.e. waist circumference >102 cm (men) or >88 cm (women), blood pressure >130/ 85 mmHg or taking medication for hypertension, fasting serum triglyceride level ≥ 150 mg/dL, fasting serum high-density lipoprotein cholesterol level <40 mg/dl (men) or <50 mg/dL (women) or taking medication for dyslipidemia and fasting blood sugar ≥ 5.6 mmol/L or taking medication for diabetes mellitus. Thus, using this criteria all the subjects finally were categorized into six metabolic phenotypes. Of them, metabolically obese normal weight, metabolically obese overweight, metabolically healthy obese and metabolically unhealthy obese were regarded as obesity phenotypes and metabolically healthy

normal weight was regarded as control.

Then by purposive sampling serum leptin and adiponectin concentration of 184 subjects with different obesity phenotypes and control group were measured by enzyme-linked immunosorbent assay technique (Diatek DR-3508G, China) and the leptin-to-adiponectin ratio also was calculated to find out adipocyte dysfunction.

Statistical analysis

The statistical analysis was carried out using the software SPSS version 22. Differences among the groups were analyzed using one-way analysis of variance or Kruskal-Wallis test as appropriate for measurement of data. Differences between groups were assessed by means of Mann-Whitney U test. Categorical values were expressed as absolute or relative frequencies and analyzed using Chi-Square test and/or two sample proportion test as adequate. Spearman's correlation coefficient by rank was used to analyze correlation between adipocyte dysfunction and different grades of obesity phenotypes. For correlation purpose obesity phenotypes were ranked according to body mass index.

Results

In this study among 1,507 study subjects, the prevalence of obesity phenotypes were metabolically obese normal weight (7.0%), metabolically obese overweight (24.9%), metabolically healthy obese (7.2%), metabolically unhealthy obese (19.5%) (Table I). Of them, metabolically obese normal weight found to be more in males but metabolically healthy obese and metabolically unhealthy obese found to be more in females; whereas, metabolically obese overweight, metabolically healthy obese and metabolically unhealthy obese were found significantly more in younger age group than older age group. Though metabolically obese normal weight, metabolically obese overweight, and metabolically unhealthy obese groups were showing more adverse metabolic profile, but metabolically healthy obese group had relatively good metabolic profile than other obesity phenotypes (Table I).

Compared to control (metabolically healthy normal weight), leptin and leptin-to-adiponectin ratio were found to be significantly high in the metabolically obese overweight, metabolically healthy obese and metabolically unhealthy obese groups ($p=0.00$). Adiponectin was found to be significantly decreased in the metabolically obese overweight compared to control ($p=0.00$). In metabolically healthy obese group, adiponectin was found to be high compared to control ($p=0.00$) (Table II).

Significantly increasing concentration of leptin and leptin-to-adiponectin ratio found from metabolically obese normal weight to metabolically obese overweight to metabolically healthy obese (Table

Table I

Baseline characteristics of different metabolic phenotypes of obesity (n=1,507)

Parameters	Normal weight		Overweight		Obese		p value
	Metabolically healthy	Metabolically obese ^b	Metabolically healthy	Metabolically obese ^b	Metabolically healthy	Metabolically obese ^b	
Frequency/percent	297/19.6	105/7.0	328/21.8	375/24.9	108/7.2	294/19.5	
Male/female	187/110	70/35 ^c	208/120	190/185	34/74 ^c	72/221 ^c	0.00 ^a
Age 20-40 year/41-60 year	231/66	49/56	225/103	204/171 ^c	82/26 ^c	188/106 ^c	0.00 ^a
Age (year)	33.7 ± 7.9	39.3 ± 8.8	35.6 ± 7.9	38.2 ± 7.9	33.2 ± 7.5	36.5 ± 8.1	0.00
Weight (kg)	60.1 ± 7.7	61.9 ± 7.6	70.8 ± 8.2	71.2 ± 7.7	81.1 ± 10.7	82.7 ± 12.5	0.00
Waist circumference (cm)	82.3 ± 6.1	86.9 ± 5.3	90.5 ± 6.1	93.8 ± 5.4	99.3 ± 8.9	103.1 ± 8.9	0.00
Systolic blood pressure (mm Hg)	115.2 ± 13.5	127.3 ± 12.3	117.2 ± 12.2	128.1 ± 12.9	117.7 ± 11.8	126.3 ± 14	0.00
Diastolic blood pressure (mm Hg)	77.6 ± 8.7	82.4 ± 7.4	79.5 ± 7.7	83.9 ± 7.9	80.7 ± 7.8	83.8 ± 8.8	0.00
Fasting plasma glucose (mmol/L)	4.7 ± 0.7	5.9 ± 2.4	4.9 ± 1.2	5.7 ± 2.3	4.6 ± 0.8	5.5 ± 1.5	0.00
Serum HDL-C (mg%)	40.5 ± 8.6	36.9 ± 7.74	40.4 ± 8.1	36.9 ± 7.5	41.0 ± 8.4	39.6 ± 7.1	0.00
Serum triglyceride (mg%)	142.5 ± 93	232.7 ± 117	156.6 ± 97	226.5 ± 134	132.5 ± 118	189.6 ± 98	0.00

Continuous variable presented as mean ± SD and categorical variables as absolute and relative frequencies. One-way ANOVA was done to find out the level of significance. ^aChi-square test was done to find out the level of significance. ^bObesity phenotypes are recognized. ^cSignificant differences were found by proportion test

II). Among obesity phenotypes, adiponectin found to decrease significantly from metabolically obese normal weight to metabolically obese overweight. Adiponectin also decrease significantly in metabolically unhealthy obese compared to metabolically healthy obese (Table II).

By Spearman rank correlation coefficient test, significant moderate positive correlation was found between obesity phenotypes and leptin concentration (Spearman rho 0.648, p=0.00) as well as leptin-to-adiponectin ratio (Spearman rho 0.594, p=0.00). But non-significant negative correlation was found between the obesity phenotypes and adiponectin (Spearman rho -0.64, p=0.87)(Figure 1).

Discussion

The prevalence of overweight (46.7%) and obese (26.7%) documented in this study was comparatively higher than previous studies done in Bangladesh.¹⁵⁻¹⁷ The age standardize prevalence of overweight and obese at rural population of Bangladesh were found 17.7% and 26.2% in 2013. However, they used Asian cut off values for BMI.¹⁵

Several other studies conducted at different points of time also used different anthropometric measurements; also conducted on different segment of population; most of the studies conducted on only women.^{16, 17} Even this study also not represent

Table II

Comparison of adipocyte dysfunction among different obesity phenotypes and control (n=184)

Parameters	MHNW (n=35)	MONW (n=29)	MOOW (n=41)	MHO (n=39)	MUO (n=40)	p value
	Median/IQR					
Leptin (ng/mL)	5.7/4.7-9.1 ^a	5.9/5-9.5 ^b	12/7.5-30.6 ^{abc}	27.6/10.3-70.3 ^{abc}	43.4/18.8-83.7 ^{abc}	0.00
Adiponectin (µg/mL)	3.3/2.3-5.5 ^a	2.7/1.7-5.7 ^b	2.0/1.4-3.1 ^{abc}	3.5/2.25-4.8 ^c	2.8/1.8-3.6 ^{ac}	0.00
Leptin-to- adiponectin ratio	1.7/1.2-3.7 ^a	2.8/1.4-4.9 ^b	7.1/6.3-13.8 ^{abc}	9.4/2.5-35.8 ^{abd}	15.6/7.6-31.1 ^{abcd}	0.00

Comparison done by Kruskal-Wallis test, after doing Mann Whitney U-test ^asignificant difference was found between metabolically healthy normal weight (MHNW) and other obesity phenotypes, ^bsignificant difference was found between metabolically healthy normal weight (MONW) and other obesity phenotypes, ^csignificant difference was found between metabolically obese overweight (MOOW) and other obesity phenotypes, ^dsignificant difference was found between metabolically healthy obese (MHO) and Metabolically unhealthy obese (MUO); IQR: interquartile range

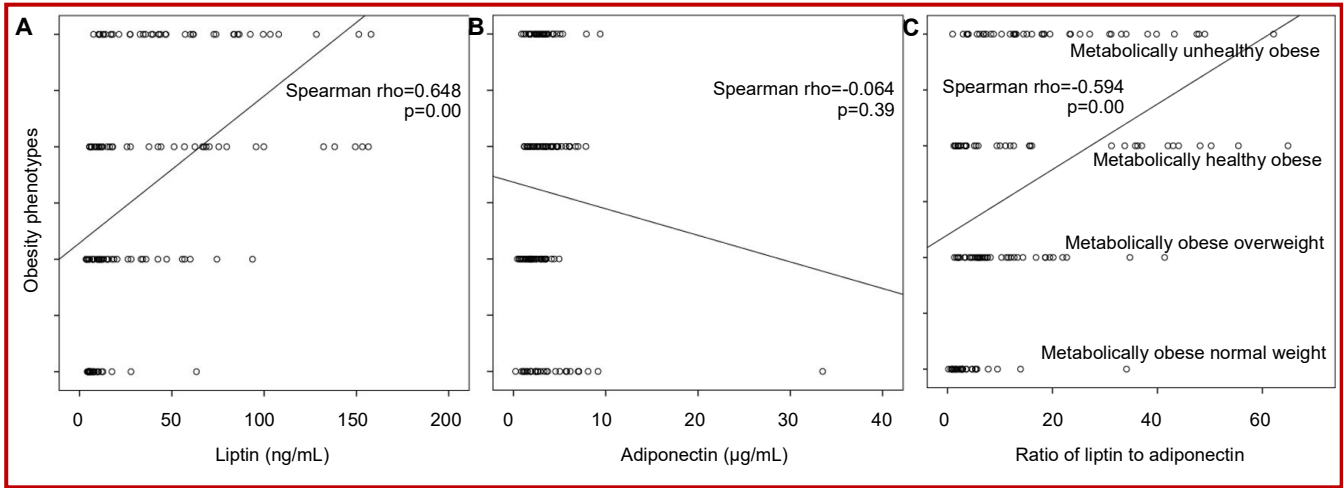


Figure 1: Correlation of adipocyte dysfunction to leptin (A), adiponectin (B) and their ratio (C) in different obesity phenotypes

the whole population. So, inconsistencies prevail among the studies, regarding the prevalence of overweight and obesity. But the previous studies also showed the increasing trend of overweight and obesity. Rapid urbanization, affluency, high educational level, shifts from manual labor to more sedentary occupations and the related decline in physical activity were claimed to be associated with higher prevalence of overweight-obesity.¹⁶

Development of obesity related cardiometabolic disorders depend on the fat weight gain, location of adipose tissue, hypertrophy, hyperplasia, inflammation and adipokine profile of adipose tissue.¹⁻³ So, the term metabolic obesity has been used to resolve this issue. We had used the metabolic syndrome criteria¹⁴ to categorize obesity phenotypes in total population as well as in every BMI classes. Frequency of metabolically obese overweight followed by metabolically unhealthy obese were found to predominant among 1,507 study subjects. Scientists, all over the world used different criteria to define metabolic health as well as metabolic obesity or body size phenotypes.^{6, 7, 18} In those studies, increasing trend of metabolically obese overweight and metabolically unhealthy obese were found.

This study showed metabolically healthy obese and metabolically unhealthy obese were found more in female than male except for metabolically obese normal weight which was found more in male. It might be due to life style differences, physical activity, smoking habit etc. In this study, metabolically obese normal weight was found more in the older age group (40-60 years). But other obesity phenotypes were found more in younger age group (20-40 years). The increasing prevalence of obese and overweight among the adult age group (20-40 years), that might be due to change in the dietary habit (increase consumption of edible oil, egg, meat) and decrease physical activity, along with financial affluency.¹⁹

In this study, we considered metabolically healthy normal weight as control. There was no significant difference between the metabolically obese normal weight with control. But this metabolically obese normal weight group has adipocyte dysfunction; are metabolically unhealthy, probably because of oxidative stress and other inflammatory markers.²⁰

Compared to control, both leptin and leptin-to-adiponectin ratio were found to be significantly high in the metabolically obese overweight, metabolically healthy obese and metabolically unhealthy obese indicating adipocyte dysfunction in these phenotypes. Again an increasing trend of leptin and leptin-to-adiponectin ratio were found from metabolically obese normal weight to metabolically obese overweight to metabolically healthy obese to metabolically unhealthy obese. Although the trend found non-significant between metabolically obese overweight and metabolically healthy obese in relation to leptin-to-adiponectin ratio. But grossly it can be said that adipocyte dysfunction was found progressively increasing in the obesity phenotypes, showing leptin resistance due to the enlargement of adipocytes.²¹

There was no significant difference between the metabolically healthy obese and metabolically healthy normal weight in relation to adiponectin. Adiponectin concentration found significantly low in metabolically obese overweight and metabolically unhealthy obese compared to the control indicating adipocyte dysfunction in these phenotypes. In adipocyte dysfunction, usually adiponectin decreases due to decrease gene expression.¹³ So, increased concentration of adiponectin, which is an anti-inflammatory, and an anti-atherogenic hormone^{11, 12} might be associated with good metabolic health, found in metabolically healthy obese group.

Among all three indicators of adipocyte dysfunction (high leptin, low adiponectin and high leptin-to-adiponectin ratio); high leptin-to-adiponectin ratio

is more dependable indicator of adipocyte dysfunction, because both the status of leptin and adiponectin are included in this marker.^{21, 22}

We have found significant moderate positive correlation between obesity phenotypes and leptin as well as leptin-to-adiponectin ratio. But non-significant correlation found between obesity phenotypes and adiponectin. Some previous studies stated that, adiponectin is not a good marker to diagnose adipocyte dysfunction, whereas leptin-to-adiponectin ratio is a very good surrogate marker for adipocyte dysfunction.^{21, 22}

Therefore, we recommend four obesity phenotypes, e.g. metabolically obese normal weight, metabolically obese overweight, metabolically healthy obese and metabolically unhealthy obese. With respect to severity, metabolically unhealthy obese is the most severe, metabolically obese normal weight is the least severe, whereas metabolically obese overweight and metabolically healthy obese are in between. Though metabolically healthy obese group was found metabolically healthy, but they are also at risk and has higher mortality risk compared to the control.²³

Conclusion

The prevalence of obesity phenotypes were found a) metabolically obese normal weight (7.0%), b) metabolically obese overweight (24.9%), c) metabolically healthy obese (7.2%), and metabolically unhealthy obese (19.5%). With respect to adipocyte dysfunction, obesity phenotypes found to show increasing trend of severity from metabolically obese normal weight to metabolically obese overweight to metabolically healthy obese to metabolically unhealthy obese. Despite of being healthy, metabolically healthy obese group also at risk of developing obesity related comorbidities, as they are featured by adipocyte dysfunction.

Ethical Issue

The study was approved by the Institutional Review Board approval of Bangabandhu Sheikh Mujib Medical University.

Conflict of interest

None of the authors have any conflict of interest to declare.

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