Circulating prolactin level is increased in metabolically healthy obesity

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Abstract

Objective: Prolactin (PRL) has been demonstrated as a metabolic hormone to regulate energy metabolism recently. The present study aims to investigate the association between PRL and metabolic alterations in different obesity phenotypes.

Methods: A total of 451 drug-naive participants were recruited, comprising 351 obese patients and 100 age- and sex-matched healthy participants with normal weight. PRL, anthropometric, and clinical parameters were measured.

Results: In the obesity group, 15.1% (53/351) were categorized as 'metabolically healthy obesity (MHO)'. Besides favorable blood pressure, glucose, and lipids profiles, the MHO group exhibited increased PRL, and lower levels of high-sensitivity C-reactive protein (hsCRP), homeostasis model assessment of insulin resistance (HOMA-IR), and adipose tissue insulin resistance (adipo-IR) than the metabolically unhealthy obesity (MUHO) group (PRL, HOMA-IR, and adipo-IR: $P < 0.01$; hsCRP: $P < 0.05$). The severe MUHO group showed significantly decreased PRL levels than the mild MUHO group ($P < 0.05$).

Multivariate linear regression analysis indicated that fasting plasma glucose (FBG) and adipo-IR were significantly associated with PRL ($\beta = -0.263, P < 0.05$; adipo-IR: $\beta = -0.464, P < 0.01$). Multivariable logistic regression analysis showed that hsCRP (OR = 0.824) and PRL (OR = 1.211) were independent predictors of MHO (all $P < 0.01$).

Conclusion: The MHO group had significantly increased circulating PRL levels when compared with the control and MUHO groups, and multivariable logistic regression analysis showed that PRL was independent predictors of MHO. Our findings suggested that increased circulating PRL might be a compensatory response for favoring energy metabolism during obesity.

Introduction

The global epidemic of obesity remains a growing public health concern owing to its short- and long-term adverse health sequelae (1, 2). Epidemiological studies have demonstrated that obesity is associated with increased risk of hypertension, dyslipidemia, and type 2 diabetes, further resulting in the development of cardiovascular diseases (2, 3). However, recent studies have found that a proportion of obese subjects appear to have a favorable metabolic profile with no aforementioned metabolic abnormalities, which was called 'metabolically healthy obesity (MHO)' (4, 5, 6, 7). The precise mechanisms responsible for such a favorable metabolic phenotype in obesity are not entirely understood.

Prolactin (PRL) is secreted from anterior pituitary and named for its crucial effect on lactation (8, 9). Recent studies have demonstrated that PRL plays an important role in regulating energy metabolism (8, 9, 10, 11, 12, 13, 14, 15, 16). PRL administration increased insulin sensitivity and regulated glucose and lipid metabolism in rodent models (10, 11, 12). PRL receptor knockout caused...
insulin resistance and severe adipose tissue dysfunction in obese mice (10). Many population-based studies found that a relatively higher PRL level was associated with lower risk of diabetes, nonalcoholic fatty liver disease and metabolic syndrome (12, 13, 14, 15). The previous study showed that obese patients had different PRL levels compared to non-obese participants (15, 16, 17). As an intermediate stage from healthy to overt metabolic abnormalities, MHO patients may have different PRL levels (7, 18). However, until now, few reports regarding the correlation of PRL and MHO have been published. The present study aims to investigate the association between PRL and metabolic alterations in different obesity phenotypes.

Materials and methods

Study design and participants

This study consecutively recruited 351 obese patients (BMI ≥ 30.0 kg/m²) attending the Obesity Clinic at Beijing Chao-yang Hospital Affiliated to Capital Medical University from January 2019 to December 2019 (2). Meanwhile, 100 age- and sex-matched healthy controls with normal weight (18.5 kg/m² ≤ BMI < 25.0 kg/m²) were consecutively enrolled from the Physical Examination Center at the same hospital (2). All participants were between 18 and 50 years old. No participants had a history of smoking (in the last 6 months), alcohol abuse, cardiovascular disease, thyroid dysfunction, disorders in thalamus and pituitary, polycystic ovarian syndrome, hypogonadism, severe hepatic insufficiency, renal function impairment, acute or chronic infections, systemic inflammatory disease, or cancer. Participants who were pregnant, lactating, or took any medications which influence PRL, glucose, lipid, or blood pressure were excluded. In order to investigate the association between PRL and metabolic alterations in the early stages of metabolic abnormalities, participants with a history of diabetes were excluded from the present study. We also excluded participants with PRL ≥ three times the upper limit of normal (ULN) or with oligo-/amenorrhea or/and-galactorrhoea (19, 20). Polyethylene glycol precipitation was routinely taken for patients with hyperprolactinemia in order to exclude the possibility of suffering from macroprolactinemia. This study was conducted in accordance with the Declaration of Helsinki ethical principles. The protocol was approved by the Ethics Committee of Beijing Chao-yang Hospital affiliated with Capital Medical University. All enrolled participants provided a written informed consent.

Measurements of clinical parameters

A standard questionnaire was performed to collect information about health status and medications. Anthropometric measurements were conducted after overnight fasting. Alcohol consumption and intercourse were forbidden 24 h before the examination. Height and body weight were respectively measured to the nearest 0.1 cm and 0.1 kg, with participants wearing indoor clothes and no shoes, by the same trained group. Waist circumference (WC) and hip circumference (HC) were measured to the nearest 0.1 cm between the lower rib margin and the iliac crest and at the maximum width of the buttocks in the horizontal plane, using an anthropometric tape, with the patient standing straight, abdomen relaxed, and feet together. Blood pressure was measured twice after a 5-min rest in a supine position, and systolic blood pressure (SBP) and diastolic blood pressure (DBP) were calculated as the average of two measurements. BMI was calculated as weight divided by height squared (kg/m²).

Venous blood samples were obtained between 08:00 and 09:00 h. after overnight fasting. The serum levels of total cholesterol (TC), triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C) and non-esterified fatty acid (NEFA) were measured by colorimetric enzymatic assays using an autoanalyzer (Hitachi 747, Roche Diagnostics). Fasting plasma glucose (FBG) was measured by glucose oxidase method (Hitachi 747, Roche Diagnostics). Fasting plasma insulin (FINS) was estimated by the chemiluminescence method (Dimension Vista, Siemens Healthcare Diagnostics). Hemoglobin A1c (HbA1c) was measured by high-performance liquid chromatography, using an HLC-723G7 analyzer (Tosoh Corporation, Tokyo, Japan). High-sensitivity C-reactive protein (hsCRP) was measured using an immunonephelometric assay. Estradiol (normal range: <56.0 pg/mL for female), total testosterone (TT) (normal range: 1.60–7.26 ng/mL for male; <0.73 ng/mL for female), thyroid stimulating hormone (TSH) (normal range: 0.55–4.78 μIU/mL), and PRL (normal range: 2.5–17.0 ng/mL for male; 1.9–25.0 ng/mL for female) were measured using a chemiluminescent immunometric assay by the Immulite 1000 Immunoassay Analyzer (Siemens). Homeostasis model assessment of insulin resistance (HOMA-IR) was calculated according to the following formulas: HOMA-IR = FINS (μIU/mL) × FBG (mmol/L)/22.5 (21). Adipose tissue insulin resistance (adipo-IR) was calculated according to the formula: Adipo-IR = fasting NEFA (mmol/L) × FINS (pmol/L) (22).
Definition of MHO

The present study used a strict definition of MHO proposed by Ortega (23). An individual was categorized as MHO if BMI ≥30 kg/m^2 and met none of the following criteria: (i) elevated TG (≥1.7 mmol/L), (ii) reduced HDL-C (<1.0 mmol/L for men and <1.3 mmol/L for women), (iii) elevated SBP (≥130 mmHg) or/and DBP (≥85 mmHg), and (iv) elevated FBG (≥5.6 mmol/L). Obese patients with one or more of the four metabolic risk components were categorized as metabolically unhealthy obesity (MUHO) (23).

Statistical analysis

Data were analyzed using SPSS 22.0 (SPSS). The Kolmogorov–Smirnov test was used to evaluate the distribution of continuous data. Normally distributed variables were expressed as mean ± S.D., while variables with a skewed distribution, including TG, FINS, hsCRP, HOMA-IR, adipo-IR, estradiol, and TT, were given as the median, upper and lower quartiles. The differences in continuous data between the three groups (control, MHO, and MUHO groups) were analyzed using ANOVA or Kruskal–Wallis H test followed by a post hoc test. The differences between two groups (two subgroups in the MUHO group) were analyzed using an independent t-test for normally distributed variables or a Mann–Whitney U-test for skewed-distribution variables. The proportions were analyzed using chi-squared tests. Pearson or Spearman correlation was used to test the correlation between two parameters. Multivariate linear regression analysis was performed to assess the relationship between PRL and metabolic parameters. Multivariable logistic regression analysis was performed to find the independent predictors for MHO in obese people. Statistical significance was considered at \( P < 0.05 \) (two-tailed).

Results

Clinical characteristics of control, MHO, and MUHO groups

A total of 451 participants comprising 351 obese patients and 100 age- and sex-matched healthy controls were included in the present study. The clinical characteristics of the control, MHO, and MUHO groups were summarized in Table 1. Among 351 obese patients, 15.1% (53/351) were categorized as MHO. The control, MHO and MUHO groups were comparable with respect to age and gender. Among the three groups, there were no significant differences in estradiol and TT levels. Significant differences were observed for BMI, WC, HC, SBP, DBP, TC, TG, HDL-C, LDL-C, NEFA, FBG, FINS, HbA1c, hsCRP, HOMA-IR, adipo-IR, TSH, and PRL levels among three groups (BMI, WC, HC, SBP, DBP, TC, TG, HDL-C, FINS, HbA1c, HOMA-IR, and adipo-IR: \( P < 0.01 \); LDL-C, NEFA, FBG, hsCRP, and TSH: \( P < 0.05 \)).

The MUHO patients were further divide into the mild MUHO group (MUHO patients with one or two metabolic risk components) and severe MUHO group (MUHO patients with three or four metabolic risk components) according to the number of the following metabolic risk components: (i) elevated TG (≥1.7 mmol/L), (ii) reduced HDL-C (<1.0 mmol/L for men and <1.3 mmol/L for women), (iii) elevated SBP (≥130 mmHg) or/and DBP (≥85 mmHg), and (iv) elevated FBG (≥5.6 mmol/L). There were no significant differences in age, gender, BMI, WC, HC, TC, LDL-C, HbA1c, estradiol, TT, or TSH between mild and severe MUHO groups (all \( P > 0.05 \), Table 2). The severe MUHO group had significantly higher PRL levels than the control and MUHO groups, while no significant difference in PRL level was observed in the latter two groups (Fig. 1 and Table 1).

Clinical characteristics in MUHO subjects with different degrees of metabolic abnormality

The MUHO patients were further divided into the mild MUHO group (MUHO patients with one or two metabolic risk components) and severe MUHO group (MUHO patients with three or four metabolic risk components) according to the number of the following metabolic risk components: (i) elevated TG (≥1.7 mmol/L), (ii) reduced HDL-C (<1.0 mmol/L for men and <1.3 mmol/L for women), (iii) elevated SBP (≥130 mmHg) or/and DBP (≥85 mmHg), and (iv) elevated FBG (≥5.6 mmol/L). There were no significant differences in age, gender, BMI, WC, HC, TC, LDL-C, HbA1c, estradiol, TT, or TSH between mild and severe MUHO groups (all \( P > 0.05 \), Table 2). The severe MUHO group had significantly higher levels of SBP, DBP, TG, NEFA, FBG, FINS, hsCRP, HOMA-IR, and adipo-IR, and lower levels of HDL-C and PRL when compared with the mild MUHO group (SBP, DBP, TG, HDL-C, FBG, and HOMA-IR: \( P < 0.01 \); NEFA, FINS, hsCRP, adipo-IR, and PRL: \( P < 0.05 \); Table 2).

The correlations between PRL and clinical parameters in all participants

Bivariate correlation analyses were used to investigate the correlations between circulating PRL levels and clinical parameters in all participants. The circulating PRL levels were
negatively correlated with WC, TG, NEFA, FINS, HOMA-IR, and adipo-IR, and positively correlated with TSH levels (Table 3). A similar pattern of correlations was also observed when the analysis was stratified by gender (Table 3).

Multivariate linear regression analysis was used to further assess the relationship between PRL and potentially relevant variables, including gender, WC, TG, NEFA, FBG, HOMA-IR, adipo-IR, and TSH. The analysis showed that only FBG and adipo-IR levels were negatively associated with PRL levels (FBG: \( \beta = -0.263, P < 0.05 \); adipo-IR: \( \beta = -0.464, P < 0.01 \)).

**Multivariate logistic regression analysis to find the independent predictors for MHO**

Multivariate logistic regression analysis was used to identify the potential predictive factors for MHO and to show that hsCRP and PRL were independent predictors of MHO after adjustment for age, gender, BMI, WC and HC levels (Table 4).

**Discussion**

The present study showed that in the obesity group, 15.1% (53/351) were categorized as MHO. Besides favorable metabolic profiles of blood pressure, glucose, and lipids, the MHO group exhibited significantly higher levels of PRL and lower levels of hsCRP, HOMA-IR, and adipo-IR than the MUHO group. Interestingly, the severe MUHO group showed significantly lower PRL levels than the mild MUHO group but similar PRL levels with the healthy controls.

Multivariate linear regression analysis indicated that FBG and adipo-IR were significantly associated with PRL levels (FBG: \( \beta = -0.263, P < 0.05 \); adipo-IR: \( \beta = -0.464, P < 0.01 \)).
and multivariable logistic regression analysis showed that hsCRP and PRL were independent predictors of MHO.

The present study showed that 15.1% were categorized as MHO in the obesity group, which was similar with many previous studies (5, 6, 7). Despite comparable BMI levels, relatively lower levels of HOMA-IR and adipo-IR were observed in the MHO group, as compared to the MUHO group. In addition, our study found that the MHO group had significantly lower hsCRP levels than the MUHO group (24, 25). A chronic inflammatory state has been demonstrated to cause insulin resistance via activating intracellular inflammatory pathways in many previous studies (26, 27). Therefore, the relatively lower inflammatory state and elevated insulin sensitivity in both systemic and adipose tissue seem to be responsible for favorable metabolic parameters in the MHO phenotype.

Accumulating evidence has suggested that PRL as a metabolic hormone to regulate energy metabolism (8, 9, 10, 11, 12, 13, 14, 15, 16). The present study showed that the MHO patients had significantly higher circulating PRL levels than the control and MUHO group. Correlation analyses found that the circulating PRL was negatively correlated with FBG, HOMA-IR, and adipo-IR in all participants. And multivariate linear regression analysis indicated that levels of FBG and adipo-IR were significantly associated with PRL levels. Adipocytes of rodents and humans expressed PRL receptors (10, 28). Previous studies found that increased circulating PRL levels were involved in healthy expansion of adipose tissue in both rodents and humans, especially during obesity (10, 29). In diet-induced obese rats, PRL administration inhibited adipocyte hypertrophy, down-regulated inflammatory cytokine expression in visceral adipose tissue, and alleviated insulin resistance (10, 30). PRL receptor knockout mice exhibited higher insulin resistance and severe adipose tissue dysfunction (10). Therefore, increased circulating PRL might be a compensatory response for favoring energy metabolism during obesity. Consistently, the concept of homeostasis functionally increased transient hyperprolactinemia (HomeoFIT-PRL) which has been proposed recently by Macotela et al. and this proposed definition reveals that elevated PRL levels favor metabolic homeostasis in a situation of metabolic need or challenge (20).

Several cohort studies have demonstrated that individuals with a lower circulating PRL level have an increased risk of insulin resistance, diabetes, and metabolic syndrome (13, 14, 15). In the present study,
Table 3  Correlation between PRL and clinical parameters in all participants.

| Parameters | PRL (all) | PRL (male) | PRL (female) |
|------------|-----------|------------|--------------|
|            | r         | p          | r            | p           | r            | p           |
| Age        | 0.006     | 0.930      | 0.135        | 0.098       | −0.123       | 0.056       |
| BMI        | −0.058    | 0.357      | 0.025        | 0.762       | −0.076       | 0.465       |
| WC         | −0.141    | 0.032      | −0.151       | 0.023       | −0.138       | 0.045       |
| HC         | −0.137    | 0.324      | −0.071       | 0.879       | −0.173       | 0.319       |
| SBP        | −0.172    | 0.564      | −0.194       | 0.431       | −0.161       | 0.502       |
| DBP        | −0.086    | 0.787      | −0.077       | 0.874       | −0.090       | 0.773       |
| TC         | −0.076    | 0.221      | 0.113        | 0.167       | −0.114       | 0.077       |
| TG         | −0.260    | 0.000      | −0.162       | 0.008       | −0.246       | 0.000       |
| HDL-C      | 0.022     | 0.726      | 0.031        | 0.617       | 0.029        | 0.769       |
| LDL-C      | −0.093    | 0.135      | −0.037       | 0.236       | −0.095       | 0.139       |
| NEFA       | −0.222    | 0.002      | −0.601       | 0.000       | −0.290       | 0.012       |
| FSB        | −0.136    | 0.030      | −0.132       | 0.043       | −0.155       | 0.033       |
| FINS       | −0.080    | 0.225      | −0.036       | 0.842       | −0.120       | 0.134       |
| HbA1c      | −0.010    | 0.879      | −0.112       | 0.172       | 0.056        | 0.400       |
| hsCRP      | −0.012    | 0.963      | −0.003       | 0.982       | −0.142       | 0.531       |
| HOMA-IR    | −0.244    | 0.000      | −0.228       | 0.000       | −0.232       | 0.000       |
| Adipo-IR   | −0.302    | 0.000      | −0.324       | 0.000       | −0.296       | 0.000       |
| Estradiol  | −0.007    | 0.905      | 0.079        | 0.497       | −0.093       | 0.181       |
| TT         | 0.106     | 0.065      | 0.226        | 0.198       | −0.104       | 0.187       |
| TSH        | 0.143     | 0.037      | 0.174        | 0.033       | 0.240        | 0.000       |

Adipo-IR, adipose tissue insulin resistance; DBP, diastolic blood pressure; FBS, fasting blood glucose; FINS, fasting insulin; HbA1c, hemoglobin A1c; HC, hip circumference; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment of insulin resistance; hsCRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; NEFA, non-esterified fatty acid; PRL, prolactin; SBP, systolic blood pressure; TC, total cholesterol; TG, triglyceride; TSH, thyroid stimulating hormone; TT, total testosterone; WC, waist circumference.

the circulating PRL level of the MUHO group was similar with the healthy controls, but significantly lower than that of MHO group. Interestingly, the severe MUHO group showed significantly lower PRL levels than the mild MUHO group, but similar PRL levels with the healthy controls. These results might suggest that the compensatory increased PRL did not occur as expected in MUHO patients, especially in severe MUHO patients. In order to investigate the association between PRL and metabolic alterations in the early stage of metabolic abnormalities, participants with a history of diabetes or taking any medications which influence glucose, lipid, or blood pressure were excluded from the present study. Therefore, the metabolic abnormality was relatively mild in the enrolled MUHO patients, which might explain why reduced PRL levels were not observed in MUHO subjects.

Levels of BP, glucose, and atherogenic lipid were relatively higher in the MHO group than the healthy control group, although they remained within the normal range. Furthermore, significantly increased hsCRP, HOMA-IR, and adipo-IR levels were also observed in the MHO group when compared with healthy controls. These results suggested that MHO manifested elevated inflammatory factor expression, decreased insulin sensitivity, and compensatory increased insulin secretion, despite without overt metabolic abnormality. Moreover, many studies have confirmed that MHO subjects were more prone to develop multiple cardiovascular diseases over time.

Table 4  Multivariate logistic regression analysis to find the independent predictors for MHO.

| Parameters | p         | MHO OR (95% CI) |
|------------|-----------|----------------|
| Age        | 0.382     | 0.941 (0.773–1.120) |
| Male gender| 0.494     | 0.902 (0.695–1.248) |
| BMI        | 0.079     | 0.892 (0.593–1.011) |
| WC         | 0.347     | 0.899 (0.639–1.053) |
| HC         | 0.690     | 0.938 (0.703–1.141) |
| HsCRP      | 0.002     | 0.824 (0.717–0.943) |
| PRL        | 0.001     | 1.211 (1.017–1.464) |

HC, hip circumference; hsCRP, high-sensitivity C-reactive protein; MHO, metabolically healthy obesity; OR, odds ratio; PRL, prolactin; WC, waist circumference.
as compared with normal-weight healthy individuals, even in the absence of metabolic abnormalities (31). Therefore, every obese individual should be encouraged to achieve normal weight in the long term.

The present study has some limitations. First, a single blood sample might not well reveal daily PRL secretion, on account of the pulsatile release of PRL (32). Although mostly pulsatile during the night, PRL secretion is relatively constant in the daytime (32). Thus, for the sake of narrowing PRL variation as much as possible, blood samples were taken between 8:00 and 9:00 h in the present study. Secondly, this study is a single center study with a relatively small sample size, which may have introduced selective bias and limited the generalizability of findings. Thirdly, PRL levels vary during the menstrual cycle but the present study did not standardize for the menstrual cycle (19). Finally, in fact, a universally accepted criterion for MHO has not yet been established so far (6). The present study used a strict definition of MHO proposed by Ortega, which was accepted by most previous studies (7, 23, 33, 34). Further research is needed to better understand the role of PRL and other relevant parameters in different obesity phenotypes and to elucidate the precise mechanisms underlying the transition from MHO to MUHO.

In conclusion, the MHO group had significantly increased circulating PRL levels when compared with the control and MUHO groups, and multivariable logistic regression analysis showed that PRL were independently associated with MHO. Our findings suggested that increased circulating PRL might be a compensatory response for favoring energy metabolism during obesity. However, further studies, including human, animal, and cell experiments, are still needed to confirm these results and get better insight into the underlying mechanisms.

Declaration of interest
The authors declare that there is no conflict of interest to that could be perceived as prejudicing the impartiality of the research reported.

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Author contribution statement
G W was involved in final approval of the manuscript, conception or design; J L, L Z, J F, and Q W were involved in acquisition, analysis, or interpretation of data; J L and L Z were involved in drafting the work or revising.

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