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Excess fat in the abdomen but not general obesity is associated with poorer metabolic and cardiovascular health in premenopausal and postmenopausal Asian women

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ABSTRACT

Objectives: To examine the associations of various metabolites and hormones and hormone replacement therapy (HRT) with obesity.

Methods: This is a cross-sectional study of 1326 Singaporean women. A DXA-derived percent body fat (PBF) of $\geq$35% and percent abdominal fat (PAbdF) of > 21.8% were used, respectively, to define women with general (GOb) and abdominal (AbdOb) obesity.

Results: Higher levels of insulin and glucose, lower levels of HDL, higher levels of TC/HDL and HOMA values, and different levels of some hormones were noted only in the women with abdominal, and not general obesity. The incidence of general and abdominal obesity was higher in postmenopausal women with or without HRT, except that those who were on conjugated estradiol-only HRT had no increase in the incidence of general obesity compared with premenopausal women.

Conclusions: Abdominal obesity is associated with insulin resistance and with higher risks of metabolic syndrome and cardiovascular diseases, whereas general obesity is not. Abdominal obesity may predispose to a higher risk of diabetes. The onset of the menopause tends to increase the incidence of general and abdominal obesity, except that postmenopausal women on conjugated estradiol HRT appear to be relatively protected from general obesity.

1. Introduction

An obesity pandemic is currently affecting most developed and developing countries [1,2]. Obesity is a common predisposing factor for elevated risk of several serious health conditions including insulin resistance, type 2 diabetes mellitus, hypertension and other cardiovascular disease, fatty liver disease and some types of cancer [3,4]. Metabolic syndrome (MetSyn) has been associated with the endocrine, metabolic and immunological functions of the adipose tissue [5]. Obesity is strongly associated with disorders of glucose, lipid metabolism and insulin resistance [6,7]. Furthermore, high insulin levels lead to an increase in bioavailability of IGF1 [8].

The high incidence of cardiometabolic comorbidities with obesity has heightened the obesity crisis. A better understanding of the associations among these cardiometabolic risk factors and obesity will lead to more appropriate therapeutic treatment of obesity [9,10].

However, there is significant variability in studies of disease association with obesity. The differences may, in part, be due to the criteria used to classify the different forms of obesity. Body Mass Index (BMI) of $\geq 30\ kg/m^2$ is commonly used to define general obesity (GOb) [11], while abdominal obesity (AbdOb) is commonly defined by either waist circumference (W), waist-hip ratio (W/H) or waist-height ratio alone or in combination [12]. These indices of adiposity have high degrees of misclassification resulting in confusing inferences derived from their use in obesity studies [13]. There is a need to use more appropriate indices for the classification of obesity and to evaluate their association with various hormonal and metabolic factors. A better understanding of the etiologic factors of obesity could also lead to more appropriate modalities for managing obesity.

In a previous study, DXA-derived percent body fat (PBF) and percent abdominal fat (PAbdF) were used to define general (GOb) and abdominal obesity (AbdOb) in men [14]. Therefore, the present study explored whether the various forms of obesity exist in women and evaluated their profiles of association with various metabolites and hormones. In addition, the study explored the relationships between the onset of menopause and different types of hormone replacement therapy (HRT) and the incidence of obesity.

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2. Materials and methods

2.1. Subjects

This study was approved by the Institutional Review Board of the National University Hospital of Singapore and each volunteer gave her written informed consent. One thousand three hundred and twenty-six Singaporean Chinese women, aged between 29y and 71y, living in the community were recruited through advertisements in the media and through word of mouth. As the primary objective of the overall study was to evaluate the determinants of the natural aging process, only women without a history of medical illnesses such as cancer, hypertension, thyroid dysfunction, diabetes, osteoporotic fracture, cardiovascular events, major sleep disorders, or major joint surgery were included in the study. Subjects were not paid for their participation. The cohort of women represented the diverse spectrum of Chinese in Singapore, ranging from those with low to high levels of education, working and non-working women, and those in various types of vocation. Their profiles were typical of women in Singapore, which is a highly urbanized city-state with no rural population. The methodology used was previously reported [15].

3. Methods

3.1. General questionnaire

Each subject answered a self-administered and investigator-guided questionnaire. Questions asked included their medical, social, sex, exercise regime, and family history.

3.2. Biochemical and hormone measurements

An overnight 12 h fasting blood sample was collected in the morning between 9.00am and 11.00am for premenopausal women between Day 3–5 of their menstrual cycle and on any day for postmenopausal women. The sera were stored at −80 °C until analysis. Serum levels of total cholesterol (TC) and triglycerides (TG), high density lipoprotein-cholesterol (HDL), low density lipoprotein cholesterol (LDL) and fasting glucose level (GLU) were measured by methods reported earlier [15]. Serum testosterone (T), dehydroepiandrosterone sulphate (DHEAS), and sex hormone binding globulin (SHBG) were measured by established radioimmunoassay methods reported earlier [15]. Serum concentrations of insulin-like growth factor-1 (IGF1) and insulin like growth factor binding protein-3 (BP3) were measured using immunoradiometric assay kits (Diagnostic Systems Laboratories, Inc., Webster, TX) as reported earlier [16,17]. Serum concentrations of insulin (INS) were measured in-house using the Axsym platform from Abbott Laboratories (Irving, TX). Bioavailable testosterone (BioT) was calculated using the computer formula of Vermeulen, which is available on the ISSAM website (www.issam.ch).

3.3. Whole body DXA scan

Every woman had a whole body scan using the dual-energy x-ray absorptiometry (DXA) (Hologic, Bedford, MA, USA). The percent total body fat (PBF), total fat mass (TFM) and percent abdominal fat (PAbdF) were calculated by the DXA machine based on the Siri formula.

3.4. Blood pressures

Brachial systolic (Sys) and diastolic (Dia) blood pressures were measured by trained clinical researchers using a standardized manual sphygmomanometer after subjects had five minutes of rest.

3.5. Intensity of exercise (METmin)

The intensity of exercise, expressed as metabolic equivalent of task-minutes (METmin), was shown in our earlier studies to correlate with body composition, and with various metabolites and hormones. In order to adjust for the effect of exercise, the METmin was used as a covariate in all the analyses. Computation of the total exercise score (METmin) was reported earlier [18]. In order to normalize the different types of exercise/sport into a single common score, exercise intensity was calculated using the Metabolic Equivalent of Task (MET) of each exercise/sport type. A score was then calculated to denote the intensity of exercise/sport per week in MET minutes (METmin) by taking into account the duration of each exercise episode and the frequency of the exercise per week in accordance with the exercise guidelines [19]. For example, a participant reported that she walked for 30 min 5 times a week, played tennis for 60 min twice a week and did line dancing for 60 min once a week. Walking is assigned a MET of 3; tennis, a MET of 7; and line dancing, a MET of 5. Her total physical/sports activities intensity per week was therefore 1590 METmin $[(3 \times 30 \times 5) + (7 \times 60 \times 2) + (5 \times 60 \times 1)]$. These data were gathered using a self-administered and investigator-guided questionnaire.

3.6. Definitions of general obesity (GOb), abdominal obesity (AbdOb)and general and abdominal obesity (G + AbdOb)

As recommended by the American Council on Exercise (ACE), a woman is considered to have obesity when her percent total body fat (PBF) computed from the DXA-whole body scan is ≥32% [20]. Using the frequency plot of all PBF of the 1326 women in the present study, the cut off at the 95 percentile was 35% PBF. Hence, women were categorised as having general obesity (GOb) when their PBF was ≥35%.

The regional distribution of body fat is not homogeneous in all women. It is possible that there are women with significantly higher accumulation of abdominal fat who may be considered to have abdominal obesity (AbdOb). For the definition of abdominal obesity (AbdOb), a frequency distribution of the DXA-derived PAbdF of the 1326 women was constructed. As with the definition in men reported earlier (8), the PAbdF at the 95 percentile (21.8%) was used as the cut-off value; any woman with a PAbdF above this cut-off value was considered to have abdominal obesity (AbdOb). Therefore, there are two groups of women with abdominal obesity: those women with PBF of < 35% and a PAbdF of > 21.8% were considered as having abdominal obesity (AbdOb), while women with PBF of > 35% and a PAbdF of > 21.8% were considered to have general as well as abdominal obesity (G + AbdOb). However, it must be noted that the DXA-derived PAbdF does not distinguish between abdominal subcutaneous and abdominal visceral fat. It is the sum total of fat in the abdominal area.

3.7. Indices of insulin resistance

3.7.1. Triglyceride and high density lipoprotein cholesterol ratio (TG/HDL) as a marker for insulin resistance

Triglyceride/HDL ratio has been considered as a cardiovascular risk factor [21]. Triglyceride/HDL ratio has also been used to identify insulin-resistant individuals [22]. As suggested by McLaughlin et al. [22], a TG/HDL of ≥1.80 was used as an indication that an individual was insulin resistant.

Homeostasis model assessment (HOMA) was also used as a measure of insulin resistance. As suggested by Matthews et al., HOMA is computed by multiplying fasting insulin by fasting glucose levels and dividing by 22.5 [23]. A HOMA value of > 2.8 computed from a single fasting blood sample correlated well with other measures of insulin resistance. The data in the present study showed that TG/HDL and HOMA were positively and significantly correlated. A HOMA value of > 2.8 was considered as indicative of an individual with insulin resistance.