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ORIGINAL ARTICLE

# Abdominal Obesity Associated with Elevated Serum Butyrylcholinesterase Activity, Insulin Resistance and Reduced High Density Lipoprotein-Cholesterol Levels

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**Abstract** Abdominal obesity (AO) has a strong correlation with cardiovascular disease and has been linked to Alzheimer's disease and type 2 diabetes. We investigated the association between AO and elevated serum butyrylcholinesterase (BChE) activity, insulin resistance and the serum lipid profile, including triglyceride (TG), HDL-cholesterol (HDL-C) and LDL-cholesterol (LDL-C) levels in AO and non-AO women subjects. A total of 500 AO subjects (age 49.1 ± 10.5 years), and 142 non-AO women subjects (age 49.9 ± 11.9 years) were enrolled for the general biochemistry tests, serum BChE, fasting insulin and homeostasis model assessment of insulin resistance (HOMA-IR). Body mass index, waist circumference, Blood pressure (BP), plasma glucose (Glu), triglyceride (TG), BChE, insulin, HOMA-IR were significantly higher and HDL-C levels were significantly lower in AO subjects ($p < 0.05$). Waist circumference was significantly correlated with BP, Glu, TG, BChE, insulin and HOMA-IR in AO subjects. Multiple logistic regression demonstrated that AO was associated with elevated BChE, HOMA-IR, hypertension and reduced HDL-C after adjusting for these variables. AO is associated with elevated BChE, insulin resistance, HT and reduced HDL-C. These may predict the development of type 2 diabetes mellitus and may be associated with cognitive disorder in the future, both are mediated through insulin resistance.

**Keywords** Abdominal obesity · Butyrylcholinesterase · High density lipoprotein-cholesterol · Insulin resistance

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## Introduction

Abdominal obesity (AO) is excessive abdominal fat around the stomach and abdomen also known as central obesity. Central obesity has a strong correlation with cardiovascular disease [1] and has been linked to Alzheimer's disease and type 2 diabetes [2], as well as other metabolic and vascular diseases [3]. Enzyme cholinesterase is present in all mammals and two classes have been identified as acetylcholinesterase (AChE, EC 3.1.1.7) and butyrylcholinesterase (non-specific, pseudocholinesterase, BChE; EC 3.1.1.8) in serum. AChE exists in the central nervous system, platelets and the erythrocyte membrane while BChE is more abundant in the serum and it is synthesized by the liver and secreted into the circulation [4]. BChE is also found in adipose tissue, the small intestine, and smooth muscle cells [5]. It is now well known that BChE acts on hydrophilic and hydrophobic choline esters [6], and hydrolyzes a variety of enobiotics [7]. BChE has attracted attention as a bioscavenger of drugs as well as of organophosphate and carbamate insecticides [8]. Previous studies have reported a significant association between the serum

BChE activity and obesity, coronary artery disease, serum levels of triglycerides (TG), very low-density lipoprotein, low-density lipoprotein, apolipoprotein B, hepatic fat content and type 2 diabetes mellitus [9–11]. All of these findings prompted us to hypothesize that AO has a significant association with the elevated serum BChE activity, dyslipidemia and insulin resistance. Therefore, we investigated the association between AO with serum BChE activity, dyslipidemia (TG and HDL-C), hypertension and insulin resistance.

## Materials and Methods

### Study Population

#### *Subjects*

This cross-sectional study was performed as part of a health survey for protection of hypertension and type 2 diabetes mellitus with residents of three districts in Phitsanulok and Kamphaengphet province (between February 2011–January 2012). Five hundred of the AO participants (age 49.1 ± 10.5 years) and 142 non-abdominal obesity (nAO) (age 49.9 ± 11.9 years) participated in the present study. Among these subjects, twenty seven women had reached menopause. The duration of menopause was from 2 months to 25 years. All women age over 40 were subjected to a medical examination. We excluded the 54 subjects with known end stage renal failure, history of coronary or cerebrovascular atherosclerotic disease, cancer, infection and any life threatening diseases from the study. Two hundred and two women used antihypertensive medication and 18 women were diagnosed during the study. One hundred women used antihyperglycemic medication, and they were kept in the study. All participants were apparently healthy with no clinical signs of associated pathologies and gave written informed consent and they all agreed to participate and to provide a blood sample for their health check. The Ethics Committee of Naresuan University approved the study protocol.

### Anthropometric and Blood Pressure Measurement

Height, weight, and blood pressure (BP) were measured and body mass index (BMI) was calculated. Waist circumference (WC) was measured at the midpoint between the both of rib cage and the top of lateral border of iliac crest during minimal respiration. Central obesity defined as waist circumference ≥80 cm or 31.5 in. (female) [12]. BP was measured after the participants were seated and rested for 5 min as the mean value of at least two measurements of these participants on the same day with a Terumo digital blood pressure monitor (ES-P110). Hypertension was defined as an average BP ≥140/90 mmHg or if the participant was taking antihypertensive medications or had been diagnosed with HT [13, 14].

### Blood Sample Collection and Biochemical Determination

Venous blood samples were collected without stasis after a 12 h fast and a 30 min rest in a supine position. Blood specimens were processed and assayed on the central laboratory of Faculty of Allied Health Sciences on the same day. Fasting plasma glucose (Glu), BUN, serum creatinine (CT), total cholesterol (TC), triglycerides (TG), high density lipoprotein cholesterol (HDL-C) and low density lipoprotein cholesterol (LDL-C) was calculated by Friedewald's equation, which is valid for TG values ≤400 mg/dl, and BChE was determined by measurement of the absorbance increase color DNTB method using Randox kit on the Hitachi 912 autoanalyzer (Roche Diagnostic, Switzerland).

### Insulin Assay

Fasting insulin levels were measured based on micro-particle enzyme immunoassay (MEIA) technology using Abbott reagents with Axsym system (Abbott laboratories, Illinois, USA). All participants underwent evaluation of Homeostasis model assessment (HOMA)-formula for insulin resistance index (HOMA-IR), HOMA %B (as beta cell function; insulin activity), and Quantitative Insulin Sensitivity Check Index (QUICKI; as insulin sensitivity) [15–17]. HOMA-IR was defined using the following formula: fasting glucose (mmol/l) × fasting insulin (μU/ml)/22.5. HOMA %B as formula: [20* insulin (μU/ml))/(glucose (mmol/l)−3.5]. QUICKI as formula: 1/[LOG (insulin (μU/ml)] + LOG [glucose (mmol/l)].

### Statistical Analysis

Categorical data are presented as continuous and percentages. Mean and standard deviation (SD) used for normally distributed data while median and interquartile range used for non-normally distributed data, as determined by using Shapiro–Wilk test. Comparisons between groups were performed by using a student's *t* test for normally distributed data and Mann–Whitney test for non-normally distributed data. The correlation between all variables was analyzed by Spearman's correlation. Odds ratios (OR) from logistic regression analyses were used to estimate the elevated BChE, risk of insulin resistance, reduced HDL-C, hypertension and age that was associated with abdominal obesity. The results of all analyses were evaluated for

statistical significance using $p$ value <0.05 and the 95 % confidence intervals (CI). All analysis was performed using the SPSS computer program version 13.0 (SPSS, Chicago, IL).

## Results

A total of 500 AO women (age 49.1 ± 10.5 years) and 142 nAO women (age 49.9 ± 11.9 years) participated as control in this study. The characteristics of the study population are shown in Table 1. AO women were significantly higher in BP, BMI, WC, Glu, CT, TG, LDL-C, BChE, insulin and HOMA-IR, and lower in HDL-C concentration ($p < 0.05$). Bivariate correlation between variables in abdominal obesity subjects are as: WC showed the positive correlation with SystBP ($r = 0.259$, $p < 0.001$), DiastBP ($r = 0.216$, $p < 0.001$), Glu ($r = 0.134$, $p = 0.003$), TG ($r = 0.177$, $p < 0.001$), BChE ($r = 0.188$, $p < 0.001$), insulin ($r = 0.390$, $p < 0.001$), HOMA-IR ($r = 0.392$, $p < 0.001$) and negative correlation with HDL-C ($r = -0.102$, $p = 0.023$), while the bivariate correlation of the other variables were shown in Table 2. We also tested the association of AO with elevated BChE, insulin resistance, reduced HDL-C, hypertension and age after adjusting with these covariates by using multiple logistic regression analysis as shown in Table 3. The risk of elevated BChE OR 2.73 (95 % CI 1.78–4.20) insulin resistance OR 3.83 (95 % CI 2.51–5.88), reduced HDL-C OR 2.19 (95 % CI 1.21–3.96), hypertension OR 1.83 (95 % CI 1.13–2.96) and age OR 0.99 (95 % CI 0.97–1.01) after adjusting with these covariates.

## Discussion

Our study, AO subjects showed higher levels of BP, BMI, WC, Glu, TG, LDL-C, BChE and lower level of HDL-C, concomitant with higher in insulin level, HOMA-IR and HOMA %B and QUICKI. AO is the one major risk factor for metabolic syndrome (MetS), a cluster of cardiovascular risk factors characterized by visceral obesity, dyslipidemia (low levels of HDL-C and elevated TG levels), hypertension, and glucose intolerance (insulin resistance). These metabolic abnormalities found in MetS heighten the risk for coronary artery disease (CAD) as well as T2DM. The

**Table 1** Comparison of general characteristics of the abdominal obesity with non-abdominal obesity

| Parameter | Abdominal obese ($n = 500$) | Non-abdominal obese ($n = 142$) | $p$ value |
|---|---|---|---|
| Age, (yr) | 49.1 ± 10.5[a] | 49.9 ± 11.9[a] | 0.508 |
| Systolic BP (mmHg) | 127.0 (116.0–139.3) | 118.5 (106.0–133.0) | <0.001 |
| Diatolic BP (mmHg) | 79.0 (72.0–85.3) | 74.0 66.0–82.0) | <0.001 |
| BMI (kg/m$^2$) | 27.2 (24.9–29.6) | 22.1 (20.2–23.8) | <0.001 |
| WC (cm) | 91.0 (84.0–95.0) | 76.0 (71.8–78.0) | <0.001 |
| Glu (mmol/L) | 5.28 (4.91–5.78) | 5.17 (4.73–5.61) | 0.025 |
| BUN (mmol/L) | 4.28 (3.57–5.36) | 4.46 (3.57–5.36) | 0.235 |
| CT (μmol/L) | 79.56 (70.72–88.4) | 70.72 (61.88–79.56) | 0.003 |
| TC (mmol/L) | 5.52 (4.82–6.32) | 5.22 (4.72–6.04) | 0.074 |
| TG (mmol/L) | 1.77 (1.21–2.53) | 1.28 (0.93–2.11) | <0.001 |
| HDL-C (mmol/L) | 1.46 (1.26–1.72) | 1.58 (1.36–1.84) | 0.001 |
| LDL-C (mmol/L) | 3.74 (2.81–4.83) | 3.50 (2.60–4.39) | 0.013 |
| BChE (U/L) | 9529.5 (9084.5–9910.3) | 9071.5 (8494.8–9430.3) | <0.001 |
| Insulin (pmol/L) | 7.7 (5.1–11.9) | 4.6 (3.3–7.2) | <0.001 |
| HOMA-IR | 1.8 (1.1–2.8) | 0.9 (0.6–1.2) | <0.001 |
| HOMA %B | 85.9 (56.4–133.5) | 61.3 (34.0–90.2) | <0.001 |
| QUICKI | 0.348 (0.325–0.373) | 0.377 (0.357–0.404) | <0.001 |
| Hypertension | 179 (35.8 %) | 31 (21.8 %) | <0.001 |
| Type 2 diabetes mellitus | 89 (17.8 %) | 11 (7.8 %) | <0.001 |

*BP* blood pressure, *BMI* body mass index, *WC* waist circumference, *Glu* plasma glucose, *BUN* blood urea nitrogen, *CT* creatinine, *TC* total cholesterol, *TG* triglyceride, *HDL-C* high density lipoprotein cholesterol, *LDL-C* low density lipoprotein cholesterol, *BChE* butyrylcholinesterase, *HOMA-IR* homeostasis model assessment for insulin resistance index, *HOMA %B* homeostasis model assessment for beta cell function, *QUICKI* quantitative insulin sensitivity check index

[a] All data are median (interquartile range), except age is mean ± SD and $n$ (%) of variables. $p$ values are given for comparisons between groups tested with non-parametric, $t$ test and Chi square tests

**Table 2** Bivariate correlation between parameters in abdominal obesity subjects using Spearman rank correlation

| Correlation between parameters | | Correlation coefficient | | Correlation between parameters | | Correlation coefficient | |
|---|---|---|---|---|---|---|---|
| | | *r* | *p* value | | | *r* | *p* value |
| Age | SystBP | 0.274 | <0.001 | Glu | TG | 0.188 | <0.001 |
| | Glu | 0.252 | <0.001 | | HDL-C | −0.115 | 0.010 |
| | TG | 0.176 | 0.018 | | Insulin | 0.116 | 0.009 |
| | LDL-C | 0.111 | 0.013 | | HOMA-IR | 0.335 | <0.001 |
| WC | SystBP | 0.259 | <0.001 | TC | BChE | 0.168 | <0.001 |
| | DiastBP | 0.216 | <0.001 | | HDL-C | 0.264 | <0.001 |
| | Glu | 0.134 | 0.003 | | | | |
| | TC | 0.111 | 0.013 | TG | BChE | 0.153 | 0.001 |
| | TG | 0.177 | <0.001 | | HDL-C | −0.521 | <0.001 |
| | HDL-C | −0.102 | 0.023 | | Insulin | 0.110 | 0.014 |
| | LDL-C | 0.134 | 0.003 | | HOMA-IR | 0.145 | 0.001 |
| | BChE | 0.188 | <0.001 | HDL-C | Insulin | −0.153 | 0.001 |
| | Insulin | 0.390 | <0.001 | | HOMA-IR | −0.165 | <0.001 |
| | HOMA-IR | 0.392 | <0.001 | LDL-C | BChE | 0.394 | <0.001 |
| BChE | Insulin | 0.274 | <0.001 | | Insulin | 0.169 | <0.001 |
| | HOMA-IR | 0.252 | <0.001 | | HOMA-IR | 0.176 | <0.001 |

*SystBP* systolic blood pressure, *DastBP* diastolic blood pressure, *WC* waist circumference, *Glu* plasma glucose, *BUN* blood urea nitrogen, *CT* creatinine, *TC* total cholesterol, *TG* triglyceride, *HDL-C* high density lipoprotein cholesterol, *LDL-C* low density lipoprotein cholesterol, *BChE* butyrylcholinesterase, *HOMA-IR* Homeostasis model assessment for insulin resistance index

**Table 3** Impact of the association of abdominal obesity with elevated BChE, insulin resistance, reduced HDL-C, hypertension and age after adjusting for their covariates in these study population

| Variables | Abdominal obesity | | |
|---|---|---|---|
| | OR | 95 % CI | *p* value |
| Elevated BChE | 2.61 | 1.71–3.98 | <0.001 |
| Insulin resistance | 3.86 | 2.53–5.87 | <0.001 |
| Reduced HDL | 2.38 | 1.33–4.27 | 0.004 |
| Hypertension | 1.85 | 1.15–2.97 | 0.012 |
| Age | 0.99 | 0.97–1.01 | 0.172 |

Model after adjusted for insulin resistance, reduced HDL, hypertension, age

*BChE* butyrylcholinesterase, *HDL-C* high density lipoprotein cholesterol

cardiovascular dysfunction occurred in both at arterial and at cardiac myocyte levels as an independent risk factor of obesity. However, all animal and clinical studies examining vascular function in obesity have shown some degree of vascular abnormalities that occur at both endothelial and smooth muscle levels [18–20]. The correlation of lipid abnormalities with obesity, diabetes as well as with the MetS may also implicate involvement of BChE. Higher levels of BChE activity are found in the serum of patients with obesity, diabetes and hyperlipidemias, especially marked increases in VLDL-C [21–23] as compared with healthy individuals. Furthermore, induction of obesity or diabetes in animal models is associated with increase in serum TG, BChE activity and rHDL-C levels. Elevated TG, Glu, and WC, these three risk factors for the MetS may independently predict serum BChE activity [24, 25]. Serum BChE was significantly correlated with WC, TC, TG, LDL-C, insulin and HOMA-IR but these correlation were not so strong ($r = 0.188$, $p < 0.001$; $r = 0.168$, $p < 0.001$; $r = 0.153$, $p < 0.001$; $r = 0.394$, $p < 0.001$; $r = 0.274$, $p < 0.001$ and $r = 0.252$, $p < 0.001$) in our study. These may use serum BChE as a marker of the pathological processes mediating the MetS. Randell et al. have previously shown that high insulin may stimulate the production of BChE in the CaCo-2 intestinal cell line [26]. The results of this study also show an association between serum BChE activity with fasting insulin levels and HOMA-IR in AO human subjects. Multiple logistic regression analysis showed the association of AO with increased BChE activity, insulin resistance, reduced HDL-C and hypertension in our present study. These results suggest hyperinsulinism and/or the pathological effects of insulin resistance may promote BChE secretion into circulation.

It is plausible to hypothesis that increased vascular disease especially at the level of the brain may in turn affect memory function. Obesity results in insulin resistance [19, 27, 28]. Insulin has a significant role on modulation of synaptic plasticity and learning memory [29]. Insulin receptors and insulin-sensitive glucose transporters are densely expressed in the medial temporal region of the brain that supports memory formation [30], indicating that insulin may have a role in maintaining normal cognitive function. Hence, abnormalities in the insulin signaling pathway may contribute to impairment of memory

function, similar to those seen in patients with Alzheimer's disease. Insulin dysregulation could act by decreased cortical glucose utilization, oxidative stress, formation of advanced glycated proteins, increased neurofibrillary formation and increased β-amyloid aggregation through inhibition of insulin-degrading enzyme [31]. Insulin resistance could therefore be a link between Alzheimer's disease and T2DM [32]. Elevated BChE could lead to decreased acetylcholine levels and anti-inflammatory molecule, thereby resulting in a low-grade systemic inflammation. That may account for the decline in cognitive function [33]. Furthermore, individuals carrying the apolipoprotein E (APOE) epsilon four allele, and particularly those with both APOE and BChE K-variant alleles, have the fastest cognitive decline among subjects with amnestic mild cognitive impairment, mild AD and the slowest decline in more advanced stages of the illness [34–36]. Then, insulin resistance concomitant with elevated BChE activity may play the synergic effect of cardiovascular diseases and the impairment of memory function in the future. The limitation of the study is in the part that we didn't perform any assessment of memory function.

## Conclusion

We propose that AO associated with elevated BChE, insulin resistance, HT and reduced HDL-C. These may predict the development of type 2 diabetes mellitus and may be associated with cognitive disorder in the future, both are mediated through insulin resistance.

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**Conflict of interest** None.

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