World Nutrition Journal |eISSN 2580-7013

ORIGINAL ARTICLE

Nutritional Status Influences High-Molecular Weight (HMW) Adiponectin Levels in Breast Cancer Patients: Comparison with Healthy Controls

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Received, 1 November 2018
Accepted, 5 December 2018

Link to DOI:
10.25220/WNJ.V02.i2.0004

Journal Website:
www.worldnutrijournal.org

Abstract

Introduction Breast cancer is the leading killer of women in Malaysia. Nutritional status and adiponectin are modifiable risk factors for breast cancer occurrence which can be efficiently targeted. The purpose of this study was to determine the relationship between nutritional status and high molecular weight (HMW) adiponectin levels among breast cancer patients as compared to controls.

Methods This was a case- control study, conducted in Hospital Universiti Sains Malaysia and Universiti Sains Malaysia campus. Newly diagnosed breast cancer cases (n=55) were assigned as cases while healthy controls (n=58) were staff members of HUSM and USM campus. Sociodemographic and reproductive data were obtained with a standard questionnaire while the dietary data was obtained from a validated diet history questionnaire. Anthropometric assessments [weight, height, hip, waist circumference (WC) and body fat composition] were measured while overnight fasting venous blood samples were analysed for lipid profiles, glucose, insulin, high sensitivity C-reactive protein and HMW adiponectin.

Results A significant linear negative relationship exists between WC and HMW adiponectin (β=-0.05; p=0.005) among breast cancer cases. Additionally, HDL cholesterol was positively associated with HMW adiponectin (β=1.83; p=0.010) among the cases. BMI was negatively associated with HMW adiponectin (β=-0.02; p=0.001) among healthy controls.

Conclusion Our findings suggest that WC, BMI and HDL cholesterol had significant relationship with HMW adiponectin. Low levels of HMW adiponectin, low WC and high HDL levels may be protective against breast cancer.

Keywords nutritional status, high-molecular weight adiponectin, waist circumference, body mass index, high density lipoprotein cholesterol, breast cancer

Introduction

Breast cancer is the most common cancer among Malaysian women, where its rates in Malaysia are higher than that reported in Southeast Asian countries. [1] One of the risk factos for breast cancer is obesity[2] where the prevalence of overweight, obesity and abdominal obesity among Malaysian women have been reported to be 28.3%, 20.6% and

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60.2%, respectively. In addition, the National Health and Morbidity Survey (NHMS) 2015 reported that there was an increasing trend in the adiposity prevalence among Malaysian women in 2015 compared with 2011.[3]

Nutritional status is an essential predictor of clinical outcome such as malnutrition. Impaired nutritional status have been linked with inadequate food intake, unsustained hunger and metabolic inefficiency.[4] Several studies modulated nutritional status as the assessment of anthropometry and body composition such as body mass index and body fat distribution.[5] In contrast, nutritional status also has been defined in the scope of dietary intake by considering food intakes and utilisation of nutrients were affecting the consumer‘s health condition.[6]

Two main modifiable risk factors in prevention of cancer are body weight and dietary intake.[7] However, the American Cancer Society provided new nutritional guidelines for prevention of cancer by grouping the recommendations into various categories of weight management, physical activity and dietary intake.[8] This recommendation is useful as nutritional education in promoting good health and optimum nutritional status among public. Moreover, in an effort to increase patient’s quality of life, nutritional status is an important concern. For example, the Subjective Global Assessment (SGA) form has been utilized to screen patients with malnutrition in HUSM. This nutritional assessment tool may guide the incorporation of nutritional intervention in overcoming disease complications.[9]

Previously, adipose tissue was thought to function only for storing fat for energy. However, recently it was recognized that adipose tissue is an endocrine organ that releases large amounts of biochemical modulators, including adipokines.[10] Among these adipokines, adiponectin which abundantly circulates in the plasma at high concentrations (0.5 to 30.0 μg/ml) and accounts for up to 0.01% of total plasma proteins[11] are thought to play a major role in breast cancer development. Adiponectin exists in the plasma as trimer, hexamer or high molecular weight (HMW) adiponectin isoforms. Among these, the HMW isoform is the most biologically active form and is strongly associated with insulin resistance, metabolic syndrome, and cardiovascular disease.[12]
Adiponectin is considered to be a protective hormone because it plays a major role in the regulation of glucose due to its potent insulin-sensitizing activity which affect the uptake of glucose in the muscle. Furthermore, it is involved in lipid homeostasis, and in the pathophysiology of atherosclerosis due to its anti-inflammatory activity.[13] Numerous studies have shown that adiponectin has an inhibitory effect on the proliferation of various cell types, including aortic smooth muscle, endothelial tissue and several types of cancer cells.[14] It has been hypothesized that adiponectin act directly on breast cancer cells by inhibiting proliferation and angiogenesis or by stimulating apoptosis.[15] Serum adiponectin is therefore a potential therapeutic target for breast cancer treatment or protection.[16]

Although adiposity is a well-established health problem related to breast cancer, the data on the association between HMW adiponectin and adiposity obtained from various epidemiological studies has remained elusive in Asian countries, particularly Malaysia. Therefore, the aim of this study was to investigate the relationship between nutritional status and HMW adiponectin levels among breast cancer patients as compared to healthy controls. It is hoped that the data will provide essential information for health professionals planning public health programs for breast cancer prevention in Malaysia with respect to weight and reproductive health management.

Methods

Setting and subjects

This is a case-control study conducted in Kelantan, Malaysia, approved by the Human Research and Ethical Committee of USM. The cases include newly diagnosed women with histologically confirmed malignant breast cancer (stages I to IV) who had not yet undergone any therapies (except for analgesics and/or surgery) while the controls comprised of healthy volunteers with no known history of breast cancer, any other medical illness or medication use. The inclusion criteria for both cases and controls were women aged 20 to 59 years old who were neither pregnant nor lactating during the study periods. Both cases and controls were recruited using a convenience sampling method while the controls were selected to match the cases for age ± 10 years.

Measurements

Written informed consents were obtained and the respondents underwent face-to-face interviews using a set of questionnaires including validated diet history questionnaire (DHQ).[17] The respondents were measured for height using a portable stadiometer, weight and fat composition using a body composition analyzer (TANITA SC-330, Japan), waist circumference (WC) and hip circumference using a non-extendible tape. BMI was calculated by dividing the weight (kg) by the square of the height (m). Fasting blood samples were collected for biochemical test. Serum HMW adiponectin concentrations were measured using a sandwich ELISA kit.

Statistical analyses were performed using SPSS for Windows, version 22.0. Categorical data were presented as frequency (percentage), while chi-squared or Fisher's exact tests were used to determine the association between any categorical variables. Independent samples t-test was used to compare means and multiple linear regression analyses were used to investigate the associations between HMW adiponectin levels and nutritional status. A p value of less than 0.05 was considered as statistically significant.

Results

A total of 55 newly diagnosed breast cancer cases and 58 healthy controls were recruited (Table 1). The mean (SD) age for cases and controls were 46.84 (7.87) years and 40.79 (9.78) years respectively. Education level of the cases mostly from primary or secondary school when compared to controls most of whom graduated from the university. The majority of the respondents were premenopausal women, practiced family planning, breastfed their babies, with no first degree family history of breast cancer. A higher percentage of cases (58.2%) were exposed to second-hand smoke as compared to controls (29.3%).

Multiple linear regression analysis revealed that there was a significant linear negative relationship between WC and HMW adiponectin (p =0.005) where a 10 cm increase in WC lowers HMW adiponectin levels by 0.5 µg/ml (95% CI: -0.8, -0.2 µg/ml) (Table 2). In addition, HDL cholesterol was positively associated with HMW adiponectin (p= 0.006). Furthermore, a 1 mmol/L increase in HDL cholesterol increases HMW adiponectin levels by 1.83 µg/ml (95% CI: 0.47, 3.02 µg/ml).

Table 3 shows the associations of nutritional status with HMW adiponectin among healthy controls. Multiple linear regression analysis revealed that there was a significant (p =0.001) linear negative relationship between BMI and HMW adiponectin where a 1 kg/m2 increase in BMI lowers HMW adiponectin levels by 0.20 µg/ml (95% CI: -0.32, -0.08 µg/ml).

Discussion

Mean age at breast cancer diagnosis showed that mean age breast cancer cases were significantly older than healthy controls. This result is in a good agreement with the previous results reported by Fuhrman et al., who also had frequency matching case control by birth year in 5- year strata in United States.[18] Age matched in this study was quite wide (±10 years) because of the difficulty faced in matching the older cases with older controls free from diseases as older women are synonym with the disease. However, one study from Vietnam found no significant difference in age between case and control groups matched on a single year of age.[19]

According to a study conducted in Malaysia on breast cancer awareness, they concluded that education level emerged to contribute to health behavior and knowledge level, based on an outcome of women had higher education level were significantly more aware of breast cancer.[20] In this present study, breast cancer cases mostly from primary and secondary school compared to healthy controls most of whom graduated from university. Poor education had accounted for late stage at presentation of breast cancer.[21] A qualitative study was conducted by exploring the decision-making experiences of breast cancer women and discovered four phases in the decision-making process (discovery, confirmatory, deliberation and decision). Their knowledge, understanding and experiences affect the final decision for treatment.[22]

Majority of the breast cancer cases were premenopausal women and this may be explained

Table 1 Baseline characteristics of the respondents[a]

Variables	Cases (n=55)	Controls (n=58)	p value[c]
Age (years)[b]	46.84 (7.87)	40.79 (9.78)	0.001
Education level			
Primary/secondary school	35 (63.6)	21 (36.2)	0.004
University	20 (36.4)	37 (63.8)	
Exposure to second-hand smoke			
Yes	32 (58.2)	17 (29.3)	0.002
No	23 (41.8)	41 (70.7)	
Monthly household income (RM)[d,e]			
<RM 2,300	31 (57.4)	4 (7.3)	<0.001
RM 2,300-5,599	13 (24.1)	34 (61.8)	0.403
>RM 5,600	10 (18.5)	17 (30.9)	
Family planning			
Yes	28 (50.9)	37 (63.8)	0.167
No	27 (49.1)	21 (36.2)	
Age during first pregnancy,years[b]	25.75 (5.23)	25.34 (2.66)	0.631
Parity[b]	3.61 (2.03)	3.25 (1.97)	0.335
Breastfeeding			
Yes	50 (90.9)	48 (82.8)	
No	5 (9.1)	10 (17.2)	0.209
Menopausal status			
Premenopause	42 (76.4)	51 (87.9)	
Postmenopause	13 (23.6)	7 (12.1)	0.113
First degree family history with breast cancer			
Yes	6 (10.9)	2 (3.4)	0.142
None	49 (89.1)	56 (96.6)	

Note. SD=Standard deviation; OR= Odds ratio; CI= Confidence interval

[a] Data are presented as frequency (percentage), unless otherwise indicated

[b] Data are presented as mean (SD)

[c] p value based on Independent t- test

[d] Based on the cut-off of the 10th Malaysia Plan

[e] Sample size was not n=113 due to missing values

through breast cancer is typically more aggressive in women under 40 years of age than in older women.[23] This is ordinarily applied to the fact that tumors in premenopausal women bear a higher percentage of biologically negative cellular or histological features which led to a worse prognosis.[24]

In this study, exposure to secondhand smoke was significantly associated with breast cancer. This finding was consistent with recent study on non-smoking breast cancer women with lifetime exposure to passive smoking. Exposure to second-hand smoke had 1.27 (95% CI: 0.97, 1.66) (less than 20 years) and 2.64 (95% CI: 1.87, 3.74) (more than 20 years) times increase risk of breast cancer than unexposed women. Besides that, Caucasian women who experienced second-hand smoke both at work and home had 2.80 (95% CI: 1.84, 4.25) times higher risk of breast cancer compared with women who were never exposed to smoke.[25]

To our knowledge, our study is the first to establish that WC and HDL cholesterol levels are associated with HMW adiponectin among breast cancer cases. In addition, BMI is also associated with HMW adiponectin among healthy controls. Our study successfully determined the association between nutritional status and HMW adiponectin among breast cancer cases and healthy controls.

WC was negatively associated with HMW adiponectin among breast cancer cases which was consistent with another study among obese and non-obese Caucasians indicating that WC is inversely correlated with HMW adiponectin level regardless

Table 2 Associations of nutritional status with HMW adiponectin among breast cancer cases

Variables	Simple linear regression		Multiple linear regression	
	b[a] (95% CI)	p value	Adjusted b[b] (95% CI)	p value
Weight (kg)	-0.05 (-0.08,-0.02)	0.001		
Height (cm)	-0.01 (-0.09,0.07)	0.870		
BMI (kg/m^2)	-0.13 (-0.21,-0.06)	0.001		
WC (cm)	-0.07 (-0.10,-0.03)	<0.001	-0.05 (-0.08,-0.02)	0.005
HC (cm)	-0.06 (-0.10,-0.02)	0.006		
Fat mass (kg)	-0.06 (-0.10,-0.02)	0.007		
Muscle mass (kg)	-0.16 (-0.26,-0.06)	0.003		
Visceral fat rating	-0.24 (-0.37,-0.10)	0.001		
TC (mmol/l)	0.22 (-0.22,0.65)	0.324		
HDL cholesterol (mmol/l)	2.60(1.24,3.97)	<0.001	1.83 (0.47,3.20)	0.010
LDL cholesterol (mmol/l)	0.16 (-0.35,0.66)	0.541		
TG (mmol/l)	-0.30 (-0.67,0.07)	0.108		
Glucose (mmol/l)	0.02 (-0.15,0.19)	0.800		
hs-CRP (mg/ml)	-0.07 (-0.14,0.01)	0.088		
Insulin (μU/ml)	-0.038 (-0.080,-0.004)	0.074		
Energy (kcal/day)	-0.001 (-0.002,0.001)	0.272		
Protein (g/day)	-0.007 (-0.036.0.021)	0.608		
Carbohydrate (g/day)	-0.006 (-0.016,0.003)	0.193		
Fat (g/day)	-0.015 (-0.054,0.024)	0.433		
Saturated fat (g/day)	0.032 (-0.122,0.185)	0.678		
MUFA (g/day)	-0.052 (-0.205,0.102)	0.501		
PUFA (g/day)	-0.107 (-0.251,0.037)	0.140		
Calcium (mg/day)	0.000 (-0.002,0.003)	0.928		
Phosphorus (mg/day)	-0.001 (-0.002,0.001)	0.274		
Iron (mg/day)	-0.070 (-0.155,0.015)	0.105		
Cholesterol (mg/day)	-0.004 (-0.012,0.003)	0.228		
Thiamin (mg/day)	0.020 (-2.251,2.291)	0.986		
Riboflavin (mg/day)	0.225 (-0.992,1.442)	0.711		
Niacin (mg NE/day)	-0.062 (-0.264,0.139)	0.536		
Folate (μg/day)	-0.002 (-0.013,0.009)	0.695		
Vitamin C (mg/day)	0.002 (-0.003,0.007)	0.511		
Vitamin E (mg/day)	-0.047 (-0.237,0.144)	0.624		
Selenium (μg/day)	-0.010 (-0.042,0.021)	0.517		
Fiber (g/day)	-0.087 (-0.369,0.194)	0.534		
Sugar (g/day)	0.003 (-0.025,0.030)	0.857		

Note. BMI=body mass index, WC= Waist circumference; HC=hip circumference; TC=total Cholesterol; HDL=high density lipoprotein cholesterol; LDL=low density lipoprotein cholesterol; TG=triglyceride; hs-CRP=high sensitivity C reactive protein; MUFA=monounsaturated fatty acid; PUFA=polyunsaturated fatty acid

[a]Crude regression coefficient

[b]Adjusted regression coefficient

Stepwise multiple linear regression method applied. Model assumptions were fulfilled.

Interactions amongst independent variables and multicollinearity were not applicable.

Coefficient of determination (R^2) = 0.377

with BMI levels[26] indicating that obese individuals commonly have lower adiponectin levels based on their abdominal adiposity. On the contrary, higher levels of adiponectin were resorted in some obese individuals with higher subcutaneous adipose tissue-to-visceral adipose tissue ratios where the ratios were significantly associated with adiponectin.[27]

Table 3 Associations of nutritional status with HMW adiponectin among healthy controls

Variables	Simple linear regression		Multiple linear regression	
	b[a] (95% CI)	p value	Adjusted b[b] (95% CI)	p value
Weight,kg	-0.08 (-0.13,-0.03)	0.001		
Height,cm	-0.09 (-0.01,-0.19)	0.083		
BMI,kg/m^2	-0.20 (-0.32,-0.08)	0.001	-0.20 (-0.32,-0.08)	0.001
WC,cm	-0.08 (-0.13,-0.03)	0.001		
HC,cm	-0.07 (-0.13,-0,01)	0.018		
Fat mass,kg	-0.11 (-0.19,-0.04)	0.002		
Muscle mass,kg	-0.08 (-0.26,0.10)	0.405		
Visceral fat rating	-0.15 (-0.29,-0.01)	0.035		
TC (mmol/l)	-0.22 (-0.78,0.33)	0.420		
HDL cholesterol (mmol/l)	2.18 (0.26,4.09)	0.027		
LDL cholesterol (mmol/l)	-0.30 (-0.92,0.32)	0.339		
TG (mmol/l)	-1.05 (-2.03,-0.08)	0.035		
Glucose (mmol/l)	-0.10 (-0.44,0.25)	0.565		
hs-CRP[a] (mg/ml)	-0.04 (-0.08,0.01)	0.110		
Insulin[a] (μU/ml)	-0.02 (-0.07,0.03)	0.459		
Energy (kcal/day)	-0.001 (-0.003,0.002)	0.545		
Protein (g/day)	-0.017 (-0.060,0.027)	0.452		
Carbohydrate (g/day)	-0.007 (-0.020,0.005)	0.255		
Fat (g/day)	-0.011 (-0.061,0.039)	0.665		
Saturated fat (g/day)	0.008 (-0.184,0.199)	0.937		
MUFA (g/day)	-0.032 (-0.163,0.100)	0.632		
PUFA (g/day)	-0.051 (-0.208,0.106)	0.518		
Calcium (mg/day)	0.001 (-0.003,0.005)	0.606		
Phosphorus (mg/day)	-0.001 (-0.003,0.001)	0.446		
Iron (mg/day)	-0.003 (-0.105,0.098)	0.946		
Cholesterol (mg/day)	-0.001 (-0.012,0.010)	0.858		
Thiamin (mg/day)	0.986 (-1.680,3.651)	0.462		
Riboflavin (mg/day)	2.114 (0.144,4.083)	0.036		
Niacin (mg NE/day)	0.009 (-0.150,0.168)	0.913		
Folate (μg/day)	0.001 (-0.013,0.015)	0.887		
Vitamin A (μg/day)	0.001 (-0.001,0.003)	0.441		
Vitamin C (mg/day)	0.006 (-0.006,0.018)	0.341		
Vitamin E (mg/day)	-0.007 (-0.362,0.347)	0.968		
Selenium (μg/day)	-0.018 (-0.066,0.031)	0.466		
Dietary fiber (g/day)	0.013 (-0.386,0.411)	0.949		
Sugar (g/day)	0.033 (-0.005,0.070)	0.084		

Note. BMI=body mass index, WC= Waist circumference; HC=hip circumference; TC=total Cholesterol; HDL=high density lipoprotein cholesterol; LDL=low density lipoprotein cholesterol; TG=triglyceride; hs-CRP=high sensitivity C reactive protein; MUFA=monounsaturated fatty acid; PUFA=polyunsaturated fatty acid

[a]Crude regression coefficient

[b]Adjusted regression coefficient

Stepwise multiple linear regression method applied. Model assumptions were fulfilled.

Interactions amongst independent variables and multicollinearity were not applicable.

Coefficient of determination (R^2) = 0.168

Obesity is recognized as risk factor for breast cancer among both post- and pre-menopausal women.[28] Excess adipose tissue significantly increases the risk of breast cancer by 30-50%.[29] Understanding the role of obesity in carcinogenesis is of major importance, especially for obese women with breast

cancer. Recently, it has been proposed that the association between cancer development and adiposity is related to (1) sex hormone metabolism, (2) insulin and insulin-like growth factor (IGF) signaling and (3) the physiology and pathological processes of adipokines.[30]

Our study also indicated that BMI was negatively associated with HMW adiponectin level among healthy controls. Similarly, Nakanishi and colleagues (2016) also who concluded that BMI was significantly lower in increased adiponectin among healthy men.[31] In contrast, a cohort study among healthy males and females showed no significant association in women between BMI and adiponectin but interestingly, positive association of BMI with adiponectin in males possibly is due to significantly higher levels of adiponectin levels in men as compared to that in women.[32] Decreased plasma testosterone in obese male[33] may also explain the higher levels of adiponectin in man since testosterone has been reported to selectively decrease circulating levels of HMW adiponectin by inhibiting its secretion from the adipocytes.[34]

A similar outcome was also be reported in a disease-related group where negative correlation between BMI and adiponectin has been established among breast cancer patients.[35] Moreover, patients with chronic obstructive pulmonary disease had remarkably higher adiponectin levels which are inversely correlated with BMI.[36] The elevation in adiponectin level may be associated with body weight loss among these patients.[37] In fact, adiponectin levels was inversely correlated with BMI and was downregulated with obesity.[38] This is supported by a dietary and exercise intervention study which indicated that weight loss was inversely associated with adiponectin concentrations.[39] However, BMI and adiponectin were positively correlated in patients with multiple sclerosis though the correlation was not significant.[40]

This study demonstrated that HDL cholesterol was significantly associated with HMW adiponectin. The current result support the previous study showing significant positive correlation between adiponectin levels and HDL cholesterol.[41] HDL cholesterol had been proposed to have cardio-protective effect[42] and it is possible that the form of HMW adiponectin may carry a lipid-soluble factor.[43] According to Rothenbacher (2005), high serum concentration may acted as protective effect when mediated by the effects of lipoprotein metabolism remarkably HDL cholesterol. This was concluded based on a study among patients with coronary heart disease presented strong correlation between adiponectin and HDL cholesterol.[44] However, no significant direct effect of HDL cholesterol on adiponectin among type 2 diabetes cases except this relationship was intervened with pre-heparin lipoprotein lipase, a major enzyme in lipoprotein metabolism.[45]

Recent epidemiological study have shown a strong relationship between breast cancer and lipid disorders, including HDL cholesterol.[46] Declined HDL cholesterol contributed to elevated breast cancer risk.[47] A case-control study conducted to determine the correlation of adiponectin with risk factors of breast cancer among premenopause and post menopause women found that HDL cholesterol levels were significantly lower in controls than cases as well as positive correlation between adiponectin and HDL cholesterol.[48]

In conclusion, this study suggests that there is an association between nutritional status and HMW adiponectin. WC, BMI and HDL cholesterol had significant relationship with HMW adiponectin. Breast cancer in Malaysia could be prevented through nutritional education via public health programs.

Conflict of Interest

The authors of this paper declare there is no conflict of interest regarding this research.

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Acknowledgement

This study was financially funded by Universiti Sains Malaysia RUT grant (1001/PPSP/853005).

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