The Relation of Serum Adipocytokines Levels and Haematological Malignancy

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Abstract: Obesity is a global health problem. Adipocytes produce adipocytokines, which participate in carcinogenesis of many solid tumours. However, reports on the effects in haematological malignancies are limited. We studied this feature in haematological malignancies. The body mass index (BMI), waist:hip ratio and serum adipocytokines levels (leptin and adiponectin) were measured in subjects (n=29) and healthy control (n=18). There was no significant difference in the mean BMI of control and subjects. However, the mean waist:hip ratio in subjects were significantly higher (0.91) compared to control (0.82); p=0.04. The mean level of leptin was raised in subjects compared to control (1.80 vs 17.41); p=0.00. The mean adiponectin level was suppressed in subjects (6.54 vs 0.15); p=0.00. The leptin:adiponectin ratio was also suppressed (0.01 vs 3.93); p=0.000. Subjects with good and poor initial clinical outcome did not show any significant difference in the adiposity index and the serum adipocytokines levels. This study supports the evidence that adiposity and adipocytokines are related to haematological malignancy similar to that reported in solid tumours. Leptin:adiponectin ratio may have the potential as a biomarker of obesity related malignancy. We also concluded that waist:hip ratio is a better index of adiposity compared to BMI. However, there is no significant relation of these parameters with the prognosis.

Keywords: Adiponectin, adiposity, biomarker, leptin, obesity.

1. INTRODUCTION

It is known that the world is facing a global pandemic of obesity and metabolic syndromes. Its prevalence has increased significantly in the last few decades, reaching epidemic proportions [1-3]. Obesity is often defined with body mass index (BMI) as a measure that can be compared across studies and populations. It is known as major risk factors for non-communicable diseases such as cardiovascular diseases, diabetes, osteoarthritis, fatty liver, gallstones, psychological disorders, and psychosocial problems [4]. Increased mortality has also been related to obesity [5]. Consequently, the obesity–cancer relationship has recently received much attention. Studies have shown that obesity is associated with increased risk of several solid tumors including colon, endometrium, breast (postmenopausal), kidney, esophagus, pancreas, gallbladder, liver, and hematological malignancy [1,6-7]. A systematic review of the evidence by the World Cancer Research Fund (WCRF) and American Institute for Cancer Research (AICR) concluded that obesity is an established risk factor for these cancers [1]. In addition, obesity can lead to worsened treatment outcome, poorer prognosis, and increased cancer-related mortality [8-9]. A number of studies have been conducted to correlate obesity, adipocytokines and haematological malignancies. However, the findings were not consistent and needed further studies to confirm their findings. These interesting findings prompt us to conduct a study on this subject especially because the local population shows an increasing trend towards overweight and obesity. Statistics by the National Cancer Registry of Malaysia (NCR) also shows increasing trends in the haematological malignancies incidence [10].

2. MATERIALS AND METHODS

2.1. Patients

This study involves patients in the Department of Hematology, Ampang Hospital, Kuala Lumpur over 1 year duration. Cases included in the study were of acute myeloid leukaemia, acute lymphoblastic leukaemia, malignant lymphoma, multiple myeloma and chronic myeloid leukaemia. The control group is composed of 18 healthy subjects within the same age range. Diagnosis was made according to World Health Organization (WHO) guidelines or the French-American-Britain (FAB) classification. All the cases are treated at the Department of Hematology, Ampang Hospital. Relapsed cases and patient with underlying chronic illness such as diabetes mellitus, cardiovascular diseases and renal diseases were

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excluded from the study. Patient with recent history of infection were also excluded. All study participants provided informed consent after being explained of the research background. Cases were followed up until the initial clinical assessment. This study has been performed in accordance with the principles of Declaration of Helsinki. The Ethics and Research Committee of the Ministry of Health Malaysia (MOH) has approved the study protocol (NMRR-10-81-5193).

2.2. Prognosis/Initial Clinical Outcome Assessment

The initial clinical outcome or prognosis of acute leukaemia cases was assessed from the post-induction bone marrow analysis. Cases of lymphoma and multiple myeloma were assessed from the bone marrow findings after 3 cycles of chemotherapy while CML cases were assessed after 3 to 6 months of therapy. We studied the relation of the adiposity index and the serum adipocytes levels with the initial clinical outcome or prognosis of the cases.

2.3. Measurement of Adiposity and Serum Adipocytokines

Adiposity was measured in subjects and control group using the body mass index (BMI) and waist:hip ratio. A fasting morning blood sample was taken before chemotherapy commencement for measurements of serum adiponectin and leptin. The serum adipocytokines levels were measured using Solid Phase Sandwich ELISA kit. Serum adiponectin was measured by ELISA kit (AdipoGen), with a sensitivity of 0.5 ng/ml, and the intra-assay coefficient of variation was 2.97% - 3.84%. The measurement of serum leptin assay was performed using ELISA kit (Elabscience) with sensitivity of 0.094 ng/ml, and the intra-assay coefficient of variation was <10%. Samples were run in duplicate and the mean value was calculated.

2.4. Statistical Analysis

Data processing were performed using Statistical Package for the Social Sciences (SPSS) program version 15.0. Analysis was done using independent sample t-test and Mann Whitney test to find the association between to categorical data.

3. RESULTS

3.1. Patient Characteristics

Subjects recruited in the studies include cases of Acute Myeloid Leukaemia (n=11), Acute Lymphoblastic Leukaemia (n=4), Malignant Lymphoma (n=11) Multiple Myeloma (n=1) and Chronic Myeloid Leukaemia (n=2). Table **1** shows the baseline characteristics of subjects and control group.

Table 1: Distribution of Subjects and Control Group According to Socio-Demographic Variables

Variable	Control	Subjects
Age		
<25	8	8
26-35	6	3
36-45	2	4
>45	2	14
BMI		
<25	8	20
25-35	8	8
>35	2	0
Waist:hip ratio		
<0.95	16	24
0.96 – 1.0	2	4
>1.0	0	1
Diagnosis		
AML		11
ALL		4
CML		2
Lymphoma		11
Myeloma		1

3.2. Adiposity Index and Serum Adipocytokines Level

The mean BMI and waist:hip ratio for subjects and control were compared using independent sample t-test while the mean serum adipocytokines levels were compared between the subjects and control using Mann Whitney test. Results were as in Table **2**. There was no significant difference in the mean BMI of the control group and subjects (25.18 vs 22.80; CI: 95%; p=0.114). However, the mean waist hip ratio in subjects was significantly higher compared to control (0.91 vs 0.82; CI: 95%; p=0.004). The mean level of leptin was markedly raised in subjects compared to control (17.41 vs 1.80; p=0.000). The mean adiponectin level was significantly suppressed in subjects compared to control (0.15 vs 6.54; p=0.000). The difference in the leptin:adiponectin level between the subjects and control was also highly significant (3.93 vs 0.01; p=0.000) (Table **2**).

3.3. Prognosis/Initial Clinical Outcome

Majority (52%) of the subjects had a good response to therapy and went into remission with initial treatment

Table 2: The Mean Adiposity Index and Adipocytokines Levels (ng/mL) in Control Group and Subjects

Variables	Mean (SD)		p-value
	Control (n=18)	Subjects (n=29)	
BMI	25.18 (5.75)	22.80(4.32)	0.114
Waist:hip ratio	0.82 (0.11)	0.91(0.06)	0.004
Adiponectin	6.54 (3.57)	0.15 (2.83)	0.000
Leptin	1.80 (1.27)	17.41 (15.68)	0.000
Leptin:Adiponectin	3.93 (2.66)	0.01 (0.24)	0.000

Table 3: The Mean Adiposity Index and Adipocytokines Levels (ng/mL) in Subjects with Good and Poor Clinical Outcome

Variables	Mean (SD)		p-value
	Good response (n=15)	Poor response (n=7)	
BMI	22.22 (7.13)	24.09 (11.39)	0.805
Waist:hip ratio	0.91 (0.07)	0.92 (0.08)	0.916
Adiponectin	0.18 (3.63)	0.36 (0.46)	0.751
Leptin	15.92 (13.22)	21.47 (17.65)	0.503
Leptin:adiponectin	0.02 (0.32)	0.02 (0.02)	0.972

(n=15). However 25% of the patients did not respond to therapy or passed away due to other complications such as infection and bleeding (n=7). Seven patients (24%) defaulted the treatment and were not contactable. Cases who defaulted treatment were excluded from the analysis based on clinical outcome. There was no significant difference in the adiposity index and serum adipocytokines levels between the patient with good response (n=15) and patients with poor response (n=7). The leptin:adiponectin ratio was similar between the two groups (Table **3**).

4. DISCUSSION

In this study, the BMI of patients with haematological malignancy were not significantly raised compared to normal control. However the waist:hip ratio in subjects was higher compared to control group. Many researchers have debated the issue on the best method of adiposity assessment. Epidemiological studies often defined obesity with body mass index (BMI) as a measure that can be compared across studies and populations. The cut-offs value for BMI to define obesity in Asian and Caucasian ethnic groups has also been debated [11-12]. WHO experts suggested a BMI of >23 as the cut-off value for Asians [13], but a Chinese working group suggested a BMI of >24 as a better cut-off point [14]. The Japanese on the other hand, have suggested a BMI of >25 as a cut-off [15]. WHO has admitted defeat in the definition of appropriate BMI for Asian population [16]. Following that, other researchers reported that central obesity is strongly associated with health risks of obesity as compared to total obesity, which was measured by BMI [17-19]. Central or abdominal obesity, which is measured around the hip, may give a better index of health risk compared to BMI. Many reports suggested waist circumference, waist:hip ratio or waist:height ratio as a measure of central obesity. Our findings supports the report that waist:hip ratio which is an index of central obesity is significantly related to cases of haematological malignancy compared to BMI.

Epidemiological studies have established the strong association between low circulating adiponectin level and a variety of cancers including endometrial, breast, colon, and renal cancers. However, the mechanisms underlying the relationship between obesity and cancer are complex and not well understood. They include adipocytokines, growth factors, modulation of energy balance and calorie restriction, multiple signaling pathways, and chronic inflammatory processes as possible mechanisms [20-26]. All these factors affect cancer cell growth and progression. It has been established that adipose tissue is an endocrine organ that produces and secretes polypeptide hormones known as adipocytokines. Leptin and adiponectin are

among the most abundant and involved in cancer development [27]. Leptin that is important in energy balance and appetite control is positively correlated with adipose stores and nutritional status. Leptin has been extensively studied as a potential mediator of obesity-related cancer [27-28]. It induces cancer progression by activating PI3K, MAPK, and STAT3 pathways [25-27]. Adiponectin, which is secreted mostly from visceral adipose tissue, in contrast to leptin, is inversely associated with adiposity [29-30]. Adiponectin was reported to exert anticancer effects by decreasing insulin/insulin-like growth factor (IGF)-1 and mTOR signaling via activation of 5′AMP-activated protein kinase (AMPK) and exerting anti-inflamatory actions by inhibition of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) [29]. Body adiposity is also reported to be associated with higher levels of pro-inflammatory cytokines, including prostaglandin-E2, TNFα, IL-2, IL-8, IL-10, and monocyte chemo-attractant protein (MCP)-1. Activation of NF-κB complex is a possible mechanism through which inflammation may stimulate cancer development [25-27].

Reports on the association of adipocytokines with haematological malignancy were scarce and were inconsistent. Damalaga *et al*. found that serum adiponectin level were low in Myelodysplastic Syndrome (MDS) and they hypothesized that it might have a protective role in MDS [31-33]. Researchers also found a low serum adiponectin in patients diagnosed with Multiple myeloma particularly the high-risk group [34]. They also concluded that there is no association between serum leptin level and risk of multiple myeloma. A cohort study among Swedish and Finnish population concluded that overweight and obesity might have an impact on some haematological malignancies particularly multiple myeloma [6]. Another study from Turkey found that serum leptin level was significantly raised in Multiple myeloma and Chronic Lymphocytic Leukaemia (CLL). They suggested that leptin is partly responsible for the pathogenesis and immune changes seen in both diseases [33]. A low adiponectin expression in CLL was reported and suggested the role of leukaemic cells in production of adiponectin [34]. They suggested that adiponection might be a possible drug for treatment of CLL. This study found that the serum adiponectin level is inversely related to the incidence of haematological malignancy while serum leptin level is positively related. The leptin:adiponectin ratio was noted to be significantly low in subjects. This index may be used a biomarker of obesity related malignancy. However, there is no significant difference in the BMI, waist:hip ratio or serum adipocytokines levels between patient with good and poor initial clinical outcome. With regards to the above findings, adiponectin has been suggested as a potential biomarker for haematological malignancies, such as leukemia, lymphoma, myeloma, and B-cell chronic lymphocytic leukemia in a recent report [35]. It has been proposed that the adipoR-mediated cellular signaling, the effects on insulin sensitivity, chronic inflammation and angiogenesis may influence the action of adiponectin on carcinogenesis. At the cellular level, elevated adiponectin gives significant pro-angiogenic and pro-mitogenic effects leading to increased tumor growth [20]. Another report suggest that adiponectin inhibited proliferation of myeloid cells [36]. Adiponectin was also thought to have the ability to prevent myeloma risk by suppressing the pro-inflammatory cytokines secretion and their activation of the NF-κB signalling pathway [37]. Serum adiponectin levels were also reported to be associated with both adult and childhood non-Hodgkin's lymphoma [20]. It was concluded that adiponectin acts by promoting the secretion of interleukin-10 (IL-10), a known growth factor produced by non-Hodgkin's lymphoma cells [38]. However, there is a positive association between leptin levels and multiple myeloma or non-Hodgkin lymphoma reported [37,39].

It has been estimated that half of the cancers incidence are preventable by application of the basic knowledge that we have [25]. About 30% of cancers in developed Western countries are attributable to preventable factors such as food, nutrition, and physical activity [1]. Although these are modifiable causes of cancer, it is challenging to identify the specific associations between these factors and cancer over a lifetime, because of the long latent period for cancer development and its complex pathogenesis. Therefore, with modification in individual and population behaviors, and effective public health contribution and social commitment, we may achieve prevention of cancer and chronic disease.

5. CONCLUSION

The results of this case-control study supports the evidence that adiposity are related to haematological malignancy similar to that reported of solid tumours. This study demonstrates that adiposity with waist:hip ratio as an index and adipocytokines are significantly different in patients with haematological malignancy

compared to control group. This observation is consistent with previous reports in CLL and MDS. However, the small number of patients limits this observation. It is hard to compare the effect of adiposity and adipocytokines in different groups of patients with haematological malignancy. Leptin:adiponectin ratio which was significantly reduced in haematoloical malignancy may have the potential as a biomarker of obesity related malignancy. There is no significant relation of these parameters with the prognosis.

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COMPETING INTERESTS

The authors have declared that no competing interest exists.

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