EVALUATION OF RESTING ENERGY EXPENDITURE FOR SOLID TUMOR AND LEUKEMIA PATIENTS IN PENANG GENERAL HOSPITAL,MALAYSIA

by

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ALL	Acute Lymphoblastic Leukemia
AML	Acute Myeloid Leukemia
BCM	Body Cell Mass
BEE	Basal Energy Expenditure
BMI	Body Mass Index
BMR	Basal Metabolic Rate
BSA	Body Surface Area
BUM	Bicarbonate Urea Method
CRC	Clinical Research Center
DC	Direct Calorimetry
DEXA	Dual Energy X-ray Absorptiometry
DIT	Diet Induced Thermogenesis
DLW	Doubly Labeled Water
DZ	Dizygotic
ECW	Extracellular Water
EE	Energy Expenditure
ER	Energy Requirement
FAO/WHO/UNU	Food of Agriculture Organization/ World Heath Organization/ United Nation Union
FFM	Fat Free Mass
FM	Fat Mass
HBE	Harris Benedict Equation
IC	Indirect Calorimetry
ICW	Intracellular Water
LBM	Lean Body Mass
MREC	Medical Research Ethic Committee
mREE	Measured Resting Energy Expenditure
mTEE	Measured Total Energy Expenditure
MZ	Monozygotic
NHL	Non Hodgkin Leukemia
PA	Physical Activity
PAL	Physical Activity Level
PCM	Protein-Calorie Malnutrition
PGH	Penang General Hospital
PIS	Patient Information Sheet
pREE	Predicted Resting Energy Expenditure
REE	Resting Energy Expenditure
RMR	Resting Metabolic Rate
RQ	Respiratory Quotient
SCLC	Small Cell Lung Cancer

SD	Standard Deviation
SGA	Subjective Global Assessment
TEE	Total Energy Expenditure
TEF	Thermic Effect of Food
VCO2	Carbon dioxide production
VO2	Oxygen utilization
WL	Weight Loss
WS	Weight Stable
Wt	Weight
Ht	Height

PENILAIAN KEPERLUAN TENAGA SEMASA REHAT UNTUK PESAKIT –PESAKIT KANSER TUMOR DAN LEUKEMIA DI HOSPITAL PULAU PINANG, MALAYSIA

ABSTRAK

Kekurangan pemakanan adalah sangat biasa berlaku di kalangan pesakit kanser. Adalah dipercayai, masalah ini berlaku disebabkan peningkatan keperluan tenaga semasa rehat bagi pesakit-pesakit ini. Oleh sebab itu, penganggaran yang tepat bagi keperluan tenaga ini adalah penting untuk mengetahui keperluan tenaga yang sebenar untuk pesakit-pesakit ini. Kajian-kajian yang telah dilakukan kebelakangan ini telah menunjukkan formula-formula seperti formula Harris Benedict, formula Schofield dan formula WHO memberi anggaran keperluan tenaga yang lebih tinggi nilainya berbanding dengan keperluan tenaga yang sebenarnya. Formula-formula ini dikatakan kurang sesuai digunakan di kalangan populasi Asia. Walaubagaimanapun, formula-formula ini masih digunakan di Malaysia. Sebaliknya, formula Ismail yang telah dihasilkan daripada populasi Malaysia tidak digunakan secara popular dalam menganggarkan keperluan tenaga semasa rehat. Justerus itu, kajian ini dilakukan bertujuan untuk mengukur keperluan tenaga ini dan dibandingkannya di antara pesakit kanser dan orang sihat. Ia juga menilai mana satu formula adalah lebih sesuai digunakan untuk mengukur keperluan tenaga ini di kalangan pesakit kanser dan orang sihat di Malaysia. Dalam kajian ini, keperluan tenaga semasa rehat telah diukur dengan menggunakan kalorimeter tak lansung untuk 60 pesakit kanser dan 60 orang sihat dengan julat umur 18- 60 tahun, dan julat Index Jisim Badan 18.5 – 25.0

kg/m^2 . Tenaga yang diukur ini dibandingkan dengan tenaga yang dianggar daripada 9 formula-formula iaitu formula *Harris Benedict, Schofield, WHO, Mifflin-St Jeor, Oxford, Jia, Liu, Ismail dan Quick Method.* Analysis data dilakukan dengan mengunakan program SPSS melalui *independent* ujian-t, ujian –t berpasangan dan one way ANOVA. Plot Bland Altman juga digunakan untuk menunjukkan perbezaan di antara tenaga yang diukur dengan tenaga yang dianggar secara individu. Adalah didapati, tenaga yang diukur adalah sama di kalangan pesakit dengan tumor, leukemia dan orang sihat ($p=0.092$) tetapi berbeza bila dibandingkan tenaga yang diukur per jisim badan bukan lemak (*Fat Free Mass*) di antara pesakit kanser kepada orang sihat ($p= 0.018$). Formula Harris Benedict didapti memberi niai tenaga yang lebih tinggi berbanding dengan keperluan tenaga yang diukur. Faktor tekanan untuk pesakit kanser tumor adalah 1.35 dan pesakit leukemia adalah 1.36. Di samping itu, didapati keperluan tenaga yang diukur adalah berbeza dengan semua tenaga yang dianggar bagi pesakit kanser dan juga orang sihat($p<0.05$). Semua formula menunjukkan perbezaan yang tinggi di antara tenaga yang diukur dengan yang dianggar (lebih daripada 400 KJ/hari). Secara kesimpulannya, keperluan tenaga yang digunakan semasa rehat untuk pesakit-pesakit kanser adalah lebih tinggi berbanding dengan orang sihat. Formula Ismail adalah formula yang terbaik untuk menganggar tenaga ini di kalangan pesakit kanser dan juga orang sihat Malaysia. Walaubagainamapun, tenaga yang diukur adalah lebih tepat dan diutamakan secara individu dibandingkan dengan formula.

EVALUATION OF RESTING ENERGY EXPENDITURE FOR SOLID TUMOR AND LEUKEMIA PATIENTS IN PENANG GENERAL HOSPITAL, MALAYSIA

ABSTRACT

Malnutrition is common in cancer patients. Generally, it is believed that Resting Energy Expenditures (REE) is elevated in cancer patients and is contributed to the development of malnutrition. Thus, accurately assessing Resting Energy Expenditure is important in planning adequate nutrition support. Current studies showed Harris Benedict, Schofield and WHO equations were overestimating the Resting Energy Expenditure in Asian. However, these equations were still commonly use in clinical practice in Malaysia. Meanwhile, the Ismail equation which derived from Malaysian healthy subjects was still not widely used in Malaysia. Thus, the purpose of this study was to measure and compare the REE for solid tumor, leukemia and control group and determined which predictive equation is more accurate to estimate the REE in Malaysian cancer and healthy group. Resting Energy Expenditure was measured in 60 cancer patients and 60 healthy subjects, age ranged from 18 to 60 years old and with Body Mass Index of 18.5 to 25.0 kg/m^2 by using Indirect Calorimetry. The measured REE were compared among cancer and healthy group and also compared to 9 predicted REE respectively (Harris Benedict, Schofield, WHO, Mifflin-St Jeor, Oxford, Jia, Liu, Ismail equation and Quick method). Statistical analysis was carried out by using SPSS with the method of independent t-test, paired t test and one way ANOVA. The approach of Bland Altman plot was used to compare the agreement between measured REE to predicted REE at individual level. There was no significant difference between measured REE in cancer and control (p=0.092), but there was significant difference between REE/ FFM in cancer group to healthy group (p=0.018). Harris Benedict equation was found to be significantly higher than measured REE. Stress factor for solid tumor were 1.35 and leukemia were 1.36. There were significant differences between measured REE and predicted REE in all predictive equations for both cancer and healthy group (p<0.05). All the predictive equations showed a wide limit of agreement (greater than 400kJ/day) in mean difference between measured REE and predicted REE. As conclusion, REE in cancer patients undergoing anticancer therapy appeared to be higher like what had been thought when adjusted to FFM . Ismail equation is the best predictive equation in estimating REE for Malaysian cancer and healthy group. Nevertheless, measured REE is preferable than predictive equation from the expect of accuracy and individualization.

CHAPTER 1

INTRODUCTION

1.1 Understanding Energy Requirement

Energy requirement is the amount of food energy needed to balance energy expenditure in order to maintain body size, body composition and a level of necessary and desirable physical activity, and allow optimal growth and development of children, deposition of tissue during pregnancy, and secretion of milk during lactation, consistent with long term good health. For healthy, well nourished adults, it is equivalent to Total Energy Expenditure (TEE) (Grosvenor & Smolin, 2006).

By definition, TEE reflects the average amount of energy spent in a 24 hour by an individual (Grosvenor & Smolin, 2006) and it is estimated from measures of:

a) Basal metabolism rate. The minimum amount of energy required to maintain vital functions in human body at complete rest. The amount of energy used for basal metabolism in a period of time is called basal metabolic rate (BMR)(Warwick, 1989). In practical considerations, the BMR is rarely measured. It is typically taken in darkened room upon awaken after 8 hours of sleep, 12 hours of fasting and must be resting in a reclined position. Thus, the resting metabolic rate (RMR)/resting energy expenditure (REE) which is determined under less straight conditions is commonly measured (Grosvenor & Smolin, 2006).

b) Metabolic response to food. It is known as dietary induced thermogenesis. This energy is used for ingestion, digestion, absorption and transportation of food in the body (Grosvenor & Smolin, 2006; Warwick, 1989).

c) Physical activity. This is the most variable and the second largest component of TEE. This energy is needed in any movement which is produced by muscles of the body. The rates of EE during physical activity vary depending on intensity, duration, and frequency of the activity and on the body mass and fitness of the person performing the activity (Grosvenor & Smolin, 2006; Rolfes *et al.*, 2009).

Estimating TEE is necessary and important for recommendations of dietary intake to maintain or attain the optimal health, physiological function and well being of hospitalization patients (Bartlett *et al.*, 1982; Barton, 1994). Thus, the success of nutrition support to avoid positive or negative energy balance relies on the accuracy of energy requirement estimation. Energy balance is achieved when dietary energy intake is equal to TEE (Grosvenor & Smolin, 2006; Rolfes *et al.*, 2009). Positive energy balance (overfeeding) may cause overweight or obesity whereas negative energy balance will cause malnutrition or weight loss (Titchenal, 1988).

1.2 Problem Statement

Weight loss and protein-calorie malnutrition (PCM) is a common problem in cancer patients (Nixon *et al.*, 1980). More than 50% of cancer patients reported to malnutrition and 20% of them die from malnutrition rather than the malignancy (Argiles, 2005). Malnutrition has been proven to reduce quality of life, chance of survival and oncologic outcome in cancer patients. This group of patients is less tolerating anticancer therapy and brings to higher morbidity and mortality (Federico, 2009; Lainscak *et al.*, 2007).

Generally, it is believed that Resting Energy Expenditure (REE) is elevated in cancer patients and contributes to the development of malnutrition. In past years, several studies have been carried out comparing REE among cancer patients and control groups. Most of these findings demonstrated no significant difference between these two groups even after being adjusted for Fat Free Mass (Fredrix *et al.*, 1991; Hansell *et al.*, 1986; Lindmark *et al.*, 1984 ; Reeves *et al,*. 2006), while other studies indicated elevated in REE (Batterham & Edwards, 2006; Jatoi *et al.*, 2001). All of these studies were done on Caucasian populations.

Recently, two studies have been done in China, and the authors found no difference on REE in cancer patients compared to control but elevated in cancer group when compared by adjusted FFM to REE (Cao *et al.*, 2010; Guo-hao *et al.*, 2008). However there is no study to investigate REE among Malaysian population.

REE contributed 60-70% of TEE. The estimation of TEE was done by multiplying the REE with the stress factor and physical factor (Reeves & Capra, 2003; Siervo *et al.,* 2003). Different types of cancer give difference metabolic stress (Elia, 2005). Inconsistent use of the stress factor was happened in the clinical setting nowadays (Green *et al.,* 2007; Reeves & Capra, 2003). These had brought to the inaccuracy in estimating TEE for patients (Green *et al.*, 2007). The finding of these studies justified the need for a study to investigate the stress factor among Malaysian cancer patient to provide more accurate TEE.

In the clinical setting, Indirect Calorimetry (IC) is still maintain as the gold standard in measuring REE (Haugen *et al.,* 2007). High cost, time consuming, and lack of IC availability in clinical setting have made the predictive equations more preferable by the clinical practitioners. Since 1919 until today, there were many equations to estimate the REE have been derived (FAO/WHO/UNU, 1985; Harris & Benedict, 1919; Henry, 2005; Ismail *et al.*, 1998; Jia, Meng, & Shan, 1999; Liu, Lu, & Chen, 1994; Mifflin *et al.*, 1990; C. Schofield, 1985). Experts observed that predictive equations derived from Caucasian populations were not suitable for the Asian populations. It appeared more likely to be overestimating REE in Asian (D. C. Frankenfield *et al.,* 2003; Horgan & Stubbs, 2003).

However, till today, the Harris Benedict equation (Harris & Benedict, 1919), Schofield equation (Schofield C., 1985) and WHO (FAO/WHO/UNU, 1985), are still commonly use in clinical practice in Malaysia. Meanwhile, Ismail equation (Ismail *et al.*, 1998) which derived from Malaysian healthy subjects is not widely used in Malaysia. Ismail *et al.* (1998) found that the WHO and Henry equations were overestimating the Malaysian populations. Up to now, there is no further validation being done for predictive equation in the Malaysian population.

This research therefore was aimed to address these three research questions:

a) Does the REE changes in patients with solid tumor and leukemia?

b) What is the most appropriate predictive equation for determining the REE in cancer and healthy subjects?

c) Can the existing stress factors be used for estimating the TEE for Malaysian cancer patients?

In this study, cancer groups were chosen because these groups of patients often experience significant weight loss and it is believed that the alteration energy metabolism causes the problem of malnutrition in this group. Appropriate nutrition management of these patients is therefore essential.

1.3 Objectives

To address the research questions, this research therefore investigated the REE in two cancer groups (solid and leukemia) and control group. The objectives are:

a) To compare the measured REE of subjects between solid tumor, leukemia and healthy control subjects.

b) To compare the measured REE (mREE) from Indirect Calorimetry with predicted REE (pREE) from equations in cancer and healthy subjects.

c) To quantitatively investigate differences in stress factor for solid tumor and leukemia in our subjects to existing stress factor.

1.4 Significant of the thesis

The nutritional management of patients with cancer is a significant clinical issue. Appropriate and intensive nutrition support and counseling can assist cancer patients to maintain weight and subsequently, improve nutrition status, quality of life, and the effectiveness undergoing treatment and the length of survival. Thus, knowledge and understanding of estimating patient’s energy requirement is very important for providing adequate energy and nutrient to patients.

This study was the first to survey on predictive equations in Malaysian cancer population. This current study aims to expand the previous survey in Caucasian and

Asian population to Malaysian population. This study was also the first step towards identifying which predictive equation to be use in Malaysian cancer patients. This study has the ability to influence the teaching and practice for estimating patients' energy requirement.

CHAPTER 2

LITERATURE REVIEW

2.1 Total Energy Expenditure

Total energy expenditure (TEE) is the amount of energy, in the form of calories that a person uses to maintain normal physiological function such as breathe, blood circulation, digestion and physical activity (FAO/WHO/UNU, 1985; Rolfes *et. al.*, 2009). TEE consists of 3 main components which are basal metabolism rate (BMR), diet-induced thermogenesis (DIT) and energy expenditure for physical activity (PA) (Figure 2.1).

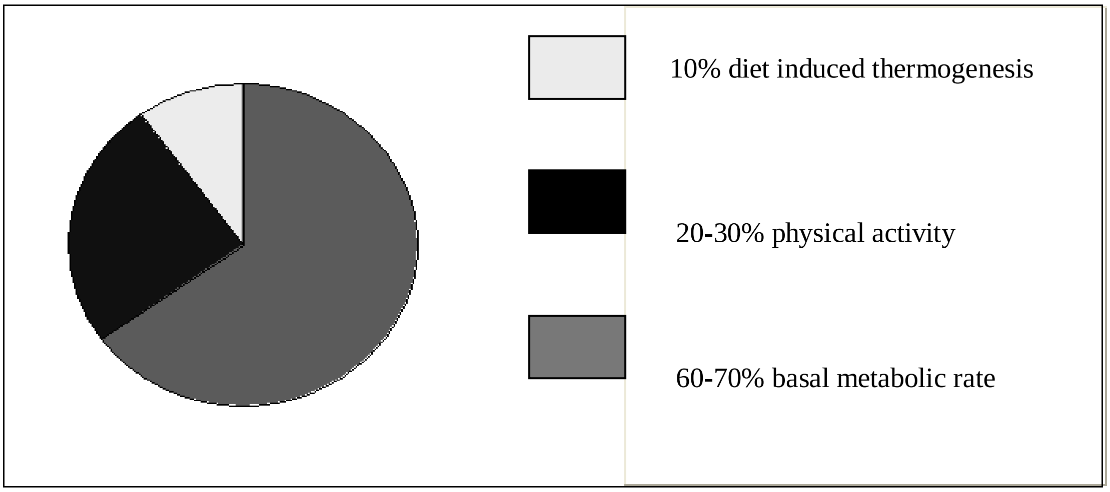

Figure 2.1 Percentage of three main components in TEE (Grosvenor & Smolin, 2006)

2.1.1 Basal Metabolic Rate (BMR)

BMR is a minimum rate of energy necessary to support normal body's function like breathing, breaking down food, keeping heart and brain working (Wong *et. al.*, 1996). It is synonymous with Basal Energy Expenditure (BEE). BMR measurements are typically taken in a darkened room upon waking after 8 hours of sleep; 12 hours of fasting to ensure that the digestive system is inactive; and the subjects are mentally and physically at rest in a reclining position and thermoneutral environment (Warwick, 1989).

It is not practical and is difficult to measure the BMR/BEE. As such, Resting Metabolic Rate (RMR) is often measured (Whitney *et al.*, 2001). It is synonymous with Resting Energy Expenditure (REE). REE measurements are typically taken under less restrictive basal conditions than BMR. Subjects may not have to fast for 12 hours or may not have to spend a night sleeping in the test facility to measure the energy immediately upon waking up (Mahan, 2000).

REE is the largest component of the TEE, approximately 50-85% of TEE (Arciero *et al.*, 1993; Battezzati & Viganò, 2001; Shetty, 2005; Toth, 1999; Wang *et al.*, 2000). The REE is taken at rest condition but not basal condition, thus the REE is approximately 10% higher that BMR (Turley, McBride, & Wilmore, 1993). However, clinical practitioners use REE for estimating TEE in patients care. In additional, health organizations also use REE routinely in defining TEE for healthy population. REE can be measured by Direct Calorimetry, Indirect Calorimetry (IC) or predicted by using predictive equations (Rolfes *et al.*, 2009).

2.1.2 Diet-Induced Thermogenesis (DIT)

DIT is also known as Thermic Effect of Food (TEF). It is the smallest component of TEE (Rolfes *et al.*, 2009). DIT is metabolic functioning related to digestion of food, and the active intake of nutrient into the blood. There is an increase in heat production by the body after eating due to secretion of digestive enzymes, active transportation of nutrients from gut, gut mobility and storage of ingested nutrients (Frankenfield DC., 1998; Toth, 2001). It accounts for approximately 10-15% of TEE (Mifflin *et al.*, 1990; Owen *et al*., 1986).

DIT varies within individuals from day to day and between individuals. It is influence by many factors like meal size, meal frequency, meal composition, meal pattern and body composition, gender, age, hormone levels and genetics (Farshchi, Taylor, & Macdonald, 2004; Kinabo & Durmin, 1990; Segal *et al.*, 1987). However, the main determinants of DIT are the meal composition and body composition (Grosvenor & Smolin, 2006).

Protein is a macronutrient that induces the largest DIT response. Table 2.1 shows that approximately 25% of the calories in pure protein and 3% in pure fat and 5 % in pure carbohydrate will be burnt after consumption due to the DIT (Kinabo & Durmin, 1990).

Besides, Westertrep (2004) also revealed that a mixed diet consumed at energy balance resulted in a DIT of 5-15% of TEE. Values are higher at relatively high protein and alcohol consumption and lower at high fat consumption (Westerterp, 2004a, 2004b).

Table 2.1 Percentage of energy using by the macronutrient.

Nutrient	Fat	Carbohydrate	Protein	Alcohol
DIT (% Energy)	0-3%	5-10%	20-30%	10-30%
Reference	Kinabo & Durmin (1990)			Westerterp *et al.*, (1999)

Body composition, or more specifically body fat percentage, also has been shown to be a significant determinant of how active the DIT will be within a given individual (Segal *et al.*, 1987). Lean people have a DIT that is approximately 2 to 3 times greater than obese people during rest, after exercise, and during exercise (Segal *et al.*, 1987).

2.1.3 Physical Activity (PA)

Physical activity is defined as any body movement produced by skeletal muscles that require energy expenditure above resting level (Grosvenor & Smolin, 2006). Physical activity in daily life can be categorized into occupational, sports, conditioning, household or other activities (Caspersen *et al.*, 1985). Physical activity is the most variable after BMR and is the second largest component of TEE, typically accounts to approximately 20-30% of energy expenditure (Jequier & Schutz, 1983) and for as little as 5% during bed rest or as much as 75% in elite athletes (Toth, 1999).

In practical, it is difficult to measure energy expended from physical activity. It varies within individuals from day to day as well as between individuals. Thus, the physical activity level (PAL) is used to express a person's daily physical activity as a number to estimate a person's TEE (Eastwood, 2003). PAL is calculated as the ratio of TEE to BMR (Gibney *et al.,* 2005). The population's lifestyles was categorized into sedentary (PAL 1.40 – 1.69), active (PAL 1.70- 1.99) or vigorous (2.00-2.40) according to the average values published by FAO/WHO/UNU (2004) (World Health, Food, Agriculture Organization of the United, & United Nations, 2004).

Generally, Malaysian adults' population is considered sedentary, only minimal time is spent on vigorous intensive activities. The overall PAL of both Malaysian men and women is at mean of 1.6 (Poh *et al.*, 2010).

2.2 Factors Affecting Total Energy Expenditure (TEE)

There are several factors influence Basal Metabolic Rate (BMR) and TEE intra and inter individuals. Figure 2.2 shows the factors influencing the components of TEE and BMR/REE. TEE consists of 3 components: BMR/REE, DIT and Physical activity (PA). These 3 components are varying inter and intra individuals. Each component is uniquely dependent upon body size or composition (Nelson *et al.*, 1992; Westerterp & Goran, 1997). However, the effect of body composition on the DIT is omitted because of its minimal contribution to TEE and the difficulty of its measurement (Toth, 2001)

Besides that, gender, growth, ethnicity and age also influence the energy expenditure. In general, women have a lower BMR than men; BMR is high in people who are growing like pregnant or lactating women , infant, children and adolescents (Rolfes *et al.*, 2009). In addition, the relationship of each TEE component to body composition may differ among groups and over a period of time. Aging and severity of the illnesses can alter TEE independent of body composition (Elia, 1992; Kehayias, 2002).

Energy needs for two people who are similarly matched in age, gender and ethnicity differ because of genetic and hormone differences (Rolfes *et al.*, 2009).

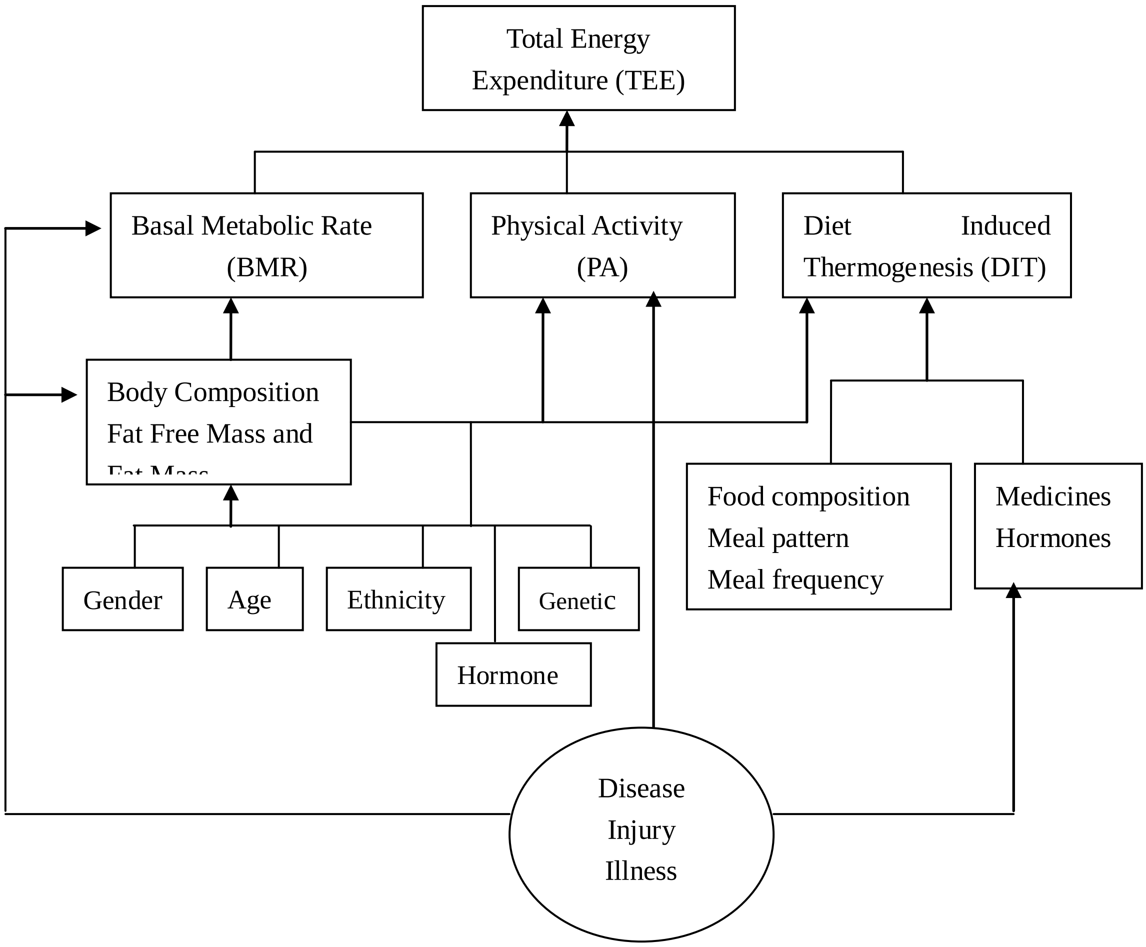

Figure 2.2 Factors that influencing the components of Total Energy Expenditure (Source: Reeves M.M., 2004)

2.2.1 Body Composition

Before going further into the relationship among Energy Expenditure and body composition, it is necessary to define each component of body composition as below (Figure 2.3):

Fat Mass (FM) - the mass of the body fat, one of the main components of body composition (Eastwood, 2003).

Fat Free Mass (FFM) – the mass of the body when ether-soluble material (fat tissue) has been removed (Nelson *et al.*, 1992).

Lean Body Mass (LBM) – the mass of all tissue in body excluding adipose tissue. Also known as adipose tissue free mass (Nelson *et al.*, 1992).

Body Cell Mass (BCM) - equal to the difference between total cell mass and cell fat mass. BCM does not contain the extracellular water (ECW) component of FFM, which is relatively inert (Nielsen *et al.*, 2000).

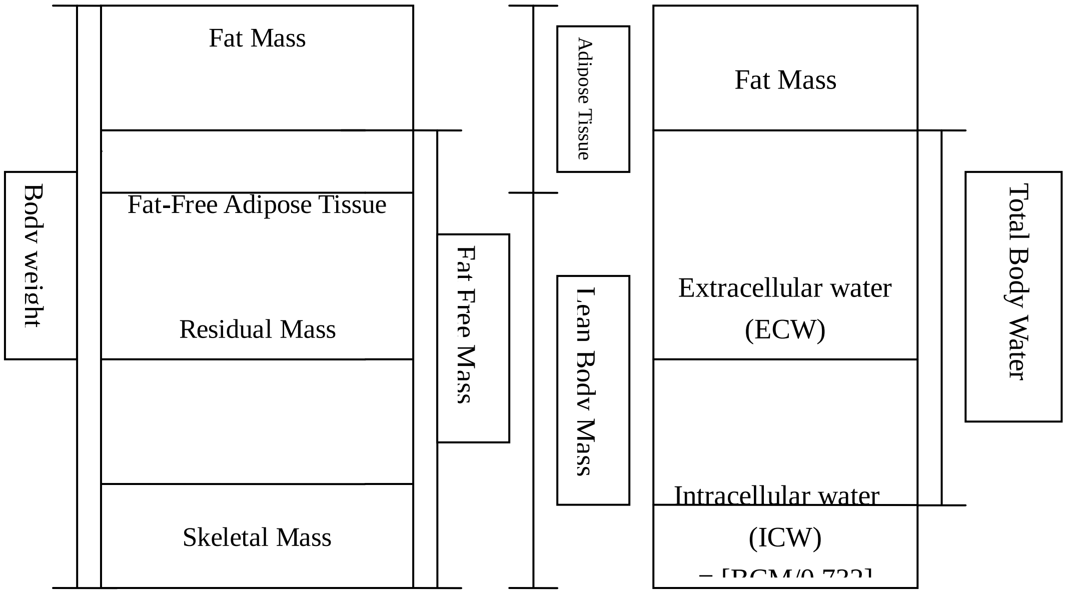

Figure 2.3 Body Compartments (Heymsfield *et al.*, 2002)

(a) Fat Free Mass (FFM)

It is well accepted that body size and energy expenditure are related. Kleiber (1947) reported that the surface law has an impact on energy metabolism. However, Benedict (1915) found substantial variability both intra and inter individual after adjusted to body surface area. Thus, the author reported that factors other than surface area determined the metabolic rate. Cunningham (1980, 1991) and Miller & Blythe (1953) also supported that the size of heat producing tissue might be a better predictor other than body surface area

Subsequently, researchers had also found that body weight is the best measurement of body size and accounts for significant variation in REE. They also reported that FFM compartment of body which contains the organ and tissue components are the most metabolically active (Buchholz *et al.,* 2001; Mifflin *et al.*, 1990; Owen *et al.*, 1986; Taaffe *et al.*, 1995).

Besides that, numerous of researchers reported that FFM is the most important factor in the estimation of REE. Difference in the FFM among individuals brought the greatest variation in REE. Table 2.2 shows the result of previous research that demonstrated FFM is the most important factor in estimation of REE. In Illner *et al.*, (2000) study, the authors had shown that the 94% of REE can be explaining by the FFM. While the others study had shown with at least 64% to 85% of REE can be explaining by the FFM. However, the FFM is more difficult to obtain than body weight.

Table 2.2 Variance in Resting Energy Expenditure explained by Fat Free Mass.

Reference	N	Percentage of variance (%)
Cunningham (1980)	223	70
Mifflin *et al.* (1990)	482	80
Nelson *et al.* (1992)	213	73
Sparti *et al.* (1997)	40	90
Illner *et al.* (2000)	26	92
Buchholz *et al.* (2001)	58	85
Heymsfield *et al.* (2002)	289	64

Body weight is the easiest measurement to obtain in clinical practice however the relationship of body weight to REE is lesser than FFM. Muller *et al.* (2004) showed that only 52% of variance by body weight to REE and Korth *et al.* (2007) also revealed that the variance in REE explained by FFM was higher than the variance explained by body weight (R^2 = 0.74 versus R^2 = 0.46). However, the authors also found that the combination of body weight, height, sex and age have increased the variance in REE. Thus, FFM can be explained by a function of age sex, height and body weight with 88.8% of the variance in FFM (Korth *et al.*, 2007).

In general, REE per kg body weight is less in females which have higher percentage of body fat compared to a male individual with the same body weight. Mifflin *et al.* (1990) and Buchholz *et al.* (2001) found that weight was better predictor for female due to higher fat mass. Figure 2.4 shows variance in REE within and between subjects. There was a large unexplained residual variance between individuals that accounted for 26% of the total variance after adjusting for FFM, FM and age (Johnstone *et al.*, 2005).

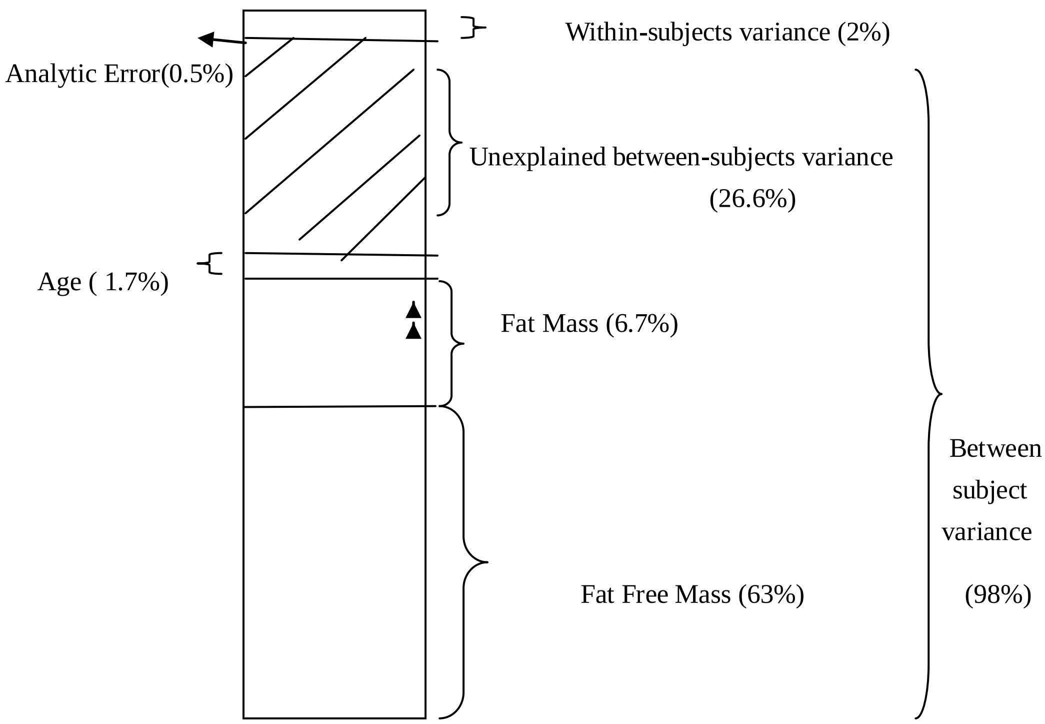

Figure 2.4 Variance in REE within and between subjects.
Source: Johnstone *et al.* (2005)

Currently, studies were carried out to find out the factor that could best explain the varying of REE. Heymsfield *et al.* (2002) reported FFM was not a homogeneous tissue and it has brought variation in the composition of FFM. The size of the organ and muscle mass contributing to FFM indeed can be separated into two distinct constituents – high metabolic rate and low metabolic rate tissue (Sparti *et al.*, 1997). Owen *et al.* (1990) also reported that heterogeneity of FFM as various tissues and organ likely explained the variance between subject in REE after adjusting for Body Surface Area (BSA), BCM or FFM (Owen *et al.*, 1990).

Adipose tissue is often grouped as low metabolic rate tissue while organs such as liver, brain, heart and kidney as high metabolic rate (Wang *et al.*, 2000). These organs only comprise 5-6% of total body weight but contributed to approximately 60% of REE. Elia,(1992) also reported that brain, liver and others visceral tissue organ have higher rate of heat production in the post absorptive state (Elia, 1992) (Table 2.3).

However, Garby and Lamment (1994) reported that the composition of FFM only explained 5% of the variance in between subject variance in REE. Johnstone *et al.* (2005) also reported that the brain tissue which is the highest metabolic tissue only contributed to 1.3% of variance in unexplained variance of REE (26.6%) (Figure 2.3). The authors concluded that the undetected variation in tissue sizes of highly energetic organs did not significantly contributed to the observed unexplained variance in

BMR for between subjects variance (Johnstone *et al.*, 2005). In addition, the potential contribution intra-individual variation in organ metabolic rate in REE was assumed to be constant (Heymsfield *et al.*, 2002; Wang *et al.*, 2000; Wang *et al.*, 2001).

Table 2.3 Organ and tissue metabolic rates

Body Compartment	Organ/ tissue metabolic rate (kcal/kg)	Percentage of Body weight (%)	Percentage of Basal Metabolic Rate (%)
Fat Mass			
Adipose tissue*	4.5	21-33	5
Fat Free Mass			
Skeletal muscle*	13	30-40	15-20
Organ**		5-6	60
- Liver	200		
- Brain	240		
- Heart	440		
- Kidneys	440		
Residual tissue* (bone, skin, intestine, glands)	12	33	15-20

*Low metabolic rate tissue; ** high metabolic rate tissue
(Source: Elia, 1992)

Another factor that can explain the unexplained variable in REE is the method of measuring the FFM. There are many methods to measure FFM such as dual energy x-ray absorptiometry (DEXA), hydro densitometry and deuterium dilution technique (Grosvenor & Smolin, 2006). Korth *et al.* (2007) found low precision from measurement of FFM using skinfold thickness and bioelectrical impedance analysis (BIA) method. Other studies that used DEXA, a highly accurate method, has shown variation in R^2 from 0.64 to 0.92 (Gallagher *et al.*, 1998; Heymsfield *et al.*, 2002).

As conclusion, FFM is the best predictor for REE compared to body weight. When FFM is not available, body weight should include the age, sex, and height to reduce the percentage of variance in REE. There were still have a little variance unexplained after adjusted to FFM. Thus, the accuracy of the adjusted REE in FFM may be questionable. Method to measure the FFM or composition of FFM is the important key to find the variance in REE.

(b) Fat Mass (FM)

The relation between subject variance to REE in fat mass is less consistent than relationship in FFM (Toth, 2001). FM is a relatively metabolically inert tissue. It contributes only a small part of the remaining variance in REE. Johnstone *et al.* (2005) found that FM contributed approximately only 6% of variance in REE. Arcieco *et al.* (1993) and Sparti *et al.* (1997) also showed only 1% variance to REE.

On the other hand, some researchers found that FM contributed as high as 49% variance from FM in REE (Owen *et al.*, 1986). The authors reported that the higher proportion of body weight as FM in females contributed to this higher variance. Buchholz *et al.* (2001), Nielsen *et al.* (2000), Sparti, *et al.* (1997) and Taaffe *et al.* (1995) also found a higher correlation of FM with REE in females compared to males. Butte *et al.*, (1995) also found some variance in REE explained by FM in adults compared to infant and children, 10% versus 64% and 41%, respectively.

As conclusion, for men alone the best predictor was FFM alone whereas for women was FFM and weight. FM didn't explain the significant amount of variation in REE in men but it did explained a significant contribution of FM to REE after adjusted for FFM in females and infant who have higher proportion of FM in body weight.

2.2.2 Age

Age is one of the factor influencing the REE, and approximately contributed to 1.7% variance in between subject's REE (Johnstone *et al.*, 2005). The elderly tends to have lower REE compared to the younger group of the same body size and height (Heymsfield *et al.*, 2002; Klausen *et al.*, 1997; Poehlman & Toth, 1995). In the 1970's, studies showed REE reduced with age as the results of changing in body composition, due to the decrease on FFM (Keys *et al.*, 1973; Tzankoff & Norris, 1977). Keys *et al.* (1973) revealed that 1-2% of reduction in BMR per decade of age in men.

In the 1990's and 2000's, researchers found that FFM did not fully account for lowering the REE in aging (Fukagawa *et al.*, 1990; Hunter *et al.*, 2001; Poehlman *et al.*, 1993). The authors found REE was still lower after adjusting FFM in REE. There was a study found that a decreasing of metabolically active tissue in FFM brought to the lower REE (Visser *et al.*,1995).

Bosy-Westphal *et al.* (2003) also found the decline of REE in aging was not due to decreasing organ metabolic rate but by reduction in FFM and proportional changes in its metabolically active components. Others studies found that a reduction of exercise or dietary intake contributed to further reduction were of REE in aging (Fleg & Lakatta, 1988; Poehlman *et al.*, 1993; Poehlman & Horton, 1990; Van Pelt *et al.*, 1997; Vaughan *et al.*, 1991). Bartali *et al.* (2003) found that poor appetite and low food intake in frail elderly has brought to an unintentional weight loss. This restriction of energy had cause the metabolic adaption and reducing 5-10% adjusted REE in FFM (Ronald *et al.*, 2001; Weyer *et al.*, 2000).

Recent studies found that the reduction of REE in the elderly might be due to reduction of muscle mass (Nair, 2005) and BCM/ FFM ratio (Wang *et al.*, 2007). Nair (2005) believed that decrease in muscle mass is responsible for approximately 30% drop of REE. This change brings to obesity and insulin resistance, as a result of abdominal fat accumulation. Luhrmann *et al.*, (2001) demonstrated the distribution of fat is significant in determining the REE. The authors found abdominal fat causes higher REE particularly in gluteal-femoral region (Luhrmann *et al.*, 2001).

Wang *et al.* (2007) demonstrated that the BCM/FFM was one of the major determinants of whole body REE. Lower BCM/ FFM in the elderly (Mazariegos *et al.*, 1994) had brought to lower REE in the elderly (Wang *et al.*, 2007).

Last but not least, reduction of sex hormone especially in women after menopause also caused the lowering REE in aging (Bisdee *et al.* 1989; Klausen *et al.*, 1997; Poehlman & Toth, 1995). Ferraro *et al.* (1992) showed that the menstrual cycle influences the REE due to hormonal fluctuations. The authors also showed the higher BMR in females during the luteal phase of the menstrual cycle compared to females during the follicular phase.

2.2.3 Gender

Similar to the relationship with age, differences in FFM and measured metabolic rate are observed in people in different gender. Measured metabolic rate is lower in females compared with males due to greater proportion of fat mass in female than males. Males have higher proportion of muscle mass which is a higher metabolically active tissue compared to fat tissue. Several studies had found that there is no significant difference for adjusted REE in FFM between these two genders (Buchholz *et al.*, 2001; Klausen *et al.*, 1997; Mifflin *et al.*, 1990; Owen *et al.*, 1987).

However, there were some studies showed significant differences of 2-5% lower for adjusted REE in FFM in men and women (Arciero *et al,*.1993; Ferraro *et al.*, 1992; Molnár & Schutz, 1997; Poehlman & Toth, 1995). These findings may be explained, in part, by the heterogeneity of the LBM compartments which contains both extracellular mass (skeleton, cartilage, connective tissue, lymph, and plasma) and BCM (skeletal muscle and organs) (Buchholz *et al*., 2001). It also may be due to lack of control for menstrual cycle phase in young women.

As conclusion, whether there are any differences on adjusted REE for FFM in both sex groups is remaining controversial. The relationship between the components of BCM and REE still requires further validation.

2.2.4 Ethnicity

W.N. Schofield *et al.,* (1985) reported on REE of Indians was significantly lower than Caucasian for the same body weight. Others studies also revealed that the measured REE of Indians were significantly lower than predicted by using equations that were developed on European and American population (Piers, 2002; Soares & Shetty, 1984; Soares & Shetty, 1988). These differences in REE were often accepted as evidence for ethnic influence on REE.

In late 1990s, Soares *et al*.,(1998) found no evidence on the influence of ethnicity in REE. The authors found no significant differences between Indian and Australian men and women were observed in adjusted REE in body composition (Soares *et al.,* 1998). Recently, a new approach to explore the tissue- organ body composition in REE according to race was done by Jones *et al*. (2004) and Hunter, Weinsier, Darnell, Zuckerman and Goran (2000). Both of the studies found same result as Soares *et al*. (1998) whereby there was no racial difference in REE after adjusted for lean tissue mass.

Jones *et al.* (2004) also revealed that African American women who have a greater musculoskeletal mass and bone than Caucasian women of similar weight, height and age had accounted for the differences between REE in these two groups. However, Hunter *et al.* (2000) found that the lower REE in African American women compared to whites is mediated by a lower mass of metabolic active organ in African American women.

Besides that, Lear *et al.,* (2009) revealed that South Asian have a phonotype of higher fat mass and lower lean mass compared to others ethnic groups. These finding had showed that the differences in body composition in different ethnics have influenced the REE. Deurenberg Deurenberg-Yap & Guricci (2002) also proven that Asian population had higher fat percentage (3-5%) at a similar BMI compared to Caucasian. These might bring to lower BMR in Asian population compared to Caucasian.

Mirjam *et al.,* (2008) also found that there exist differences in body composition between Asian and Caucasian. The authors revealed that no racial differences in REE after adjusting for FFM. The lower REE in Asians is mediated by lower FFM in Asian population.

In the past, possible effects of tropical climate, food intake and other environmental factors on REE have been suggested but reports are inconclusive (Geissler & Aldouri, 1985; Snodgrass *et al.,*2005). It may wonder whether