DETECTION OF BROWN ADIPOSE TISSUE USING INFRARED THERMAL IMAGING MODALITY AND CHANGES OF RELATED BIOMARKERS AFTER LOW CARBOHYDRATE HIGH FAT DIET

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DEDICATION

This thesis is dedicated to my love, Dr Sriwathi Angeline Hendricks

"Thank you for being the significant other whom I can walk this path of live with ",

To my teacher(s) who taught me that knowledge has no boundaries,

and those who are fighting for a cause…

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ABSTRACT

In Malaysia, approximately 17, 18 and 30 percent are diabetic, obese and overweight respectively. A low carbohydrate high fat diet (LCHF) surfaced since the 1920s, has numerous clinical impacts and yet has not been used widely to combat obesity due to concerns about its safety, applicability and sustainability towards patients. Brown Adipose Tissue (BAT) is an endocrine organ which increases metabolism by generating non shivering thermogenesis (NST). Chronic exposure to ketones from LCHF is known to stimulate the BAT as proven in animal studies. Although, nuclear imaging is considered the gold standard for BAT quantification, the thermal imaging is a non-invasive yet cheap modality that is at par for clinical translation. The objective of this study is to determine whether LCHF increases the BAT heat dispersion area and its biomarkers more effectively than the unrestricted normal diet. This was a single-center, randomized, crossover trial of low LCHF versus unrestrictive normal (UN) diet. Each subject underwent one week of either LCHF or UN diet after randomization, followed by a week of washout period before completing the study with the opposite diet for one week. There were two dietary sequence of the study and four sampling points. The sampling included thermal imaging of the supraclavicular area, body composition and blood glucose and ketones. The primary outcome measure was the mean change in BAT thermal dispersion area and heat energy during using ANCOVA adjusted to the baselines. Secondary outcomes include, changes in body weight, BMI, body fat, visceral fat, fasting blood glucose, fasting blood ketone. Tertiary outcome was the correlation between the primary and secondary outcomes at both dietary periods. Fourteen subjects were recruited between June 2019 and October 2019. Twelve subjects completed the four points of the study and two subjects dropped out. None of the subjects reported any side effect of the LCHF diet. The primary outcome of this study was that no significant changes were seen in the BAT Thermal dispersion area and heat energy at both dietary periods and sequence. Secondary outcomes showed significant decrease in body weight in both dietary period and sequence ($F(1,8)=15.775$, and $F(1,8)=7.210$). There was also a significant decrease in BMI during first dietary period ($F(1,8)=10.069$). Elevation of ketones were only significant during the second dietary period ($F(1,8) = 11.56$). There were significant positive correlation between the BAT thermal properties and body weight, BMI, glucose and ketones during both dietary period. One week of LCHF diet did not increase both BAT heat dispersion area and heat energy. It was also not sufficient to reduce visceral fat, body fat and fasting blood glucose. Nevertheless, it lowered body weight, BMI and increased fasting blood ketones in the same timeframe.

ABSTRAK

Di Malaysia, kira-kira 17, 18 dan 30 peratus dari masyarakat menghidap penyakit kencing manis, obesiti dan berat badan berlebihan. Diet tinggi lemak rendah karbohidrat (LCHF) wujud sejak tahun 1920-an tetapi tidak digunakan secara meluas oleh kerana kebimbangan tentang keselamatan, kebolehgunaan dan kemampanan terhadap pesakit. Lemak perang (BAT) adalah organ endokrin yang meningkatkan metabolisme dengan menghasilkan termogenesis tanpa gigil (NST). Pendedahan kronik kepada keton dari LCHF akan merangsang BAT seperti yang terbukti dalam kajian haiwan. Walaupun pengimejan nuklear dianggap sebagai modaliti utama untuk kuantifikasi BAT tetapi pengimejan haba adalah modaliti tanpa invasif, murah dan setara efektif. Objektif kajian ini adalah untuk menentukan sama ada LCHF meningkatkan kawasan penyebaran haba BAT dan bio-penandanya dengan lebih berkesan daripada permakanan biasa. Subjek yang terpilih di golongkan dalam kumpulan secara rawak dan menjalankan diet secara bersilang. Pada awalnya, setiap subjek menjalani sama ada diet LCHF atau pemakanan biasa selama seminggu. Setelah itu, mereka berehat untuk seminggu sebelum menyelesaikan tahap kedua diet dengan kaedah yang bertentangan. Terdapat dua tempoh kajian dan empat titik pensampelan. Pensampelan ini termasuk pengimejan haba kawasan leher, komposisi badan dan kandungan glukosa dan keton darah. Hasil utama kajian ini adalah perubahan pada kawasan penyebaran haba BAT dan tenaga haba dengan menggunakan kaedah statistic ANCOVA diselaraskan kepada nilai dasar. Hasil sekunder termasuk, perubahan berat badan, BMI, lemak badan, lemak viseral, nilai glukosa dan keton darah. Hasil tertier adalah korelasi antara hasil utama dan sekunder pada kedua-dua tempoh kajian. Seramai empat belas subjek telah di rekrut bermula dari Jun 2019 sehingga Oktober 2019. Dua belas subjek berjaya mnyelesaikan kajian ini. Dua subjek mengundurkan diri dari kajian ini. Tiada subjek yang melaporkan apa-apa kesan sampingan dari diet LCHF. Hasil utama kajian ini menunjukkan tidak ada perubahan yang signifikan dalam kawasan penyebaran haba BAT dan tenaga. Hasil sekunder menunjukkan penurunan signifikan dalam berat badan pada kedua-dua tempoh kajian dan jenis diet ($F(1,8) = 15.775$, dan $F(1,8) = 7.210$). Terdapat juga penurunan signifikan pada BMI semasa tempoh diet pertama ($F(1,8) = 10.069$). Peningkatan keton hanya signifikan semasa tempoh pemakanan kedua ($F(1,8) = 11.56$). Terdapat korelasi positif yang signifikan diantara BAT dan berat badan, BMI, glukosa dan keton pada kedua-dua tempoh diet. Kesimpulannya, diet LCHF selama seminggu tidak meningkatkan kawasan penyebaran haba dan tenaga BAT. Diet ini juga juga tidak mengurangkan lemak visceral, lemak badan dan nilai glukosa darah dalam tempoh seminggu. Namun demikian, ia menurunkan berat badan, BMI dan meningkatkan nilai keton darah.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

18-FDG	-	Deoxy-2-[^{18}F]fluoro-D-glucose
AcAc	-	Acetoacetate
ATP	-	Adenosine Triphosphate
BAT	-	Brown Adipose Tissue
BMI	-	Body Mass Index
DKA	-	Diabetes Ketoacidosis
DM	-	Diabetes Mellitus
HMG-CoA	-	β-Hydroxy β-methylglutaryl-CoA
IRTI	-	Infrared Thermal Imaging
K:AK	-	Ketogenic Potenitial to Antiketogenic Potential
LCHF	-	Low Carbohydrate High Fat
NAD	-	Nicotanamide Adenine Dinucleotide
NAD+	-	Free Nicotanamide Adenine Dinucleotide
NADH	-	Reduced Nicotanamide Adenine Dinucleotide
NEFA	-	Non - Esterified Fatty Acid
PET	-	Positron Emission Tomography
ROI	-	Region Of Interest
SPCV	-	Supraclavicular
UCP-1	-	Uncoupling Protein-1
UTM	-	Universiti Teknologi Malaysia
VLCHF	-	Very Low Carbohydrate High Fat
WAT	-	White Adipose Tissue
β-OHB	-	Beta-Hydroxybutyrate

LIST OF SYMBOLS

J	-	Joule
W	-	Watts
°C	-	Degree Celsius
K	-	Kelvin
mmol	-	Milimolar
mm	-	Millimetre
m	-	Metre
µm	-	Micrometre
Δ	-	Entalphy
ε	-	Emissivity
T	-	Temperature
σ	-	Stefan Boltzmann constant

LIST OF APPENDICES

CHAPTER 1

INTRODUCTION

1.1 Background

In 2018, an alarming 21% of the total deaths in Malaysia were due to non-communicable diseases (NCD). From the 21%, a staggering 14 % was caused by ischemic heart diasese (Mahidin, 2018). In recent years, the NCD has been both a health and economic burden in Malaysia (Milton, 2019; Hussein *et al.*, 2016). In 2014, Malaysia became the second fattest country in the South East Asia. The obesity percentage rose from 10.5 in 2010 to 13.3 in 2014. In addition, the population that were overweight in 2014 was 38.5 and the average BMI of a Malaysian in the same year was 25.3. Malaysia was only superseeded by Brunei who had the largest percentage of obese and overweight individuals (Hassan *et al.*, 2018). Newer statistics from the National Health and Morbidity Survey Malaysia (NHMS) reported an increment in both overweight and obesity to 30 and 17.7% respectively (Institute for Public Health Malaysia, 2015). Other than, it is estimated that almost 17% of the Malaysian are diabetic which leads to common complications of diabetes are neuropathy, nephropathy, retinopathy, vascular complications such as stroke and ischemic heart disease (Hussein *et al.*, 2016).

As an effort to curb obesity in Malaysia, the National Research Priority Malaysia (NRPM) for 11th Malaysia Plan was developed in 2016 to identified potential scopes anmd priorities for overweight and obesity (Ministry of Health Malaysia, 2016). From a scoping review in 2018, the trend of obesity research explored the perspectives, perceived barriers, quality of life and factors for weight loss and obesity among adult population. This review also showed that, there were only 2 randomized control trial and 4 obesity intervention cohorts from 2008 to 2017. Majority of the studies were observational with cross section contributing to 79% of the research. In addition, the authors concluded that only 22% of the publications from

2008 to 207 were relevant to the development of new modalities to curb obesity (Mohamad Nor *et al.*, 2018).

The current dietary food pyramid recommends 65% of the caloric intake to be carbohydrate (Allen et al, 2014). This food pyramid is outdated, has not been revised and has led to the unnecessary prevalence of DM due to the unseen effect of insulin resistance and occurrence of metabolic syndrome (Esmaillzadeh *et al.,* 2007). The easiest possible way to overcome insulin resistance by a method known to man is caloric restriction diet (Johnson *et al.,* 2015: Larson-Meyer *et al.,* 2006). A popular yet controversial type of caloric restriction diet is the Low Carb High Fat (LCHF) Diet which is also known as the ketogenic diet (Allen *et al.,* 2014). A LCHF diet is unique in such a way that it can enable utilization of both glucose and ketones as the energy substrates, thus lowering insulin resistance by promoting adipolysis, glycolysis and lowering the spike of insulin after food intake and throughout the day (Allen *et al.,* 2014). Up to date there are more than 60 clinical trials which utilize the LCHF diet in clinical practice (Allen *et al.,* 2014).

Apart from that, recent research shows that LCHF diet also reduces inflammation and increases the conversion of white adipose tissue (WAT) to brown adipose tissue (BAT) (Veech, 2013: Srivastava *et al.,* 2012). The BAT is a form of adipose tissue which is found in abundance in newborns and diminishes over time (Carter& Schucany 2008). BAT regulates body temperature by mediating the expression of uncoupling protein 1 (UCP-1) which is also known as thermogenin, via non-shivering thermogenesis (Marlatt & Ravussin 2017). BAT is almost non-existent in overweight and obese adults. The presence of BAT is also said to be inversely proportional to the occurrence of metabolic diseases such as DM, hypertension and obesity (Cypess & Kahn 2010). A paper in 2016 stated that BAT can be increased after LCHF diet (Mulya & Kirwan 2016). Animal studies with LCHF for 3 weeks increased its BAT and browning of the WAT (Yamazaki, Okawa & Takahashi, 2016). BAT would be a strategic choice as one of the most difficult task in managing obesity is to reduce energy uptake and increase the energy expenditure (Muscogiuiri *et al.,* 2019).

Currently, the gold standard to determine BAT is by using positron emission tomography (PET) with 2 – deoxy - 2 - [fluorine-18] fluoro – D - glucose (18FDG) radionuclide (Chakraborty, Bhattacharya, & Mittal 2015: Almuhaideb, Papathanasiou & Bomanji 2011). This method is however troublesome as it is invasive as it requires a radionuclide to be injected intravenously prior to the PET-Scan and is relatively expensive (Law *et al.,* 2018b). A low cost, non-invasive and more convenient alternative is the usage of infrared thermal imaging (IRTI) as reported in several previous studies. (Law *et al.,* 2018c; Gatidis *et al.,* 2016; Jang *et al.,* 2014).

Therefore this study was proposed to determine the increment of BAT after a LCHF diet therapy plan with the usage of thermal imaging

1.2 Problem Statement

There has been a growing interest in research since 2009 in the area of BAT and the usage of thermal imaging in detecting it. Many conditions such as cold climate changes, and ingestion of certain pharmaceuticals and its effect in increasing the BAT or activating it has been studied through the thermal imaging of the supraclavicular fat. Although LCHF diet has been used extensively in the medical literature since 1920s, there is no direct study to measure its activity on the effect of BAT. Animal studies which involved biopsy of the fat pads after an experimental phase of LCHF have proven increment of BAT and browning of white adipose tissue (WAT) through the abundance of newly formed mitochondria. The LCHF diet has been proven to reduce insulin resistance and visceral fat, while increasing adipokines, thermogenin, irisin, basal metabolism rate (BMR) and resting energy expenditure (REE). This favors the increment of BAT in the body which is dormant in non-paediatric populations who consume carbohydrate rich and energy abundant staple food. Currently, the conventional way of BAT imaging relies on the 18-FDG PET scan. However, this modality is relatively expensive and invasive. The IRTI seems to be a growing modality of interest amongst both the clinicians and researchers alike. The IRTI could be facilitated well as the most superficial anatomical landmarks of the BAT are at the supraclavicular area. This too without the need of a contrast and a radionuclide, could

be easily stimulated via sympathetic activation of the body or situations that mimic it such as cold thermogenesis.

1.3 Objective of Study

The objectives of this study are:

1. To perform bio-sampling data collection on subject undergoing both LCHF and unrestricted normal diet (UND) during four separate point of study
2. To determine Brown Adipose Tissue (BAT) thermal heat dispersion area increment over the supraclavicular (SPCV) area with LCHF diet using infrared thermal imaging technique
3. To conduct statistical analysis between parameters obtained from bio-sampling and thermal properties extracted from thermal images.

1.4 Scope of Study

The scope of the study involves evaluation of brown adipose tissue (BAT) activation and changes upon induction of a ketotic state of the body. This was carried out on healthy subjects where body re-composition was expected via lowering of visceral fat, body fat and insulin resistance. It is postulated that the browning of white adipose tissue (WAT) would then take place. The evaluation of BAT was done at the supraclavicular (SPCV) where it is the most superficial anatomical landmark. A cold protocol in the thermal lab stimulates the BAT to produce heat signal and this was captured by the thermal camera.

1.5 Significance of Study

Among the anticipated beneficial outcomes from this research are:

1. To promote wider usage of IRTI as it is cheaper and non–invasive when compared with 18FDG-PET Scan to determine BAT
2. To promote the safety, ease, feasibility and personalization in applying LCHF in the outpatient setting
3. To create awareness and promote usage of LCHF to reduce BMI, visceral fat, in translation as a means to curb obesity.

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