



UNIVERSITI PUTRA MALAYSIA

***EVALUATION OF HYPERTENSION AND DIABETES RISK FACTORS
AND THE EFFECTS OF OMEGA-3 FATTY ACIDS AND VITAMIN C ON
INFLAMMATORY MARKERS IN HYPERTENSIVE AND DIABETIC
OBESE ADULTS IN PALESTINE***

MOHAMMED S. S. ELLULU

FPSK(p) 2015 30



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ADULTS IN PALESTINE**

By

MOHAMMED S. S. ELLULU

**Thesis Submitted to the School of Graduate Studies, Universiti Putra
Malaysia, in Fulfilment of the Requirements for the Degree of Doctor of
Philosophy**

December 2015

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Abstract of thesis presented to the Senate of Universiti Putra Malaysia in fulfillment of the requirement for the degree of the Doctor of Philosophy

EVALUATION OF HYPERTENSION AND DIABETES RISK FACTORS AND THE EFFECTS OF OMEGA-3 FATTY ACIDS AND VITAMIN C ON INFLAMMATORY MARKERS IN HYPERTENSIVE AND DIABETIC OBESE ADULTS IN PALESTINE

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December 2015

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Obesity or an increase in body adiposity has been envisaged by WHO as the fifth leading risk of global deaths. It was well associated with metabolic disorders as hypertension (HT) and type-2 diabetes (T2DM). Adipose tissue plays an active role in endocrine function by secreting adipokines that involve inflammatory and anti-inflammatory cytokines. A cross-sectional study involved 484 adult subjects in seven primary healthcare centers in Gaza City, Palestine, was carried out to determine whether the alteration of inflammatory indicators was associated with obesity and/or disease conditions. After that, 108 obese patients of HT and/or T2DM were selected from the cross-sectional part and assigned into three equal groups (each group 36 patients); Control, Vitamin C (1 gram/daily), and Omega-3 FAs (0.5 gram/daily) via a randomized controlled trial (RCT); in order to identify the effects of intervention factors on inflammatory and metabolic markers. The results of cross-sectional part indicated that obesity was the main risk factor associated with alteration of Adiponectin, C reactive protein (CRP), and interleukin 6 (IL-6). Uncontrolled HT and T2DM were also risk factors associated with Adiponectin and CRP alteration. In the RCT part, balance was achieved between the groups and the confounders were neutralized at the randomization time. 95 (88%) patients were completed to final analysis. Within Vitamin C group, the significant reductions ($P < 0.05$) were detected for CRP [from 14.86 ± 9.20 to 7.74 ± 4.53 mg/L], IL-6 [from 2.20 ± 0.75 to 1.40 ± 0.53 pg/mL], fasting blood glucose (FBG) [from 188.13 ± 81.24 to 126.16 ± 34.06 mg/dL], and triglyceride (TG) [from 223.81 ± 87.88 to 155.10 ± 48.12 mg/dL]. Within Omega-3 FAs group, the significant changes ($P < 0.05$) were detected for CRP [from 14.78 ± 10.73 to 8.49 ± 6.69 mg/L], FBG [from 178.13 ± 58.5 to 157.32 ± 59.7 mg/dL], and TG [from 209.23 ± 108.3 to 167.0 ± 79.9 mg/dL]. Within control group, the significant changes ($P < 0.05$) were detected for FBG [from 187.15 ± 64.8 to 161.91 ± 37.9

mg/dL] and TG [from 202.91 ± 107.0 to 183.45 ± 95.82 mg/dL]. In conclusion, at the endpoint, repeated comparisons between the groups detected the efficacy of Vitamin C on CRP, IL-6, and FBG, meaning that Vitamin C supplementation has treating effects while Omega-3 FAs supplementation has protective effect.



Abstrak tesis dikemukakan kepada Senat Universiti Putra Malaysia sebagai memenuhi keperluan untuk Ijazah Doktor Falsafah

PENILAIAN FAKTOR RISIKO HIPERTENSI DAN DIABETES DAN KESAN ASID LEMAK OMEGA-3 SERTA VITAMIN C KEATAS PENANDA KERADANGAN DI DALAM INDIVIDU DEWASA YANG OBES SERTA HIPERTENSI DAN DIABETES DI PALESTIN

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Obesiti atau peningkatan adipositi badan telah diramalkan oleh WHO sebagai risiko kelima penyebab kematian global. Ianya sering dikaitkan dengan gangguan metabolik sebagai hipertensi (HT) dan diabetes jenis-2 (T2DM). Tisu adipos memainkan peranan aktif dalam fungsi endokrin dengan merembeskan adipoksin yang terlibat dalam pengeluaran sitokin keradangan dan anti-radang. Kajian keratan rentas yang melibatkan 484 subjek dewasa di tujuh pusat penjagaan kesihatan utama di bandar Gaza, Palestin, telah dijalankan bagi menentukan samada perubahan penanda keradangan mempunyai kaitan dengan obesiti dan/atau status penyakit. Seterusnya seramai 108 subjek yang obes dan HT dan/atau T2DM telah dipilih daripada kajian keratan rentas dan dibahagikan kepada 3 kumpulan yang setara (setiap kumpulan dengan 36 pesakit); kawalan vitamin C (1gram/sehari) dan asid lemak omega-3 (0.5gram/sehari) melalui kajian kawalan rawak (RCT); bagi menentukan kesan faktor intervensi keatas penanda metabolik. Hasil kajian keratan rentas menunjukkan obesiti adalah risiko utama yang berkaitan dengan perubahan aras adiponektin, protein C-reaktif (CRP) dan interleukin-6 (IL-6). HT dan T2DM yang tak terkawal juga merupakan faktor risiko yang berkaitan dengan perubahan aras adiponektin dan CRP. Dalam kajian RCT, keseimbangan tercapai diantara kumpulan dan ralat telah dineutralkan semasa proses perawakan. Sejumlah 95 pesakit (88%) telah akhirnya selesai sehingga analisa terakhir. Penurunan yang signifikan ($p < 0.05$) bagi kumpulan vitamin C telah dikesan dengan aras CRP [daripada 14.86 ± 9.20 ke 7.74 ± 4.53 mg/L], IL-6 [2.20 ± 0.75 ke 1.40 ± 0.53 pg/mL], aras glukos puasa (FBG) [188.13 ± 81.24 ke 126.16 ± 34.06 mg/dL], dan trigliserid (TG) [223.81 ± 87.88 ke 155.10 ± 48.12 mg/dL]. Didalam kumpulan asid lemak omega-3, perubahan signifikan ($P < 0.05$) telah dikesan untuk aras CRP [14.78 ± 10.73 ke 8.49 ± 6.69 mg/L], FBG [178.13 ± 58.5 ke 157.32 ± 59.7 mg/dL], dan TG [209.23 ± 108.3 ke 167.0 ± 79.9 mg/dL]. Manakala, kumpulan kawalan perubahan signifikan ($P < 0.05$) hanya dikesan bagi aras FBG [187.15 ± 64.8 ke

161.91±37.9 mg/dL] dan TG [202.91±107.0 ke 183.45±95.82 mg/dL]. Kesimpulan akhir daripada kajian ini menunjukkan perbandingan berulang diantara kumpulan dengan mengesan efikasi vitamin C keatas CRP, IL-6 dan FBG, yang menunjukkan suplemen vitamin C berkesan dalam rawatan dan asid lemak omega-3 mempunyai kesan perlindungan.



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I certify that a Thesis Examination Committee has met on December 30, 2015 to conduct the final examination of Mohammed S.S. Ellulu on his thesis entitled "Evaluation of Hypertension and Diabetes Risk Factors and The Effects of Omega-3 Fatty Acids and Vitamin C on Inflammatory Markers in Hypertensive and Diabetic Obese Adults in Palestine" in accordance with the Universities and University Colleges Act 1971 and the Constitution of the Universiti Putra Malaysia [P.U.(A) 106] 15 March 1998. The Committee recommends that the student be awarded the Doctor of Philosophy.

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LIST OF ABBREVIATIONS

ATP	: Adult Treatment Panel
AHA	: American Heart Association
BP	: Blood Pressure
BMI	: Body Mass Index
CDC	: Center for Disease Control and Prevention
CRP	: C Reactive Protein
DM	: Diabetes Mellitus
DBP	: Diastolic Blood Pressure
FBG	: Fasting Blood Glucose
FAs	: Fatty Acids
hs-CRP	: High Sensitivity C Reactive Protein
IL-6	: Interleukin 6
IQR	: Interquartile range
LC <i>n</i> -3	: Long Chain Omega-3
MOH	: Ministry of Health (Palestine)
NCEP	: National Cholesterol Education Program
NHANES	: National Health and Nutrition Examination Survey
PUFAs	: Polyunsaturated Fatty Acids
SBP	: Systolic Blood Pressure
T2DM	: Type-2 diabetes mellitus
TC	: Total Cholesterol
TG	: Triglyceride
WC	: Waist Circumference
UNRWA	: United Nations for Relief and Works Agency
WHO	: World Health Organization

CHAPTER 1

INTRODUCTION

1.1 Background

Obesity is a worldwide public health issue; it is defined as abnormal or excessive fat accumulation. According to a report of 2014, there are 1.9 billion overweight adults in the world, and over 600 million of whom are obese [1]. Total body and abdominal obesity have well-known associations with all-cause mortality [2, 3], morbidity [4], disability, resulting in an unhealthy life-years with poor quality of life [5, 6], and increased healthcare cost [7, 8].

A report of the Prospective Studies Collaboration, with data from 900,000 participants and 57 prospective studies, found that obesity is associated with an increased mortality rate of vascular diseases, diabetes, renal, hepatic, respiratory diseases and cancer [3]. Obesity is also linked to higher rates of cardiovascular diseases (CVDs), cancer, osteoarthritis, gallbladder disease, sleep apnea, and certain psychological problems such as depression [9]. For a group of people whom ages ranged from age 18 to 80 years; the obese had an increased risk of becoming diseased by or die from a broad range of diseases [10].

Obesity is defined as “*abnormal or excessive fat accumulation in adipose tissue that may impair health*” [1], it is measured by using Body Mass Index (BMI) (weight (kg)/height (m²)) cut-point of 30. The prevalence of obesity increased in both developed and developing countries [11]. In the Eastern Mediterranean region, the status of obesity reached an alarming level [12], and in Palestine (both Gaza Strip and the West Bank), obesity was clearly visible according to “*First National Health and Nutrition Survey*” (1999-2000), the overall prevalence of overweight was 62.4%, and 24.4% of who were obese [13]. Specifically in Gaza Strip, 57.0%, 66.8%, and 67.5% indicated the prevalence of overweight people including obese in urban area, refugee camp, and rural area, respectively [14].

As a risk factor, obesity is the major contributor in the development of diabetes and CVDs [15]. Hence, in Palestine, the prevalence of obesity-linked diseases has increased including CVDs [14], metabolic diseases [16], and type-2 diabetes [17, 18]. In addition, obesity has the potentiality to generate oxidative stress and inflammation in healthy population [19, 20], and both of them can mediate the development of metabolic syndrome due to obesity [21, 22]. The inflammatory status and metabolic abnormalities become worse if obese subjects were having hypertension or diabetes [23-27].

The adipose tissue was considered a passive storage depot for fat in the past, and is now known to play an active role in metabolism. Among the recently discovered compounds expressed in human adipose tissue are the pro-inflammatory cytokine interleukin 6 (IL-6) and the Adiponectin which is totally

anti-inflammatory marker [28]. Moreover, IL-6 produced in the adipose tissue of healthy humans is released into the circulation inducing systemic inflammation, which is evaluated by the sensitive marker synthesized primarily by the liver C-reactive protein (CRP) [29]. Inflammation is linked strongly to increased morbidity and mortality [30], and it is accompanied with obesity and metabolic abnormalities featured by dyslipidemia and hyperglycemia to develop metabolic syndrome, coagulations, atherosclerosis, and coronary heart disease [23, 24, 31, 32].

On the other hand, the antioxidant defense factors become lower due to obesity and accumulation of fat [33], so, the nutritional intervention took greater attention in treating problematic conditions like inflammation in diabetic or CVD patients [34, 35]. Micronutrients like vitamins (E, D and C), trace elements like (Zink and Selenium), or certain unsaturated fatty acids were linked to improvement in the immune function by inhibiting the overexpression and synthesis of cytokines like IL-6 that generated due to obesity [36]. Hence, Omega-3 Fatty Acids (Omega-3 FAs) and Vitamin C were used to treat inflammation and metabolic dysregulation [35, 37]. The effect of Omega-3 FAs was observed on many health conditions; they could improve health by reducing the risks of cancers, CVDs, metabolic syndrome, atherosclerosis, hypertension and diabetes [38]. Similarly, Vitamin C has distinct effects on treating conditions like hypertension and CVDs [39, 40], and diabetes [41, 42]. Due to their capacity of treatment, Omega-3 FAs and Vitamin C supplementations were used to help against inflammation and metabolic abnormalities in different populations [43, 44]. Thus, in the present study, intervention of Vitamin C and Omega-3 FAs were used to treat inflammatory status characterized by increased CRP and IL-6, and reduce their consequences in obese patients diseased of hypertensive (HT) and/or diabetes type-2 (T2DM).

1.2 Problem statement

Many studies worldwide have indicated obesity as a risk factor in many diseases, which may lead to disability, and even death. Prevalence of obesity increased in both developed and developing countries, and the associated diseases such as cardiovascular diseases [45] and non-cardiovascular mortalities such as cancer [46] are the leading causes of death in the world, which strongly related to inflammatory markers especially IL-6 and CRP [47]. However, studies on the relationship between the adiposity on adults and inflammatory markers needed more attention. Related studies like Klisic *et al.* [48], Dayal *et al.* [49], Thompson *et al.* [50], Fontana *et al.* [51], and Ajani *et al.* [32] addressed the link between obesity and inflammatory markers in one aspect without considering the variables related strongly with the indicators of inflammation, like social factors, lifestyle habits, and health state. Moreover, the previous studies did not address the comprehensive interrelationship between inflammatory, anti-inflammatory, metabolic markers and blood pressure, which may illustrate and clarify the degree of risks in healthy and unhealthy subjects. In addition, it remains unclear whether the observed alterations in plasma cytokines and/or inflammatory markers in diseased population like diabetes are

due to excess adipose tissue mass and/or directly associated with the diabetic state [52].

On the other hand, different studies attempted to find solutions for problematic health status, but few of them help in correcting the risk factors, at the time, inflammatory markers are not yet considered applicable for routine risk assessment due to the lack of measurement standardization, and lack of consistency in epidemiological findings from prospective studies with endpoints [53]. Furthermore, prior prospective studies have assessed the associations of Omega-3 FAs and Vitamin C with biomedical data in different diseases, the majority of these studies assessed estimated dietary intake through the use of questionnaires with conflicting results [54], or by using cross-sectional estimation [55]. Such dietary estimates limited separate assessment of individual intake, which may have differing effects [56], and stated a question about the efficacy of intervention [57].

Moreover, the studies depended on randomized controlled trials (RCTs) provided inconsistent recommendation, and they have not identified a unique dose and the needed duration interval of treatment to help reduce inflammation and associated risks [44]. Additionally, the studies depended on RCTs majorly evaluate the effects of intervention by calculating the change resulted on parameter by before and after test, and little of them directed to evaluate the clinical significance by evaluating the difference between the groups after the treatment like Shaikh *et al.* [58] and Samimi *et al.* [59].

1.3 Significance

The inflammatory condition is used frequently to predict many diseases might affect the quality of life. The proposed topic of investigation as the findings from this study would provide more understanding on the relationship of inflammatory and anti-inflammatory markers with high BMI among healthy and unhealthy subjects. The study also sheds light on the impact of various lifestyle factors; such as smoking and physical activity, as well as socio-demographic variables such as education, number of family members, and menopause status (in females). Furthermore, it identifies the association of inflammatory indicators including IL-6, CRP and Adiponectin with metabolic markers including fasting blood glucose (FBG), total cholesterol (TC), and triglyceride (TG), as well as the measure of systolic blood pressure (SBP) and diastolic blood pressure (DBP) based on health status as illustrated in the conceptual framework of the study in Figure 1.1.

The study focuses on suitable interventions to reduce inflammation by decreasing the level of CRP and IL-6 through supplementing Omega-3 FAs and Vitamin C. The outcomes of this study provide the baseline data for further interventional studies in inflammatory markers among obese adults. Findings of the survey also serve as recommendation to related organizations on effective lifestyle modification strategies for reducing the risks of obesity related inflammation. Thus, the current study contributes to the clinical and epidemiological aspects of nutritional science database regarding the relation

of high BMI with IL-6, CRP and Adiponectin, and the possible ways of intervention. In addition, the selection of Vitamin C and Omega-3 FAs as intervention factors depended on the difference of physiological mechanism of action on inflammatory and metabolic markers, which can provide a distinct distinguishing between two different nutritional interventions.

1.4 Objectives

The main objective of the study is:

To elucidate the effects of Omega-3 Fatty Acids and Vitamin C on inflammatory markers in hypertensive and/or diabetic obese patients.

The specific objectives are:

1. To identify the impact of obesity and health status on biomedical data.
2. To evaluate the differences of biomedical data according to lifestyle habits and socio-demographic factors.
3. To assess the interrelationships of inflammatory indicators, metabolic markers, and blood pressure.
4. To predict risk factors associated with inflammation.
5. To determine the effect of Omega-3 FAs and Vitamin C on metabolic markers.

1.5 Hypotheses

1. Obesity and health status have significant effect on inflammation and metabolic abnormalities.
2. Omega-3 FAs and Vitamin C improve significantly the inflammatory and metabolic markers.

1.6 Conceptual Framework of the study

Different factors give rise to serum level of inflammatory markers (CRP and IL-6), and reduce the level of Adiponectin with regards to the identified problem, which indicated insufficient knowledge on treating the elevated levels of inflammatory markers in unhealthy obese subjects in the described setting of the present study, the following conceptual framework (Figure 1.1) was developed.

As illustrated in Figure 1.1, serum level of CRP, IL-6 and Adiponectin are affected by four major categories of risk factors, including individual's lifestyle, involvement of obesity, current health status, and socio-demographic variables.

Epidemiological studies indicated many diseases would develop by an elevated level of IL-6 and CRP as heart diseases, cancer, diabetes, and hypertension [9], but few of them explained the causes of elevation. Kushner [60] illustrated that the serum level of CRP could elevate due to inflammatory or non-inflammatory physiological response, however; it may also be a marker of biologic aging, a condition known to predispose to poor prognoses and to death. According to that, the proposed variables affecting majorely the IL-6, CRP and Adiponectin and other biomedical data including FBG, TC, TG and BP could be classified into four groups as follow:

1. Inflammatory history including infections and injuries.
2. Lifestyle risk factors: smoking, physical inactivity and stress.
3. Related diseases: diabetes and hypertension.
4. Obesity status: high measure of BMI (≥ 30 kg/m²) and high measure of WC (≥ 102 cm for male and ≥ 88 cm for female).

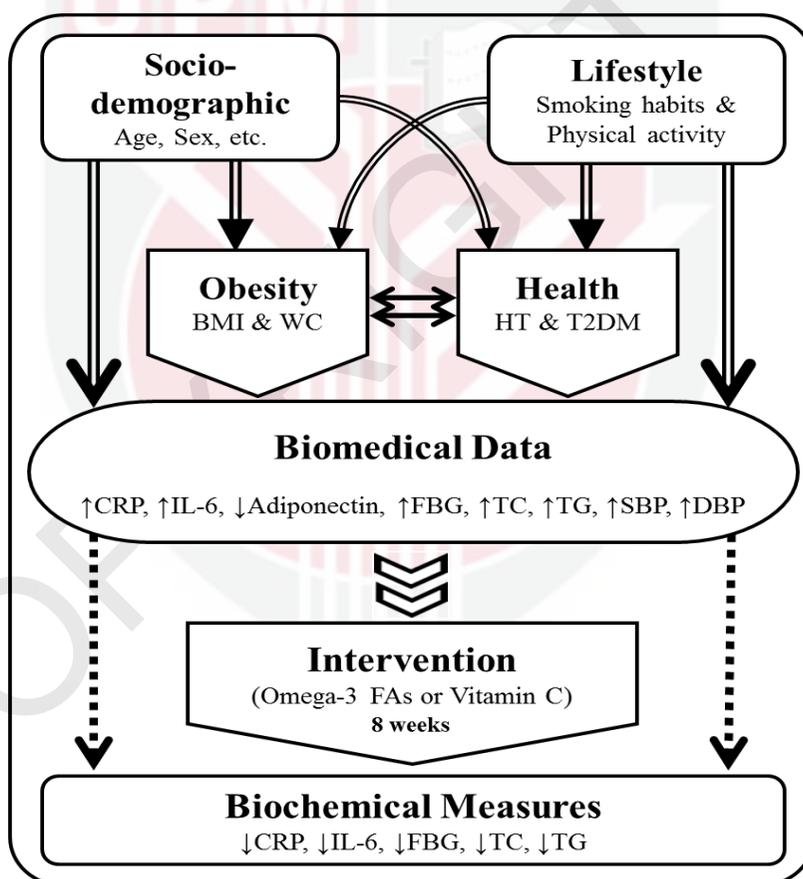


Figure 1.1 Conceptual Framework of the Study

Two un-related group factors have the direct effects on obesity and health status, as the risk factors were found to change biomedical data negatively including inflammatory indicators: (1) socio-demographic factors including sex,

age, education, marital status, and menopause, (2) lifestyle factors including physical activity, and smoking habits. Two related groups have also the direct effects on changing biomedical data, they are: (1) obesity components including physical factors, height and weight expressed by BMI, and waist circumference, (2) medical history of participants including the current health status like hypertension, diabetes, or healthy. Biomedical data including FBG, TC, TG, and blood pressure are the main variables related to CRP, IL-6 and Adiponectin.

Intervention factors including Omega-3 FAs and Vitamin C are related directly to biomedical data, and indirectly with characteristics and groups affecting biomedical data. Biochemical measures including CRP, IL-6, FBG, TC, and TG are factors affected by the intervention. Finally, it's worth noting that due to limitations of the present study; only a limited number of socio-demographic and lifestyle variables were included in the analysis.

1.7 Operational definitions

- **Inflammatory indicators:** a statement refers to a set of inflammatory markers (interleukin 6 and C reactive protein), and anti-inflammatory marker (Adiponectin).
- **Metabolic markers:** a statement refers to a set of fasting blood glucose and lipid profile (total cholesterol and triglyceride).
- **Biochemical measures:** a statement refers to a group of blood biomarkers that involved inflammatory indicators and metabolic markers.
- **Biomedical data:** a statement refers to a constellation of biochemical measures and blood pressure (systolic and diastolic).

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