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METABOLIC SYNDROME AND ITS RELATIONSHIPS WITH ADIPONECTIN, VITAMIN D AND PHYSICAL ACTIVITY AMONGADULTS IN AN INSTITUTE OF HIGHER LEARNING IN THE UNITED ARAB EMIRATES

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UNIVERSITI SAINS MALAYSIA

2017

METABOLIC SYNDROME AND ITS RELATIONSHIPS WITH ADIPONECTIN, VITAMIN D AND PHYSICAL ACTIVITY AMONG ADULTS IN AN INSTITUTE OF HIGHER LEARNING IN THE UNITED ARAB EMIRATES

by

HAYDER ABBAS HASAN

Thesis submitted in fulfillment of the requirement

for the degree of

Doctor of Philosophy

March 2017

DECLARATION

I hereby declare that this thesis is my original work except for the quotations and citations which have been duly acknowledged. I also declare that it has not been previously and is not currently submitted for any other degree or purpose in the Universiti Sains Malaysia or at any other institution.

Hayder Abbas Hasan

DEDICATION

I dedicate this humble work to my beloved wife Elham Kotubi, to the spring of loyalty, affection and virtue, my mother and to the soul of my father; and to my children

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LIST OF ABBREVIATIONS

BMI	Body mass index
CDC	Centers for Disease Control and Prevention
CI	Confidence interval
DBP	Diastolic blood pressure
EBBS	Exercise Benefits/Barriers Scale
FFM	Fat free mass
H_0	Null Hypothesis
H_a	Alternative Hypothesis
HDL-C	High-density lipoprotein-cholesterol
HMW	High molecular weight
HOMA-IR	Homeostasis model assessment of insulin resistance
IDF	International Diabetes Federation
IFG	Impaired fasting glucose
IGT	Impaired glucose tolerance
IL	Interleukin
LDL-C	Low-density lipoprotein-cholesterol
MetS	Metabolic syndrome
NCDs	Non-communicable diseases
OR	Odds ratio
PAI-1	Plasminogen activator inhibitor-1
PBF	Percentage body fat

RAS	Renin- angiotensin system
SBP	Systolic blood pressure
SNPs	Single nucleotide polymorphisms
TG	Triglycerides
TNF-α	Tumor necrosis factor-alpha
VDR	Vitamin D receptor
VFA	Visceral fat area
WC	Waist circumference
WHO	World Health Organization
WHR	Waist-hip ratio

SINDROM METABOLIK DAN PERKAITANNYA DENGAN ADIPONEKTIN, VITAMIN D DAN AKTIVITI FIZIKAL DALAM KALANGAN ORANG DEWASA DI SEBUAH INSTITUSI PENGAJIAN TINGGI DI EMIRIAH ARAB BERSATU

ABSTRAK

Sindrom metabolik (MetS) adalah kelompok faktor risiko penyakit kardiovaskular dan diabetes jenis 2. Ia dikaitkan dengan disfungsi tisu adipos akibat dari obesiti, satu fenomena global berkaitan gaya hidup yang sedang meningkat. Sementara itu, hypovitaminosis D semakin mendapat perhatian selain kesan klasik pada tulang. Faktor gaya hidup, biokimia dan genetik dihipotesis untuk menyumbang kepada patofisiologi MetS . Tujuan kajian ini adalah untuk mengkaji hubungan MetS dan komponennya dengan adiponektin, vitamin D, polimorfisme gen VDR, dan aktiviti fizikal. Kajian ini telah dijalankan dari tahun 2012 hingga 2015 dalam 2 fasa (P-1 dan P-2). P-1 (keratan rentas): Seramai 235 orang dewasa (64 lelaki dan 171 wanita) dari komuniti Universiti Sharjah telah diambil menyertai kajian. Pengukuran antropometri, ujian biokimia (glukosa, insulin, profil lipid, vitamin D dan HMW adiponektin) dan analisis genetik (untuk polimorfisme gen VDR: Taqii, FokI, dan BsmI) telah dijalankan. Profil demografi, pengambilan diet (kekerapan makanan semi-kuantitatif) dan persepsi senaman (skala faedah Senaman / halangan) telah digunakan. P-2 (intervensi): Seramia 52 peserta wanita memakai pedometers untuk 9 minggu selepas sesi pendidikan dengan matlamat untuk mencapai 10,000 langkah setiap hari. Semua parameter asas telah dinilai semula selepas intervensi. Prevalens Sindrom metabolik adalah 17.5%; lebih tinggi pada

lelaki (OR = 10.97, 95% CI: 5.1-23.61, p <0.001) dan orang dewasa berumur 40 tahun ke atas (OR = 9.59, 95% CI: 3.98-23.1, p <0.001). HMW adiponektin adalah lebih tinggi dalam kalangan wanita dan mereka yang tidak mempunyai MetS ; ia berkait secara langsung dengan HDL-kolesterol dan berkait secara songsang dengan ukuran obesiti dan tekanan darah. Tahap Vitamin D adalah 22.49 (19.6) nmol/L dan hanya 9.8% mempunyai tahap yang optimum. Vitamin D adalah lebih rendah secara ketara pada wanita [26.6 (13.58) nmol/L vs 34.03 (21.34) nmol/L, p <0.001] dan peserta tanpa MetS [29.6 (18.75) nmol/L vs 21.06 (19.1) nmol/L, p <0.001] berbanding peserta lain. Kejadian MetS adalah bebas daripada status vitamin D (OR = 1.78, 95% CI: 0.65-4.84, p = 0.25). Tiga reseptor polimorfisma gen vitamin D tidak menunjukkan hubungan dengan Sindrom metabolik. Walau bagaimanapun, polimorfisme Foki dan allele F pada wanita dikaitkan dengan tekanan darah sistolik lebih tinggi. Peserta melaporkan nisbah persepsi faedah / halangan latihan pada nilai 1.48. Peserta berjalan sebanyak 7056 ± 1570 langkah setiap hari, mencatatkan peningkatan marginal pada akhir minggu ke 9. Pengurangan kecil tetapi ketara diperolehi dalam hampir semua parameter antropometri dan LDL-kolesterol (63.8 ± 18.04 mg/dl vs 59.17 ± 18.61 mg/dl; p = 0.01), manakala peningkatan sebanyak HMW adiponektin (4.08 ± 0.55 µg / ml vs 4.15 ± 0.53 µg / ml; p = 0.03) diperolehi. Hubungan songsang antara bilangan langkah dan pengukuran obesiti, dan hubungan positif dengan tahap HMW adiponektin telah dilihat dengan nyata. Walaupun bilangan langkah dalam kalangan peserta indeks jisim tubuh (IJT) normal adalah lebih tinggi (7488.49 ± 1098) daripada peserta yang lebih tinggi IJT (6739.18 ± 1793), bagaimanapun, peningkatan yang ketara dicatatkan pada lebih banyak varibel komposisi badan dalam peserta dengan IJT lebih tinggi berbanding peserta yang mempunyai BMI normal . Begitu juga dengan peningkatan yang ketara dalam profil

biokimia diperolehi dalam peserta dengan IJT tinggi sahaja pada nilai trigliserida (71.62 ± 29.22 – 62.50 ± 29.16 mg/dl, p = 0.003) dan tahap insulin (21.7 ± 8,33-18,64 ± 8.25 μU/L, p = 0.046) dan peningkatan dalam HMW adiponectin (3.77 ± 0.46 – 3.80 ± 0.44 μg/ml, p = 0.034). Kesimpulannya, prevalen MetS adalah 17.5%, yang lebih ketara pada lelaki. HMW adiponektin boleh memainkan peranan dalam kejadian MetS manakala vitamin D dan polimorfisme gen VDR boleh menjejaskan komponen MetS. Para peserta terdiri daripada "rendah aktif", walaupun berpersepsi lebih banyak manfaat senaman daripada halangan. Peningkatan nominal yang minima dalam aktiviti fizikal boleh memodulasi ukuran obesiti, HMW adiponektin dan profil lipid yang seterusnya mengurangkan risiko kardiovaskular, terutama dalam kalangan individu yang berlebihan berat badan/obes.

METABOLIC SYNDROME AND ITS RELATIONSHIPS WITH ADIPONECTIN, VITAMIN D AND PHYSICAL ACTIVITY AMONG ADULTS IN AN INSTITUTE OF HIGHER LEARNING IN THE UNITED ARAB EMIRATES

ABSTRACT

Metabolic syndrome (MetS) is a cluster of risk factors for cardiovascular disease and type 2 diabetes. It is associated with adipose tissue dysfunction resulting from obesity, an escalating global phenomenon related to lifestyle. Meanwhile, hypovitaminosis D is gaining attention beyond the classical effects on the skeleton. Lifestyle, biochemical and genetic factors are hypothesized to contribute to the pathophysiology of MetS. The aim of this study was to examine the relationships of MetS and its components with adiponectin, vitamin D, VDR gene polymorphisms, and physical activity. The study was conducted from year 2012 until year 2015 in 2 phases (P-1 and P-2). P-1 (cross-sectional): A total of 235 adults (64 males and 171 females) from the University of Sharjah community were recruited. Anthropometric measures, biochemical tests (glucose, insulin, lipid profile, vitamin D and HMW adiponectin) and genetic analyses (for VDR gene polymorphisms: TaqI, FokI, and BsmI) were performed. Demographic profile, habitual dietary intake and exercise perception (Exercise benefits/barriers Scale) were used accordingly. P-2 (interventional): A total of 52 female participants wore pedometers for 9 weeks after an educational session and goal setting of 10,000 steps per day. All baseline parameters were reassessed post-intervention. The prevalence of MetS was 17.5%; higher in males (OR=10.97, 95%CI: 5.1-23.61, $p < 0.001$) and adults above 40 years old (OR=9.59, 95%CI: 3.98-23.1, $p < 0.001$). HMW adiponectin was higher in females and in those without MetS; being directly correlated with HDL-cholesterol and inversely correlated with obesity measures and blood

pressure. Vitamin D level was 22.49(19.6) nmol/L and only 9.8% had an optimal level. Vitamin D was significantly lower in females [26.6(13.58) nmol/L vs. 34.03(21.34) nmol/L, $p < 0.001$] and in those without MetS [29.6(18.75) nmol/L vs. 21.06(19.1) nmol/L, $p < 0.001$] than their counterparts. MetS occurrence was independent of vitamin D status (OR=1.78, 95%CI: 0.65-4.84, p=0.25). The three vitamin D receptor gene polymorphisms did not show any relationship with MetS. However, FokI polymorphisms and F allele in females were associated with higher systolic blood pressure. The participants reported exercise perception benefit/barrier ratio of 1.48. The participants walked 7056±1570 steps per day, recording a marginal increase toward the end of week 9. Small, though, significant reductions were noted in almost all anthropometric parameters and LDL-cholesterol (63.8±18.04 mg/dl vs. 59.17±18.61 mg/dl; p=0.01), while an increase of HMW adiponectin (4.08±0.55 µg/ml vs. 4.15±0.53 µg/ml; p = 0.03) was obtained. An inverse relationship between the number of steps and obesity measures, and positive relation with HMW adiponectin level were evident. While the number of steps in normal body mass index (BMI) participants was marginally higher (7488.49±1098) than those with higher BMI (6739.18±1793), however, significant improvement was recorded in more measures of body composition variables in participants with higher BMI than those with normal BMI. Similarly, significant improvement in biochemical profiles were observed in participants with high BMI on the level of triglycerides (71.62±29.22 to 62.50±29.16 mg/dl, p=0.003) and insulin levels (21.7±8.33 to 18.64±8.25 µU/l, p=0.046) and increase in HMW adiponectin (3.77±0.46 to 3.80±0.44 µg/ml, p=0.034). In conclusion, the prevalence of MetS was 17.5%, being more common in males. HMW adiponectin could play a role in the development of MetS while vitamin D and VDR gene polymorphisms could affect

the components of MetS. The participants were “low active”, though perceived more benefits of exercise than barriers. Minimum nominal increase in physical activity can modulate obesity measure, HMW adiponectin and lipid profile with a possible subsequent decrease of cardiovascular risks, particularly in overweight/obese individuals.

CHAPTER 1

INTRODUCTION

1.1 Background

Overweight and obesity are becoming major global health problems, which may look like an unstoppable phenomenon. Worldwide, more than one billion adults are overweight and 500 million are obese (World Obesity Organization, n.d.). They predispose to non-communicable diseases (NCDs), which include cardiovascular diseases, stroke, type 2 diabetes mellitus and certain types of cancer. These NCDs cause massive human loss through disabling and killing people in their productive ages i.e. premature death (before they reach the age of 70 years) (WHO, 2015). Despite the global efforts for the prevention of NCDs, they are still the leading causes of death in many countries (Beaglehole et al., 2011). Around 2.2 million die each year from NCDs in countries of the Eastern Mediterranean Region and without effective steps, it is expected that this number will reach to 4 million in 2030 (WHO, 2015). The latest Global Status Report on non-communicable diseases of the World Health Organization (WHO) indicated that smoking, alcohol consumption, obesity, low physical activity, elevated blood pressure and dyslipidemia are important risk factors for NCDs in which cardiovascular diseases and type 2 diabetes mellitus make most of the load (World Health Organization, 2014).

The United Arab Emirates is one of the countries of the Eastern Mediterranean Region (WHO, n.d.). It is one of the rapidly developing countries (Gardner and Howarth, 2009) and it became a modern and wealthy country with a Western lifestyle.

The country comprises of a multinational population with a variety of educational backgrounds, religious beliefs and cultural practices (Loney et al., 2013). In the United

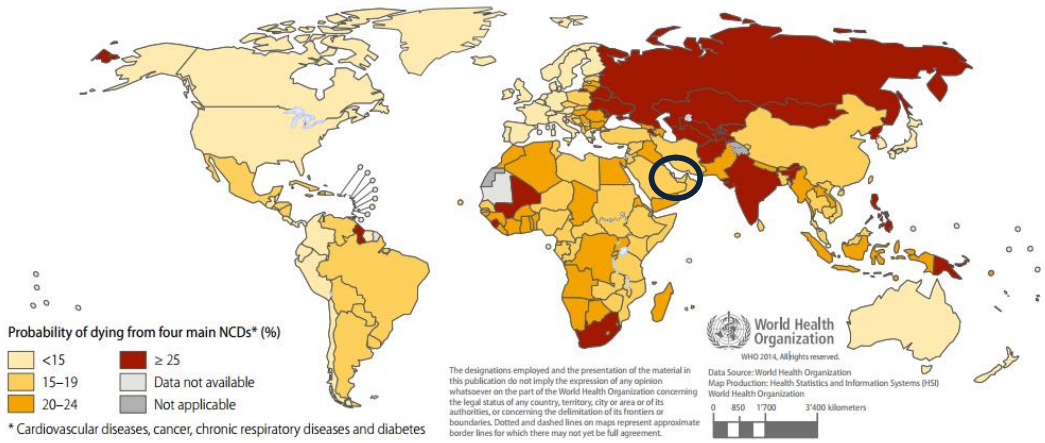

Figure 1.1 Probability of dying from the four main non-communicable diseases between the ages of 30 and 70 years, comparable estimates, 2012 (World Health Organization, 2014)

Arab Emirates, lifestyle changes have been the highlight of debate during the last decades. High incomes with increased consumption of fast food including sugar loaded drinks combined with low levels of physical activity have put the United Arab Emirates population at high risk for obesity and its related co-morbidities (Loney et al., 2013). Recently, a screening program called "Weqaya" has been launched in the United Arab Emirates. It is a screening program for the health status of individuals in order to provide a proper follow up in the event of being affected by or at risk of developing cardiovascular disease and diabetes or having the risk factors associated with these preventable diseases (Health Authority of Abu Dhabi, n.d.). Results from Weqaya showed that the risk factor prevalence rates were as follows: obesity, 35%; overweight,

32%; central obesity, 55% (Hajat et al., 2012). This rapidly increasing incidence of obesity is associated with 37% and 4% of total deaths because of cardiovascular diseases and type 2 diabetes mellitus respectively (World Health Organization, 2014).

Metabolic syndrome is a bunch of risk factors for the development of cardiovascular diseases and type 2 diabetes mellitus of metabolic origin ("Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report.," 2002). Typically, metabolic syndrome includes a group of components such as obesity, high blood pressure, high blood sugar, and dyslipidemia. Other risk factors for the development of metabolic syndrome include increasing age, changes in the levels of male, female and stress hormones, physical inactivity and genetic predisposition (MedlinePlus, n.d.). However, metabolic syndrome is not a new concept, but it has received a lot of attention in the past few years probably because of the high prevalence of cardiovascular diseases and type 2 diabetes mellitus.

Obesity, which is an important component of metabolic syndrome, is marked by excessive accumulation of fat in the adipose tissue. Currently, adipose tissue is widely accepted as an active and dynamic tissue with endocrine functions (Kershaw and Flier, 2004; Scherer, 2006) rather than just a storage depot. Recent progress in the research about the metabolic properties of the adipose tissue and the discovery of its ability to produce biologically active molecules known as "adipocytokines, is rebuilding the concepts about adipose tissue biology and opens the gate to study the role of adipose tissue in metabolic syndrome.

The adipocytokines are produced by the adipocytes and macrophages of the adipose tissue and are engaged in many physiological and pathophysiological processes (Rasouli and Kern, 2008). In obesity, there is an alteration in the metabolic and endocrine functions of adipose tissue that leads to a change in the levels of the adipocytokines. Hence, the adipocytokines are proposed to be important determinants of obesity associated complications such as insulin resistance (Xu et al., 2003), type 2 diabetes mellitus (Rajkovic et al., 2014)`and atherogenic dyslipidemia (Ha et al., 2014). Also, the adipocytokines were suggested to be involved in hypertension, cardiovascular diseases (Hubert et al., 1983) and certain types of cancers (Calle et al., 2003). Examples of the adipocytokines are adiponectin, leptin, resistin, tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), angiotensinogen and plasminogen activator inhibitor-1 (PAI-1) and many more.

Adiponectin is the most abundant and relatively new adipocytokine that is exclusively secreted by the adipocytes (Scherer et al., 1995). It exhibits insulin-sensitizing, fat-burning (Yamauchi et al., 2001), anti-atherogenic (Shimada et al., 2004) and anti-inflammatory properties (Ouchi et al., 2003). It is distinct from other adipocytokines in that adipose tissue production and circulating level of adiponectin is decreased with obesity. In addition, low level of adiponectin in healthy individuals is linked to increased risk of cardiovascular events (Pischon et al., 2004). The levels of adiponectin were found to be affected by genetic factors (Yamamoto et al., 2002), ethnicity (Martin et al., 2008; Pereira et al., 2011), dietary fat content (Barnea et al., 2006), exercise (Lee et al., 2013) and drugs (Li et al., 2010; von Eynatten et al., 2009).

Vitamin D, vitamin D receptor (VDR) and the necessary enzymes which are engaged in the formation of the biologically active form of vitamin D [1,25(OH)2D], play an important role in the vitamin D endocrine system. This system is well known as a key player for the normal development and mineralization of a healthy skeleton. Non-classic effects of low level of vitamin D is being potentially associated with many conditions including hypertension, type 2 diabetes mellitus, common cancers and autoimmune diseases (Demay, 2006). Meanwhile, vitamin D deficiency has been identified as a pandemic and worldwide health problem, especially in the United Arab Emirates due to infrequent exposure to sunlight because of a change in the lifestyle of the local population (Al Anouti et al., 2011). Hence, vitamin D status may be related to metabolic syndrome development.

The increasing prevalence of obesity has been in part attributed to the changes in the lifestyle; dietary factors and physical activity patterns. Current evidence suggests that the increase in the prevalence of obesity occurs after or at the same time of decrease in physical activity (Wareham et al., 2005). Thus, physical activity was suggested to counteract the development of obesity and could improve the risk factors for cardiovascular diseases and type 2 diabetes mellitus and metabolic syndrome in turn. Moreover, physical activity can improve cardiorespiratory fitness with subsequent reduction of death from cardiovascular events, in another word being physically active may decrease the burden and hazard of obesity (Lee et al., 1999). Despite the known benefits of physical activity, still, there is a significant decrease in the level of physical activity which includes every day occupation-related (Church et al., 2011) and household management physical activity (Archer et al., 2013). This decline in energy expenditure substantially contributes to the increase of body weights for men and

women, and the Global Status Report (2014) indicates that the prevalence of insufficient physical activity in adults from the United Arab Emirates aged 18 years and over is 38.4% which necessitates an urgent interference (World Health Organization, 2014). Nevertheless, in order to plan an effective physical activity promotion programs, sufficient evidence of individuals' attitudes toward engagement in physical activity program is required. So far, only one study has examined barriers towards physical activity in patients with type 2 diabetes mellitus in the United Arab Emirates (Al-Kaabi et al., 2009). Therefore, it is important to explore how the individuals perceive the benefits and barriers to exercise.

1.2 Statement of Problem

Based on this background, it seems that the simultaneous increase in the prevalence of obesity, low level of physical activity and low blood levels of adiponectin and vitamin D, could contribute to the pathophysiology of metabolic syndrome.

Since the mid of the 1970s, the prevalence of obesity and its related disorders have increased in the population of the United Arab Emirates, with a subsequent increase in premature mortality. People who were obese and physically inactive with reduced vitamin D level and adiponectin were more prone to have metabolic syndrome.

In recent decades, many researchers showed interest in studying different aspects of metabolic syndrome. These include prevalence and incidence of metabolic syndrome and risks that lead to the development of other conditions such as type 2 diabetes mellitus, cardiovascular diseases, and stroke in an attempt to have a better understanding of the pathophysiology of development of the syndrome. Early identification of the risk

factors among adults from the United Arab Emirates may be useful in the improvement of the conditions associated with metabolic syndrome.

The best available treatment of metabolic syndrome is to prevent its occurrence by modification of the lifestyle, followed by identification and treatment of individual risk factors of metabolic syndrome in young population so as to prevent the development of cardiovascular diseases and type 2 diabetes mellitus with their complications later in life.

In spite of all the efforts in the understanding of metabolic syndrome, its risk factors and the possible management and its epidemiology among adults from the United Arab Emirates are largely indefinite. This study aimed at illustrating the prevalence and risk factors of metabolic syndrome among study population from the United Arab Emirates.

1.3 Objectives

1.3.1 General Objective

The objectives of this study were to examine the relationships of metabolic syndrome and its components with high molecular weight (HMW) adiponectin, vitamin D, and VDR gene polymorphisms, and to explore the effect of minimal physical activity on metabolic syndrome components.

1.3.2 Specific Objective

1. To determine the prevalence of metabolic syndrome and its individual components in adults from the United Arab Emirates using the International Diabetes Federation (IDF) criteria for the diagnosis of metabolic syndrome.
2. To investigating the relationships between high molecular weight adiponectin with the metabolic syndrome and its components in adults from the University of Sharjah, United Arab Emirates.
3. To assess the vitamin D status and to investigate the associations of vitamin D with metabolic syndrome and its components in adults from the University of Sharjah, United Arab Emirates.
4. To determine the associations between three (FokI, TaqI and BsmI) VDR gene polymorphisms and metabolic syndrome and its components in Arab adults from the University of Sharjah, United Arab Emirates.
5. To examine the perceived exercise benefits and barriers of adults from the University of Sharjah, United Arab Emirates using the Exercise Benefits/Barriers Scale (EBBS) questionnaire.
6. To examine the effects of steps counts (using pedometers) on metabolic syndrome components and HMW Adiponectin. Also, to compare the effect of steps counts in lean and overweight/obese participants.

1.4 Research questions

i. What is the prevalence of metabolic syndrome and its individual components in adults from the University of Sharjah, United Arab Emirates using the International Diabetes Federation (IDF) criteria for the diagnosis of metabolic syndrome?

ii. What are the relationships between high molecular weight adiponectin with the metabolic syndrome and its components in adults from the University of Sharjah, United Arab Emirates?

iii. What is the status of vitamin D in the study population?

iv. Is there any association between vitamin D and metabolic syndrome and its components?

v. Is there any association between three (FokI, TaqI and BsmI) VDR gene polymorphisms and metabolic syndrome and its components in Arab adults from the University of Sharjah, United Arab Emirates?

vi. How adults from the University of Sharjah, United Arab Emirates perceive the exercise benefits and barriers?

vii. What are the effects of steps counts on metabolic syndrome components and HMW Adiponectin?

viii. Do steps counts have different effects in lean and overweight/obese participants?

1.5 Research Hypothesis

$\mathbf{H_a}$: HMW adiponectin, vitamin D, and physical activity are associated with metabolic syndrome.

1.6 Significance of study

The findings of this study will have a direct influence on different stakeholders. For researchers, the data will add value to the pool of scientific evidence regarding the epidemiological aspects of metabolic syndrome in terms of obesity, insulin resistance, hypertension and lipid profiles amongst healthy young adults (population section with lesser health priorities) residing in the UAE. The insight on the differential analysis of metabolically healthy v/s metabolically unhealthy adults sheds new light on their body constitutional differences and association with metabolic syndrome. The focus on nutritional status, biochemical profiles and effect of physical activity will uncover important links of vitamin D, adiponectin and physical activity with metabolic syndrome components in young adults.

The translation of the results of this research will have an important bearing on the community, at large. The health policy makers will be able to emphasize on lifestyle improvement through promoting healthy diets and moderate physical activity as the mainstay of prevention strategies for metabolic syndrome. The role of vitamin D, in particular, in the health of the young adults will be addressed.

1.7 Conceptual framework

Figure 1.2 shows the possible mechanism of development of metabolic syndrome. The bad dietary habits together with the decrease in the levels of physical activity and genetic susceptibility contribute to increasing body weight i.e. overweight/obesity. The increase in body weight is mainly due to the accumulation of

excess fat particularly around the waist (central obesity), which is associated with adipose tissue dysfunction and decrease the bioavailability of vitamin D.

Adipose tissue dysfunction is characterized by increase production of almost all adipocytokines with the exception of adiponectin that shows reduced level with obesity. This is together with reduced serum levels of vitamin D can result in inflammation, which affects organs involved in the insulin sensitivity such as liver, skeletal muscles and adipose tissue and ultimately leads to insulin resistance.

Insulin resistance with its prominent feature of high serum levels of insulin could be the starting point in the development of the components of metabolic syndrome (atherogenic dyslipidemia, hyperglycemia, and hypertension) and eventually the metabolic syndrome with the increased risk of development cardiovascular disease and type 2 diabetes mellitus.

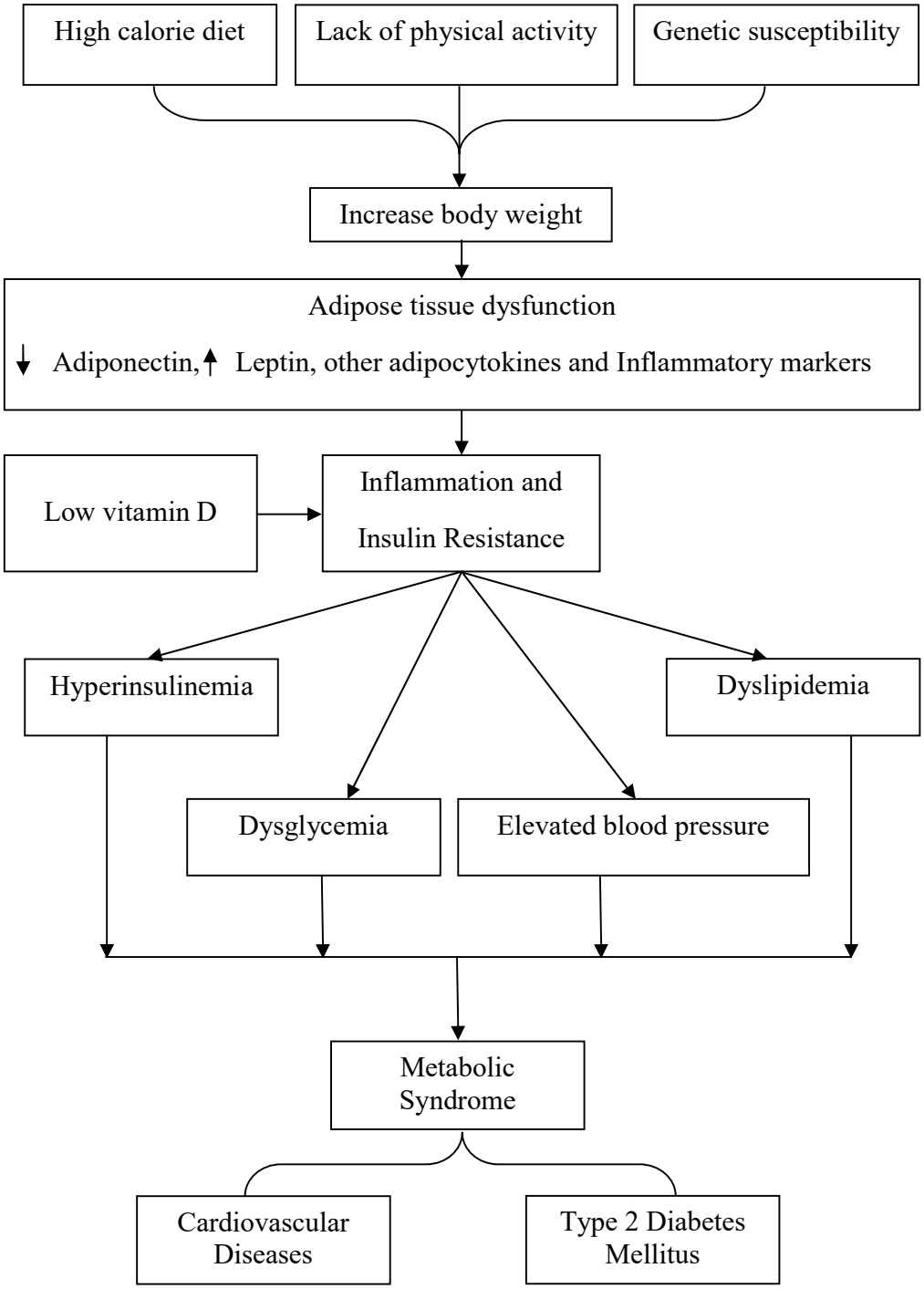

Figure 1.2 Possible mechanism of development of metabolic syndrome

CHAPTER 2

REVIEW OF LITERATURE

Metabolic syndrome has been described as a cluster of inter-related risk factors, the etiology of which is multifaceted (Reaven, 1988). The syndrome ultimately increases the risk of development of diabetes mellitus and cardiovascular diseases. This review is trying to shed light on the history, definitions, prevalence, and pathophysiology of metabolic syndrome and also to report what have been studied so far in relation to adiponectin, vitamin D, and physical activity.

2.1 Metabolic Syndrome

2.1.1 Metabolic syndrome definition and diagnostic criteria

In fact, as early as the 1920s Kylin (1923) reported the association of high blood glucose, high blood pressure, and high serum uric acid in certain groups of patients(as cited in Oladejo, 2011, p. 78). In 1947, Vague found that upper body obesity (android or male pattern) was associated with diabetes mellitus and cardiovascular diseases in contrast to the lower body obesity (gynecoid pattern)(as cited in Hanley & Wagenknecht, 2008, p. 1153). Afterward, Avogaro et al (1967) added obesity and hyperlipidemia to the three features described by Kylin (as cited in Haffner & Taegtmeyer, 2003, p. 1541). Haller (1977) used the term “metabolic syndrome” for patients having obesity, diabetes mellitus, hyperlipoproteinemia, hyperuricemia and hepatic steatosis. In addition to these risk factors, he reported that there is an increase of

blood viscosity with disturbances of coagulation that further increase risk of development of arteriosclerosis (Haller, 1977).

Later, Reaven (1988) suggested that insulin resistance and the consequent hyperinsulinemia could clarify the mechanism of the clustering phenomenon of the risk factors and he named it as “syndrome X” (Reaven, 1988). Ferrannini et al (1991) reported similar clustering of interrelated abnormalities (decreased insulin sensitivity, glucose intolerance, elevated blood pressure, increased body fat mass and distribution, and dyslipidemia) and concluded that insulin resistance underlined each and all of the abnormalities. Hence “insulin resistance syndrome” was proposed to be the suitable term for such clustering (Ferranniniet al., 1991).

In 1998, the World Health Organization (WHO) suggested the first definition of metabolic syndrome and in 1999 the WHO proposed the criteria of metabolic syndrome, which mandates the presence of insulin resistance for the diagnosis of metabolic syndrome. Accordingly, the diagnosis of metabolic syndrome can be made if there is type 2 diabetes mellitus, impaired fasting glucose (IFG), impaired glucose tolerance (IGT) or insulin resistance plus two other abnormalities (high blood pressure, dyslipidemia, obesity, and microalbuminuria) (WHO, 1999). In the same year the European Group for the study of Insulin Resistance (EGIR) defined insulin resistance syndrome as fasting hyperinsulinemia plus two additional abnormalities (high blood pressure, dyslipidemia, large waist circumference and high fasting blood glucose) (Balkau and Charles, 1999). In 2001, the National Cholesterol Education Program-Adult Treatment Panel III (NCEP-ATP III) suggested the presence of any three of the following for the diagnosis of metabolic syndrome: abdominal obesity, atherogenic

dyslipidemia, elevated blood pressure, insulin resistance (with or without glucose intolerance), and prothrombotic and proinflammatory states ("Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III).," 2001).

The American College of Endocrinology (ACE) /American Association of Clinical Endocrinologists (AACE) statement in 2003 suggested that the diagnosis of insulin resistance syndrome or metabolic syndrome should rely on clinical judgment and proposed the presence of at least one of the following factors: diagnosis of cardiovascular diseases, hypertension, family history of type 2 diabetes mellitus and hypertension, or cardiovascular diseases, non-Caucasian ethnicity, sedentary lifestyle, high body mass index and/or large waist circumference and age above 40 years, and at least two of the following criteria: high triglycerides (TG), low high-density lipoprotein-cholesterol (HDL-C), high blood pressure, high fasting blood glucose or postglucose challenge 140-200 mg/dl (Einhorn et al., 2003).

In spite of little difference in the prognostic implications when applying different definitions of metabolic syndrome (Hanley et al., 2005), the existence of numerous definitions of metabolic syndrome has led to a confusion, which made the International Diabetes Federation (IDF) to gather experts from different parts of the world to formulate a single definition, with generally accepted diagnostic criteria, that is easy to use in clinical practice. Moreover, because the problem of metabolic syndrome has reached at an alarming rate (estimated to be around 20–25% of the population) (Dunstan et al., 2002), the IDF suggested more strict criteria for the diagnosis of metabolic

syndrome. The IDF suggested five criteria for the diagnosis of metabolic syndrome and made abdominal obesity (large waist circumference) necessary plus the presence of any two of the following: high TG, low HDL-C, high blood pressure, high fasting blood glucose (Alberti et al., 2006). Table 2.1 summarizes selected definitions of metabolic syndrome established by different organizations and experts.

Table 2.1 Selected definitions for metabolic syndrome

		IDF	ACE/AACE	NCEP-ATP III	WHO	EGIR
Year		2006	2003	2001	1999	1999
Mandatory criterion		Central obesity	IGT or IFG	None	Insulin resistance	Hyperinsulinemia
Obesity		Central obesity (Large WC)*	BMI≥25 kg/m^2	Central obesity (Large WC)	Obesity (Large WHR) or BMI > 30 kg/m^2	Central obesity (Large WC)
	Male	≥ 94 cm		≥102 cm	> 0.9cm	≥ 94 cm
	Female	≥ 80 cm		≥88 cm	> 0.85	≥ 80 cm
Serum Triglycerides		≥150 mg/dl	≥150 mg/dl	≥150 mg/dl	≥150 mg/dl	≥ 177 mg/dl
Serum HDL-Cholesterol	Male	<40 mg/dl	<40 mg/dl	<40 mg/dl	≤35 mg/dl	< 39 mg/dl
	Female	<50mg/dl	<50mg/dl	<50mg/dl	≤39 mg/dl	< 39 mg/dl
Blood Pressure	Systolic	≥130 mmHg	≥130 mmHg	≥130 mmHg	≥140 mmHg	≥140 mmHg
	Diastolic	≥85 mmHg	≥85 mmHg	≥85 mmHg	≥90 mmHg	≥90 mmHg
Fasting Glucose		≥100 mg/dl	>110 mg/dl	≥110 mg/dl	DM, IGT, IFG or IR	≥110 mg/dl
Microalbuminuria	--	--	--	--	Urinary albumin excretion ratio ≥20 µg/min Or Albumin: creatinine ratio ≥30mg/g	--

* Ethnicity-specific values

2.1.2 Prevalence of metabolic syndrome

Globally, the prevalence of metabolic syndrome varies from less than 10% to more than 84%. Such variations are related to the region, sex, age, race and ethnicity, and whether the population from the urban or rural area, in addition to metabolic syndrome definition used in the study (Kolovou et al., 2007). The prevalence of metabolic syndrome in the states of Gulf Cooperation Council is about 10-15% greater than in most industrialized countries, with generally lower prevalence rates for men (Mabry et al., 2010). A report of the United Arab Emirates national survey showed that the prevalence of metabolic syndrome was 39.6% and 40.5% using the NCEP and IDF definition respectively. Also, showed that the occurrence of metabolic syndrome was associated with increasing age and female gender (Malik and Razig, 2008). In another study in the United Arab Emirates which recruited overweight and obese subjects aged 18–50 years, the prevalence of metabolic syndrome was 40.5% (Al-Sarraj et al., 2010). In a school-based study on Emirati adolescents (12-18 years), the prevalence of metabolic syndrome was 13% and boys (21%) were more likely to have metabolic syndrome than girls (4%) (Mehairi et al., 2013). Most recent study elucidated that the prevalence of metabolic syndrome was around 22% among rural adults from the United Arab Emirates (Luz Espina, 2014).

2.1.3 Pathophysiology of metabolic syndrome

Metabolic syndrome is a complex condition and the mechanisms underlying metabolic syndrome are incompletely understood (Eckel et al., 2005) and its causes were described to be multi-factorial. Yet, the interaction of genetic and environmental factors together with dietary habits could play a role in metabolic syndrome development. Abdominal obesity and insulin resistance were proposed to

be the most accepted underlying factors that contribute to the pathophysiology of the syndrome (Grundy et al., 2005; Reaven, 1988; Wassink et al., 2007). However, additional factors like inflammation (Esposito and Giugliano, 2004), endothelial dysfunction (Pinkney et al., 1997) and unbalanced autonomic nervous system stimulation (Kreier et al., 2003) may also be involved.

2.1.3 (a) Obesity and adipose tissue

The American Medical Association (2013) stated that obesity should be considered as a chronic medical disease state (AMA, 2013), which is characterized by excessive accumulation of adipose tissue (WHO, 2016). There is a continues global increase in the incidence of overweight and obesity among adults with more than one billion adults are overweight and 500 million are obese (World Obesity Organization, n.d.). Recent reports on the prevalence of overweight and obesity are shocking in Arabian Gulf states especially in Bahrain, Qatar, Kuwait, and Saudi Arabia where more than two-thirds of adults and adolescents are overweight or obese (Ng et al., 2011). In a survey released by Zurich International Life, 47.5% and 13% of UAE residents were overweight and obese respectively (Geranpayeh, 2015), with more than 50% had central obesity (Hajat et al., 2012).

In order to understand the pathophysiology of metabolic syndrome, one should have an overview of the adipose tissue structure and functions. Adipose tissue is a loose connective tissue that consists of different cell types. The main cells are adipocytes (fat cells), fibroblasts (fiber-forming cells), macrophages (type M1 and M2), endothelial cells and blood cells which are embedded in a matrix of connective tissue (Cinti, 2009). There are two main histological types of adipose tissue; brown adipose tissue and white adipose tissue. The brown adipose tissue is well

vascularized with many mitochondria and its function is to generate heat and therefore it maintains body temperature (Cannon and Nedergaard, 2004). While, white adipose tissue represents the main part of the adipose tissue, which is poorly vascularized with fewer mitochondria and it is the site of accumulation of lipid (mainly triglycerides). Recent research showed that white adipose tissue is not just a silent structure that passively acts as a storage site for excess energy, but it is a dynamic endocrine organ (Scherer, 2006) with multiple metabolic roles in regulating whole-body physiology. The white adipose tissue is subdivided into two parts: visceral adipose tissue and subcutaneous adipose tissue. They are different in their location, cellular, molecular and physiological aspects. As compared to subcutaneous adipose tissue, visceral adipose tissue is found mainly in the omentum and mesentery, and directly connected to the liver via the portal circulation. The visceral adipose tissue is more cellular, and has rich blood and nerve supply, with many inflammatory and immune cells. Its adipocytes are metabolically more active, with higher sensitivity to lipolysis and are more insulin resistant compared to the adipocytes of subcutaneous adipose tissue. Cells of visceral adipose tissue secrete biologically active molecules known as adipokines (produced by the adipocytes) and cytokines (produced by the macrophages) and are collectively called adipocytokines. Macrophage type M1 produces proinflammatory cytokines like TNF-α and IL-6, while type M2 produces anti-inflammatory cytokines such as IL-10 (Mills, 2012). In obesity, there is domination of M1 over M2 i.e. more production of proinflammatory than anti-inflammatory cytokines. It has been suggested that these cytokines, which are secreted by the adipose tissue in obese individuals, could contribute to the high inflammatory (C-reactive protein; CRP) proteins secretion by the liver and results in the state of chronic low-grade inflammation (Maachi et al., 2004). In 1993, two

independent groups of researchers reported that TNF-α, which is produced by the adipose tissue and overproduced by enlarged adipose tissue, was able to induce insulin resistance (Feinstein et al., 1993; Hotamisligil et al., 1993) via its local and possibly systemic effects on metabolism.

The concept of adipose tissue as a dynamic endocrine organ capable of producing other bioactive molecules quickly broadens beyond TNF-α to include a long list of adipocytokines. Many of these adipocytokines play a role in inflammation and may affect insulin action with subsequent development of insulin resistance. These include leptin (Zhang et al., 1994), adiponectin (Scherer et al., 1995), IL-6 (Fried et al., 1998), resistin (Steppan et al., 2001), PAI-1 (Shimomura et al., 1996), angiotensinogen, visfatin (Fukuhara et al., 2005) and others. It has been suggested that inflammation is an important contributor in the pathophysiology of hypertension and cardiovascular diseases (Savoia and Schiffrin, 2006) and also found to play a role in the pathogenesis of type 2 diabetes mellitus (Spranger et al., 2003).

2.1.3 (b) Autonomic nervous system overactivity

During the last decade, overactivity of the sympathetic nervous system was noticed in obese individuals and in those with central obesity in particular (Grassi et al., 2004). This excessive sympathetic system stimulation could be due to dysfunction of the arterial baroreceptors, insulin resistance, and increase levels of adipokines such as angiotensin II and leptin. The effects of the sympathetic nervous system on the regulation of blood pressure and cardiovascular system functions are well acknowledged. A recent study also demonstrated the association of sympathetic activity with elevated cholesterol levels, which may play a role in the development of cardiovascular disease (Lambert et al., 2013). However, its effects on energy

homeostasis and body metabolism are less well appreciated. Therefore, all these findings, which are summarized in Figure 2.1, on the role of the activated sympathetic nervous system in the development of metabolic syndrome should be considered (Thorp and Schlaich, 2015).

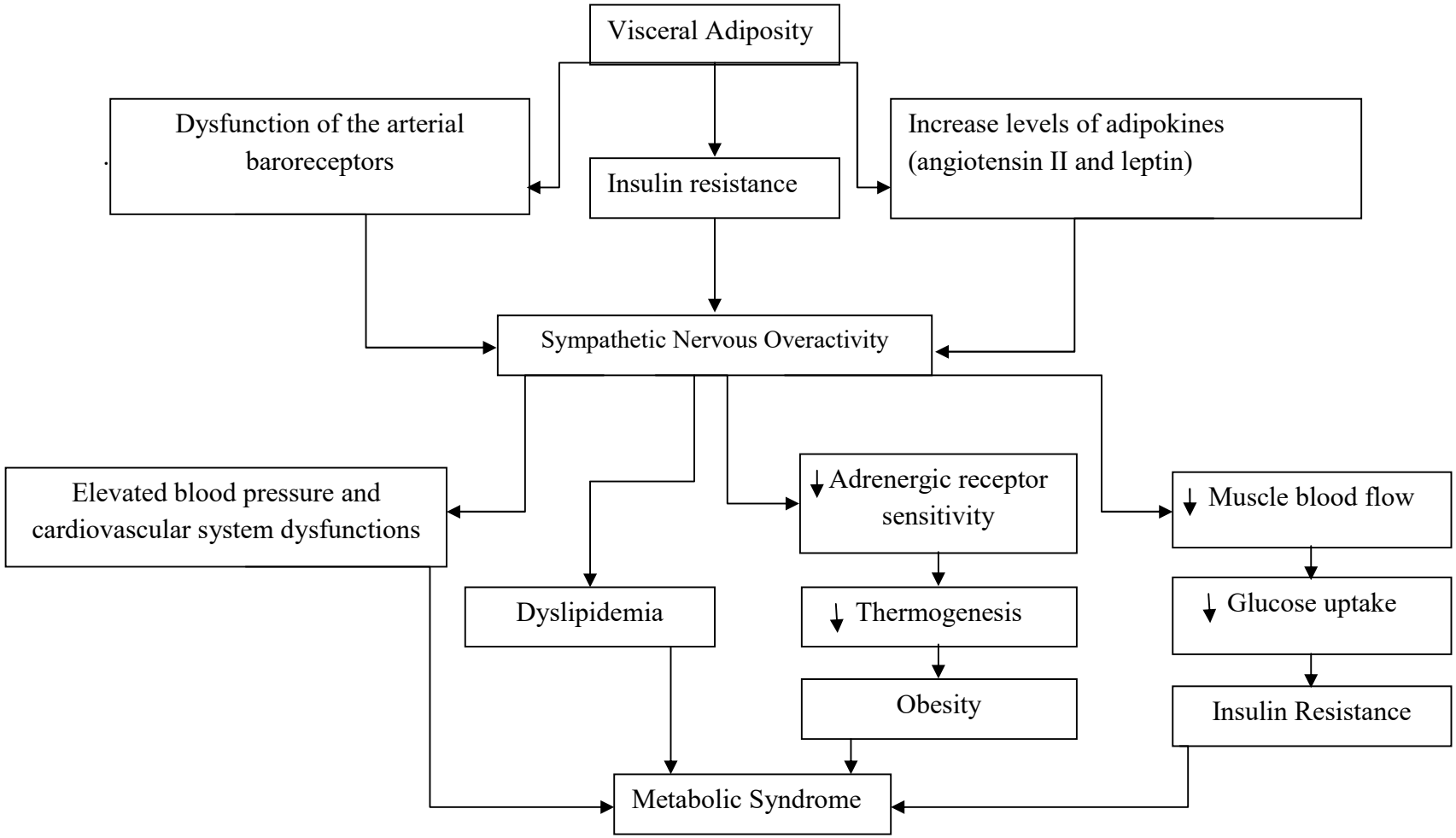

Figure 2.1 Role of the sympathetic nervous system in the development of metabolic syndrome

2.2 Adiponectin

Adiponectin, which is also known as Acrp30 (Scherer et al., 1995), AdipoQ (Huet al., 1996), apM1 (Maeda et al., 1996) and GBP28 (Nakano et al., 1996)is the most abundant and relatively new adipocytokine that is exclusively secreted by the adipocytes (Scherer et al., 1995). A few years ago, two adiponectin receptors were identified; adiponectin receptor 1 (AdipoR1) and adiponectin receptor 2 (AdipoR2). AdipoR1 is plentifully expressed in the skeletal muscle, while AdipoR2 is primarily expressed in the liver (Yamauchi et al., 2003). Adiponectin exhibits insulin-sensitizing, fat-burning (Yamauchi et al., 2001), anti-atherogenic (Shimada et al., 2004) and anti-inflammatory properties (Ouchi et al., 2003). It is distinct from other adipocytokines in that the production and circulating level of adiponectin are decreased with obesity. Hence, low adiponectin levels are commonly reported in obesity and related disorders (Lara-Castroet al., 2006) such as type 2 diabetes mellitus (Hotta et al., 2000) and certain types of cancer (van Kruijsdijk et al., 2009). In addition, low adiponectin levels in healthy individuals could be linked to increased risk of cardiovascular events (Pischon et al., 2004). Serum levels of adiponectin have been reported to be affected by genetic factors (Yamamoto et al., 2002), ethnicity (Martin et al., 2008; Pereira et al., 2011), dietary fat content (Barnea et al., 2006), exercise(Lee et al., 2013) and drugs like thiazolidinediones (Li et al., 2010) and statins (von Eynatten et al., 2009). Adiponectin has been reported to play a protective role in the development of metabolic syndrome (Calton et al., 2013; Hunget al., 2008; Koh et al., 2010). Thus, serum adiponectin level has been expected to serve as a valuable biomarker to predict the development of metabolic syndrome. The possible role of adiponectin the development of metabolic syndrome is summarized in Figure 2.2.