THE EFFECTIVENESS OF THE EXERCISE IN COMMUNITY ON THE RISK MARKERS OF TYPE 2 DIABETES MELLITUS AND CARDIOVASCULAR DISEASES

SUWADEE MEEMARK

A Thesis Submitted to the Graduate School of Naresuan University
in Partial Fulfillment of the Requirements
for the Master of Science in Biomedical Sciences - (Type A 1)
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By SUWADEE MEEMARK

has been approved by the Graduate School as partial fulfillment of the requirements for the Master of Science in Biomedical Sciences - (Type A 1) of Naresuan University

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Title	THE EFFECTIVENESS OF THE EXERCISE IN COMMUNITY ON THE RISK MARKERS OF TYPE 2 DIABETES MELLITUS AND CARDIOVASCULAR DISEASES
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ABSTRACT

Oxidative stress (OS) and inflammation have been suggested to play a pivotal role in the pathogenesis of chronic diseases such as Type 2 Diabetes Mellitus and increased risk to develop cardiovascular disease. Oxidative stress and inflammatory markers (IM) maybe change after regular physical exercise. However, physical activity affects the redox balance and inflammatory markers in obese women are still unclear. This study assesses OS, IM, and total antioxidant in obese women before and after participation in an aerobic dance exercise period. One hundred and fifty-one obese women have participated in two months of aerobic dance exercise. They agreed to have anthropometric, blood pressure (BP) measurements and venous blood samples collected before and after 2 months of participation in the study. The results show that at the end of the study, the median glucose (Glu), triglyceride (TG), insulin levels, Model Assessment of insulin resistance (HOMA-IR), malondialdehyde (MDA), C-reactive protein (hs-CRP), tumor necrosis factor α (TNFα) and interleukin-6 (IL-6) were significantly decreased (p<0.05) and HDL-C and total antioxidant capacity (TAC) were significantly increased (p<0.05) after participation in aerobic dance exercise. Oxidative stress, TAC, and IM are involved in the adaptive metabolic changes and redox responses induced by physical exercise. Therefore, aerobic dance exercise reduces these potential OS and IM that protects the risks of developing diseases in obesity that are pathophysiologically linked to OS and IM.

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ABBREVIATIONS

ADMA	=	Asymmetric dimethyl arginine
AGEs	=	Advanced glycation end products
AHA	=	American Heart Association
AO	=	Abdominal obesity
AP-1	=	Activated protein 1
apoB	=	Apolipoprotein B
apoB100	=	Apolipoprotein B100
ASCVD	=	Atherosclerotic cardiovascular disease
ATP	=	Adenosine triphosphate
BH_4	=	Tetrahydrobiopterin
BMI	=	Body mass index
BP	=	Blood pressure
BUN	=	Blood urea nitrogen
CRP	=	C-reactive protein
CVD	=	Cardiovascular disease
DDAH	=	Dimethylarginine dimethylaminohydrolase
DM	=	Diabetes mellitus
DNA	=	Deoxyribonucleic acid
EGIR	=	The European Group for the Study of Insulin Resistance
eNOS	=	Endothelial nitric oxide synthase
FFA	=	Free fatty acids
FMS	=	Fundamental Movement Skills
FPG	=	Fasting plasma glucose
GLP-I	=	Glucagon-like peptide-1
Glu	=	Glucose
GLUT4	=	Glucose transporter 4
GTPCH	=	GTP-cyclohydrolase I
GS	=	Glycogen synthesis
HDL-C	=	High-density lipoprotein cholesterol
HIIT	=	High-intensity interval training
HOMA-IR	=	Homeostatic model assessment of insulin resistance
IDDM	=	Insulin-dependent diabetes mellitus

IDF = International Diabetes Federation
IFG = Impaired fasting glucose
IGT = Impaired glucose tolerance
IL-1β = Interleukin-1β
IL-6 = Interleukin-6
IL-8 = Interleukin-8
IR = Insulin resistance
LDL-C = Low-density lipoprotein cholesterol
LOX-1 = Lectin-like oxLDL receptor-1
LPL = Lipoprotein lipase
MCP-1 = Monocyte chemoattractant protein-1
MDA = Malondialdehyde
MetS = Metabolic syndrome
MFI = Multidimensional Fatigue Inventory
MICT = Moderate-intensity continuous training
MMP-9 = Matrix metalloproteinase-9
MVPA = Moderate-to-vigorous physical activity
NADH = Nicotinamide adenine dinucleotide
NADPH = Nicotinamide adenine dinucleotide phosphate
NAFLD = Nonalcoholic fatty liver disease
NCEP = The US National Cholesterol Education Program Adult Treatment Panel III
NEFA = Non-esterified fatty acids
NF-κB = Nuclear factor kappaB
O_2^- = Superoxide
OGTT = Oral glucose tolerance test
OXLDL = Oxidized LDL
p38MAPK = P38 mitogen-activated kinase
PA = Physical activity
PDGF = Platelet derived growth factor
PDGR-R = PDGF receptor
PGC1-α = Peroxisome proliferator-activated receptor-gamma coactivator 1 alpha
PI3K = Phosphoinositide 3-kinase

PKC = Protein kinase C
PLA_2 = Phospholipase A_2
ROS = Reactive oxygen species
SES = Socioeconomic status
SOD = Superoxide dismutase
STZ = Streptozotocin
T2DM = Type 2 diabetes mellites
TAC = Total Antioxidant
TAG = Triacylglycerol
TBA = Thiobarbituric acid
TC = Total cholesterol
TFAM = Mitochondrial transcription factor A
TG = Triglyceride
TNF-α = Tumor necrosis factor-alpha
UA = Uric acid
VLDL = Very-low-density lipoprotein
VCAM-1 = Vascular cellular adhesion molecule-1
VSMC = Vascular smooth muscle cell
WHO = The World Health Organization
WC = Waist circumference

CHAPTER I
INTRODUCTION

The World Health Organization (WHO) reports that in 2014, the number of people with diabetes was from 108 million in 1980 to 422 million(1). Diabetes is a major cause of blindness, kidney failure, cardiovascular disease, stroke, and lower limb amputation. In 2017, approximately 462 million individuals were affected by type 2 diabetes mellites (T2DM) corresponding to 6.28% of the world's population(2). These diseases are driven by forces that include rapid unplanned urbanization, globalization of unhealthy lifestyles, and population aging. Lack of physical activity and unhealthy diets may show up in people as raised blood pressure, increased blood glucose, elevated blood lipids, and obesity. These are called metabolic risk factors that can lead to cardiovascular disease and diabetes. Noncommunicable diseases are most commonly caused by behavioral and metabolic factors. Hyperlipidemia, hyperglycemia, smoking, blood pressure, unhealthy diet, obesity, overweight, and alcohol consumption behavior, it is a very important risk factors for developing chronic non-communicable diseases. Although all these risk factors play a major role in generating noncommunicable diseases, a group of them called "metabolic syndrome" has been very concerned in recent past years. Metabolic syndrome is the most commonplace metabolic disorder, which develops into cardiovascular diseases and diabetes. A more accurate definition of metabolic syndrome defines it as a cluster of deformation that includes abdominal obesity, hyperglycemia or glucose metabolic disorder, hypertension, and heterogenic dyslipidemia. This risk factor greatly increases the incidence of cardiovascular disease and diabetes, increasing the number of people suffering from this disease.

Metabolic dyslipidemia is the most common complication of insulin resistance and T2DM leading to risk of cardiovascular diseases. Insulin resistance is an important factor of T2DM and is associated with a cardiovascular cluster of disorders and metabolic (dyslipidemia, obesity, glucose intolerance, endothelial dysfunction, hypertension), each of which is an individualistic risk factor for cardiovascular disease (CVD). The most conventional findings are low levels of high-density lipoprotein cholesterol (HDL-C), high triglyceride (TG) concentration, and normal or

slightly increased low-density lipoprotein cholesterol (LDL-C). Dyslipidemia have resulted in an epidemic of atherosclerotic disease in developed countries. The interaction of genetic and acquired disorders of lipoproteins with the prevalence of high fat diet, obesity and low physical activity leads to the premature development of atherosclerosis. In Thailand, atherosclerotic cardiovascular disease remains the common cause of death among both man and woman, the mortality in 2002 is 199 per 100,000 patients. Although high LDL level and low HDL level are the major atherosclerotic cardiovascular risk factors as well as aging, male gender, hypertension, diabetes mellitus, smoking, and family history of premature dyslipidemia. Oxidation of LDL-C is believed to be an important step in the atherogenic process(3).

Hyperglycemia is an important factor in cardiovascular damage, induced mitochondrial dysfunction and endoplasmic reticulum stress, promote reactive oxygen species (ROS) accumulation that, in turn, promote cellular damage and contribute to the diabetic complication's development and progression. ROS can directly damage lipids, proteins or deoxyribonucleic acid (DNA) and modulate intracellular signaling pathways. Hyperglycemia induced oxidative stress induces endothelial dysfunction that plays an important role in the pathogenesis of micro and macrovascular diseases. It may also increase pro-inflammatory and procoagulant factors expression, induce apoptosis and impair nitric oxide release.

Oxidative stress is caused by an imbalance between the physiological and the production of ROS ability to immediately eliminate the reactive intermediates or easily repair the resulting damage. There are many molecules that contain one or more unpaired electrons. There is increasing evidence in both experimental and clinical studies suggesting that oxidative stress a pivotal role in the pathogenesis of both types of diabetes mellitus. Free radicals are produced excessively in diabetes via glucose oxidation, non-enzymatic glycation of proteins, and subsequent oxidative degradation of glycoproteins. The uncontrolled process of antioxidant defense and abnormally high levels of free radicals can be responsible for physiological damages such as damage of cellular organelles and enzymes, lipid peroxidation, and the development of insulin resistance. In it's the enediol form, glucose is oxidized in a transition metal-

dependent reaction to enediol anion radical that is converted into reactive ketoaldehydes and to superoxide anion radicals. The superoxide radicals are dismutase by superoxide dismutase (SOD) to hydrogen peroxide, which can catalyze free transition metal leading to the production of harmfully reactive hydroxyl radicals if hydrogen peroxide is not eliminated by catalase or glutathione peroxidase. Superoxide anion can also react with nitric oxide to form reactive peroxynitrite radicals. By superoxide-dependent pathway, extremely lipid peroxidation of LDL-C has been observed in patients with hyperglycemia. Free or non-esterified fatty acids (FFA) are elevated in diabetic patients. Excess FFA enters the citric acid cycle and generates acetyl-CoA to produce excess nicotinamide adenine dinucleotide (NADH), with increased mitochondrial superoxide production. In humans, infused FFA has been shown increased lipid peroxidation by elevated isoprostanes marker levels. Another source of free radicals in diabetes is the interaction of glucose with proteins, which can be responsible for the formation of an Amadori product and then advance glycation end-products (AGEs). These AGEs result from the inactivation of enzymes, the induction of free radical formation, and inhibition of antiproliferative effect of nitric oxide. AGEs also stimulate the transcription factor (nuclear factor-kappaB; NF-κB), which enhances increased nitric oxide. This result is believed to be a mediator of islet beta-cell damage. Obesity and insulin resistance and excessive consumption of saturated fats and free fatty acids cause beta cells to be insultingly by cytokine-induced inflammation. The progressive degeneration of beta-cell function leading to beta-cell exhaustion display beta cell demise. Insulin resistance is a key component of beta-cell dysfunction in patients with T2DM. The relationship between beta-cell dysfunction and insulin resistance is highly complex, which initially hyperglycemia can trigger insulin resistance and result in beta-cell dysfunction. The severity of beta-cell dysfunction was greater than that of insulin resistance. With beta-cell dysfunction, insulin secretion is reduced while in insulin resistance. Insulin is still secreted, but insulin insensitivity appears in the targeted tissues. As beta-cell dysfunction and insulin resistance exacerbates, hyperglycemia amplifies leading to the progression to T2DM(3).

Thailand is inevitably moving towards the burden of such a public health problem. According to the cross-country survey in the Inter-Asia study, the

prevalence of T2DM in Thailand was 9.8%. T2DM is much more than type 1 diabetes mellitus and accounts for around 90% of all diabetes cases worldwide. It is found in adults the most frequently, but is being noted that the increasing in adolescents as well. T2DM is a common disease worldwide. The International Diabetes Federation (IDF) estimated that, in the next 20 years, the number of people with diabetes will increase from 366 million in 2011 to 552 million in 2030(4). According to the 4th Thai National Health survey, 7.5% of people aged >20 years old had type 2 diabetes and the prevalence of diabetes was greater in women than in men (8.3% vs 6.6%)(5). Comparing people with diabetes and those without diabetes, people with diabetes had a lower quality of life and higher rates of morbidity and mortality.

The survey by the Thai Health Promotion Foundation represented that most of the Thai population were lack of exercise. Only 19% of adults in the working-age group and 23.6% of the elderly have regular exercise, meanwhile, children and teenagers hold the highest percentage of exercise participation(6). The benefits of regular physical activity (PA) for children's health range from short-term exercise to the long-term potential to reduce the incidence of chronic disease manifesting in adulthood. One study found that 60 minutes of moderate-to-vigorous physical activity (MVPA) each day was positively correlated with physical health status. Fundamental Movement Skills (FMS), bone health, cognitive function, and socio-emotional development of children(7). However, despite global efforts to improve the health of young people, 80% of children and young people worldwide still do not exercise or are at the PA recommended daily levels of physical activity. PA participation is a complex and multidimensional behavior that is determined by socio-cultural, economic, and policy-related factors that operate across intra-/interpersonal, organizational, and environmental dimensions. Although the influence of PA is highly diverse, in general, children from lower socioeconomic status (SES) households, girls, parents/friends who raise low and those who live in unsupported/unsafe neighborhoods are less likely to get adequate MVPA. Identically, in the Thai context, the factors of age, gender, geographical location of residence/school, and support from parents/friends also determines the PA level of Thai children and youth(7).

Purpose of the study

To assess oxidative stress, inflammatory markers and total antioxidant in obese women before and after participation an aerobic dance exercise period.

CHAPTER II
REVIEW LITERATURE

The metabolic syndrome (MetS) has been recognized as a clinical entity for more than 50 years. Obesity is a predisposing factor in the development of diabetes mellitus, atherosclerosis, and gout. The importance of insulin resistance and a related cluster of metabolic abnormalities that were associated with an increase in coronary artery disease. This cluster included resistance to insulin-stimulated glucose uptake, glucose intolerance, hyperinsulinemia, increased very-low-density lipoprotein (VLDL) triglyceride, decreased high-density lipoprotein (HDL) cholesterol, and hypertension. This cluster was called ‘syndrome X’ and raised the possibility that resistance to insulin-stimulated glucose uptake and hyperinsulinemia were involved in the etiology of the metabolic abnormalities and the clinical diseases associated with them. Obesity and, particularly, visceral obesity have been recognized as major contributors to the MetS since precise techniques to quantitate regional body composition became available. The MetS was initially thought of as an insulin resistance syndrome, implying that insulin resistance was the underlying unifying abnormality.

Definition and diagnostic

Metabolic syndrome is the name for a group of risk factors that raises risk for heart disease and other health problems. The metabolic syndrome is a group of related risk factors of metabolic origin, metabolic risk factors that present to directly stimulate the development of atherosclerotic cardiovascular disease (ASCVD). Patients with the metabolic syndrome also are at increased risk for developing T2DM. In the last few years, the groups of professionals have attempted to set simple diagnostic criteria to be used in clinical practice to defined patients who revealed several components of the metabolic syndrome. These criteria were difference in some feature. These main risk factors include hyperglycaemia, dyslipidemia, hypertension, and obesity. Individuals with these characteristics commonly manifest a prothrombotic state and a pro-inflammatory state as well. Atherogenic dyslipidemia consists of an aggregation of lipoprotein abnormalities including elevated serum

triglyceride and apolipoprotein B (apoB), increased small LDL particles, and a reduced level of HDL cholesterol (HDL-C).

The metabolic syndrome is a cluster of the most dangerous heart attack risk factors: diabetes and prediabetes, abdominal obesity, high cholesterol and high blood pressure. There are several "official" definitions of the metabolic syndrome.

International Diabetes Federation (IDF)

Consensus for worldwide definition of the metabolic syndrome. Central obesity (defined as waist circumference with ethnicity specific values of Asia: men ≥ 90 cm and women ≥ 80 cm).

And any two of the following:

1. Raised triglycerides: ≥ 150 mg/dL (1.7 mmol/L) or specific treatment for this lipid abnormality.
2. Reduced HDL cholesterol: < 40 mg/dL or 1.03 mmol/L in males, < 50 mg/dL or 1.29 mmol/L in females, or specific treatment for this lipid abnormality.
3. Raised blood pressure: systolic BP ≥ 130 or diastolic BP ≥ 85 mmHg, or treatment of previously diagnosed hypertension.
4. Raised fasting plasma glucose: (FPG) ≥ 100 mg/dL or 5.6 mmol/L, or previously diagnosed T2DM. If FPG ≥ 5.6 mmol/L or 100 mg/dL, OGTT, Glucose tolerance test is strongly recommended but is not necessary to define presence of the Syndrome.

   If BMI is > 30 kg/m^2, central obesity can be assumed and waist circumference does not need to be measured.

WHO: The World Health Organization criteria requires presence of one of:

1. Diabetes mellitus.
2. Impaired glucose tolerance.
3. Impaired fasting glucose.
4. Insulin resistance.

And two of the following:

1. Blood pressure: ≥ 140/90 mmHg.
2. Dyslipidemia: triglycerides (TG): ≥ 1.695 mmol/L and high- density lipoprotein cholesterol (HDL-C) ≤ 0.9 mmol/L (male), ≤ 1.0 mmol/L (female)
3. Central obesity: waist: hip ratio > 0.90 (male); > 0.85 (female), or body mass index > 30 kg/m^2.
4. Microalbuminuria: urinary albumin excretion ratio ≥ 20 ug/min or albumin: creatinine ratio ≥ 30 mg/g.

EGIR: The European Group for the Study of Insulin Resistance

Requires insulin resistance defined as the top 25% of the fasting insulin vales among non-diabetic individuals. AND two or more of the followings:

1. Central obesity waist circumference ≥ 94 cm (male), ≥ 80 cm (female).
2. Dyslipidemia: TG ≥ 2.0 mmol/L and/or HDL-C < 1.0 mmol/L or treated for dyslipidemia
3. Hypertension: blood pressure ≥ 140/90 mmHg or antihypertensive medication.
4. Fasting plasma glucose ≥ 6.1 mmol/L.

NCEP: The US National Cholesterol Education Program Adult Treatment Panel III

Requires at least three of the following:

1. Central obesity: waist circumference ≥ 102 cm or 40 inches (male), ≥ 88 cm or 36 inches(female).
2. Dyslipidemia: TG ≥ 1.7 mmol/L (150 mg/dl)
3. Dyslipidemia: HDL-C < 40 mg/dL (male), < 50 mg/dL (female).
4. Blood pressure ≥ 130/85 mmHg.
5. Fasting plasma glucose ≥ 6.1 mmol/L (110 mg/dl).

American Heart Association/Updated NCEP

There is confusion as to whether, the AHA/NHLBI intended to create another set of guidelines or simply update the NCEP ATP III definition. According to Scott Grundy, University of Texas Southwestern Medical School, Dallas, Texas, the intent was just to update the NCEP ATP III definition and not create a new definition.

1. Elevated waist circumference Men: greater than 40 inches or 102 cm, Women: greater than 35 inches or 88 cm.
2. Elevated triglycerides: Equal 10 greater 01 150 mg/dL or 1.7 mmol/L.
3. Reduced HDL-Cholesterol: Men: Less than 40 mg/dL or 1.03 mmol/L, Women: Less than 50 mg/dL or 1.29 mmol/L.
4. Elevated blood pressure: Equal to or greater than 130/85 mm H or use of medication for hypertension.
5. Elevated fasting glucose: Equal to or greater than 100 mg/dL or 5.6 mmol/1. or use of medication for hyperglycemia.

Clinical Outcome of metabolic syndrome

The experts confirmed cardiovascular disease (CVD) as a major clinical outcome of metabolic syndrome and specified 6 important components of the metabolic syndrome abdominal obesity, insulin resistance glucose intolerance, elevated blood pressure, atherogenic dyslipidemia, a proinflammatory state, and a prothrombotic state(8). The primary clinical outcome of metabolic syndrome most individuals who develop CVD has multiple risk factors. Most people with this syndrome have insulin resistance, which confers increased risk for T2DM. When diabetes becomes clinically apparent, CVD risk rises sharply. Beyond CVD and T2DM, individuals with metabolic syndrome seemingly are susceptible to other conditions, notably polycystic ovary syndrome, fatty liver, cholesterol gallstones, asthma, sleep disturbances, and some forms of cancer. Although genetic and environmental factors contribute to the pathogenesis of metabolic syndrome, modifiable risk factors like obesity and sedentary lifestyle seem to be the most important. Inflammation is strongly associated with metabolic syndrome, and

inflammatory markers like CRP, interleukin-6, and other procoagulant states have a significant role to play in its pathogenesis(9).

Diabetes mellitus

Diabetes mellitus (DM) is a chronic metabolic disorder characterized by persistently high blood sugar (hyperglycemia). This may be due to impaired insulin secretion. insulin resistance or both. The term diabetes mellitus is characterized by disordered metabolism and inappropriately high blood sugar caused by either low levels of the hormone insulin or from abnormal resistance to insulin's effects coupled with inadequate levels of insulin secretion to compensate. The glucose accumulates in the circulation as well as hyperglycemia leading to various potential medical complications.

The criteria for diabetes have been categorized by fasting plasma glucose (FPG) and oral glucose tolerance test (OGTT).

The categories of FPG values are as follows:

FPG <100 mg / dl (5.6 mmol / l) = normal fasting glucose;

FPG 100-125 mg/dl (5.6-6.9 mmol/l) = IFG (impaired fasting glucose);

FPG ≥126 mg/dl (7.0 mmol/l) = provisional diagnosis of diabetes.

The OGTT is used are the following:

2-h postload glucose <140 mg/dl or 7.8 mmol/l = normal glucose tolerance;

2-h postload glucose 140-199 mg/dl or 7.8-11.1 mmol/l = IGT: impaired glucose tolerance;

2-h postload glucose ≥200 mg/dl or 11.1 mmol/l provisional diagnosis of diabetes.

Classification of diabetes mellitus

The new classification can be distinguished into four type of diabetes mellitus; type 1, type 2, other specific type, and gestational diabetes.

Type 1 diabetes mellitus, called insulin-dependent DM (IDDM) or juvenile diabetes, is characterized by β-cell distinction caused by autoimmune disease, typically leading to absolute insulin deficiency. Type 1 diabetes mellitus is usually acute growing over a period of a few days to weeks. Almost of person with type 1 diabetes mellitus possess the symptom of the disease before 25 years old. A family history of type 1 diabetes mellitus is often found because of genetic disease.

On type 2 diabetes mellitus (T2DM), this type is called non-insulin dependent DM caused from the body's ineffective use of insulin. This is the most common of DM and is related with a family history of diabetes, obesity, older age, and lack of exercise. The etiology of T2DM is multi-factorial and probably genetically based, but has strong behavioral components.

Other specific type combines various knows etiologies including persons with genetic defects of β-cell function or with defects of insulin action, persons with diseases of the exocrine pancreas (e.g. pancreatitis or cystic fibrosis), persons with dysfunction associated with other endocrinopathies (such as acromegaly), and persons with pancreatic dysfunction caused by drugs, chemical and infections.

The last category of diabetes mellitus is a gestational disease DM that is hyperglycemia with onset or first recognition during pregnancy. However, most women classified with gestational diabetes mellitus have normal glucose homeostasis during the first half of the pregnancy and develop a relative insulin deficiency during the last half of the pregnancy leading to hyperglycemia(10).

Type 2 Diabetes mellitus

Type 2 diabetes mellitus (T2DM) accounts for about 90% of all cases of diabetes. In T2DM, the insulin response is impaired. And this is insulin resistance during this state, Insulin is ineffective and is initially resisted by increasing insulin production to maintain glucose balance but over time Insulin production is reduced, resulting in T2DM. T2DM is the most common in people over 45 years of age. Still, it

is increasingly seen in children, adolescents, and younger adults due to rising levels of obesity, physical inactivity, and energy-dense diets(11).

The abnormality of beta cells in insulin resistance leads to type 2 diabetes mellitus. Primarily compensated for increased insulin secretion which keeps glucose levels within the normal range. As the disease progresses, the beta cells change and insulin secretion is unable to maintain glucose homeostasis, causing hyperglycemia. Most of the patients with T2DM have a higher body fat percentage or are obese, distributed predominantly in the abdominal region. This adipose tissue itself promotes insulin resistance through various inflammatory mechanisms, including increased FFA release and regulating adipokine dysregulation. Lack of exercise or physical inactivity and previous gestational diabetes in people with high blood pressure or dyslipidemia. It also increases the risk factor of developing T2DM. Developing data suggest a role in regulating adipokine dysregulation, inflammation, abnormal incretin biology with decreased incretin such as glucagon-like peptide-1 (GLP-I) or increased resistance, hyperglucagonemia, renal glucose reabsorption, and abnormalities in the gut microbiota.

Insulin resistance is recognized as a debilitated biological reaction to insulin stimulation in target tissues, principally the liver, muscle, and adipose tissue. Insulin resistance disables glucose removal. This results in increased production of insulin beta cells and compensatory hyperglycemia. The metabolic consequences of insulin resistance can result in hypertension, hyperglycemia, dyslipidemia, visceral adiposity, hyperuricemia, endothelial dysfunction, elevated inflammatory markers, and a prothrombic state. Progression of insulin resistance can lead to metabolic syndrome, nonalcoholic fatty liver disease (NAFLD), and T2DM(12). Insulin resistance in the context of glucose metabolism leads to impaired suppression of endogenous glucose production, under basal conditions as well as after eating, when the physiological rise in insulin in response to glucose entry from the gut normally shuts down glucose production by the liver, and to reduced peripheral uptake of glucose. These alterations result in hyperglycemia and a compensatory increase in insulin secretion. Resistance to the ability of insulin to suppress very-low-density lipoprotein (VLDL) production from the liver increases circulating serum triglycerides, which, in turn, leads to a

decrease in high-density lipoprotein (HDL) cholesterol and formation of atherogenic, small, dense, low-density lipoprotein (LDL) particles. Resistance in adipose tissue increases the flux of non-esterified fatty acids (NEFA) both to the liver and skeletal muscle, and impairs the action of insulin on glucose metabolism in these tissues. Resistance to other actions of insulin, such as its vasodilator and antiplatelet aggregation effects, also characterize insulin resistance in patients with T2DM.

Although obesity and physical inactivity are the main causes of insulin resistance and have precipitated the present epidemic of T2DM, these factors are poorer predictors of cardiovascular disease than the combination of risk factors that define the metabolic syndrome(13). Diagnosis of the metabolic syndrome provides a tool to diagnose insulin resistance in the clinic. According to the definition proposed by the International Diabetes Federation, it requires measurement of waist circumference, blood pressure, and the concentrations of glucose, triglycerides, and HDL cholesterol, A person has the metabolic syndrome if they have any three of the following: central obesity (defined with ethnicity-specific values); raised triglycerides; reduced HDL cholesterol; increased blood pressure; and/or raised fasting plasma glucose. The risk of death from cardiovascular disease is increased approximately two-fold in subjects with the metabolic syndrome, as compared to those not meeting these criteria. In addition, subjects with the metabolic syndrome have a five-fold greater risk of developing T2DM(13).

Inflammatory processes contribute to insulin resistance in T2DM.

Insulin resistance begins prior to the onset of T2DM, at which time impaired glucose tolerance occurs as a result of beta cell decomposition and relative insulin deficiency. Several factors are linked to the development of insulin resistance in individuals with impaired glucose tolerance and T2DM, including genetics and environmental influences, obesity, and other conditions associated with chronic inflammation or infection. The possibility that obesity, and the activation of adipose tissue in particular, may enhance the release of inflammatory factors that underlie the development of insulin resistance has generated intense interest in the field of diabetes for a number of reasons. First, a significant proportion of individuals with T2DM are overweight or obese, and obesity is a risk factor for developing T2DM. Second, the

increased release of adipocyte-derived metabolites, such as lipids, fatty acids, and various inflammatory cytokines, in obese individuals has been linked to the development of insulin resistance. Third, chronic inflammation is associated with obesity, insulin resistance, and T2DM, all of which are features of the clustering of metabolic pathologies known as ‘‘metabolic syndrome.’’ It ought to emphasize, however, that despite interest in obesity as a predisposing factor to insulin resistance in T2DM, other equally important mechanisms for the loss of insulin sensitivity have been proposed. One study (14) of young, lean offspring of patients with T2DM demonstrated similar body mass index measurements and plasma concentrations of inflammatory markers tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and adiponectin in insulin-resistant and insulin-sensitive individuals. This suggested that obesity and systemic inflammatory factors do not play a significant role in the development of insulin resistance in this population; the loss of insulin sensitivity was ascribed to a dysregulation of intramyocellular fatty acid metabolism. Other studies(15) demonstrated a high risk for T2DM in Asian subjects, despite low concentrations of C-reactive protein (CRP) and other inflammatory markers compared to other ethnic groups. Taken together, such findings suggest that mechanisms in addition to obesity and systemic inflammation are involved in predisposing individuals to insulin resistance and T2DM. In the obesity-related model for the development of insulin resistance, adipocytes, once activated, release abnormal levels of bioactive molecules, such as lipids, fatty acids, monocyte chemoattractant protein-1 (MCP-1), and various inflammatory cytokines, e.g., CRP, plasminogen activator inhibitor-1, and TNF-α. The release of these cytokines and other mediators results in the local recruitment of monocytes within adipose tissues. With differentiation of the monocytes into macrophages comes an increased release of inflammatory factors and chemokines locally within adipose tissue and systemically, such that the inflammatory response is propagated to various tissues.

Chronic low-grade inflammation in type 2 diabetes in the pancreas, adipose tissue, liver, and kidney. Inflammatory responses include recruitment and activation of antigen-presenting cells such as dendritic cells and macrophages, different T cell subsets, secretion of proinflammatory cytokines and other mediators, and consequent

impairment of beta-cell function, liver dysfunction, and renal damage. The immune pathophysiology of T2DM is presented in Figure 1.

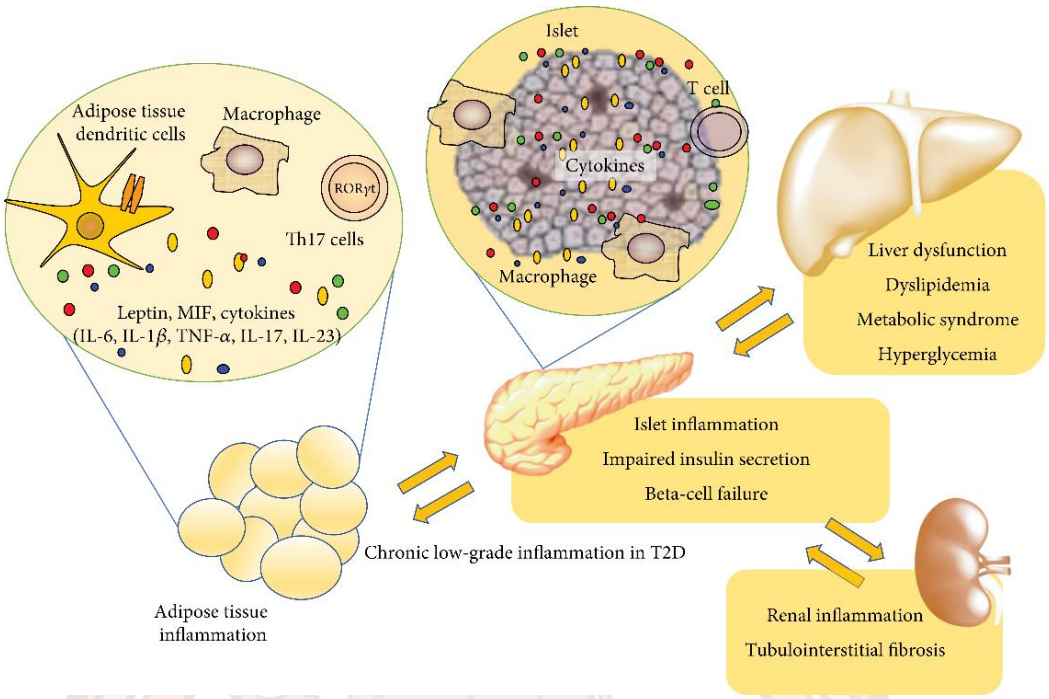

Figure 1 The immune pathophysiology of T2DM

Abbreviations: Th17: T-helper 17 cells; MIF: macrophage migration inhibitory factor; IL: interleukin; RORγt: retinoid-related orphan receptor gamma t; TNF-α: tumor necrosis factor-alpha.

The liver, tissue, fat, and skeletal muscle It is a target organ for insulin resistance(IR) and pancreatic beta-cell dysfunction, which plays a fundamental role in the mechanisms causing T2DM. IR is characterized by impaired insulin-mediated glucose uptake in target cells, and it is the most common driving feature presenting throughout the progression from prediabetes to overt T2DM(16). In the pancreas, islet beta cells react to IR by enlarging their mass, which results in compensatory increased insulin secretion. About a third of all obese people will develop T2DM depending on the individual for insulin resistance caused by islet beta cells function. (17). Furthermore, some T2DM patients will gradually progress to overt insulin deficiency and will need insulin replacement therapy.

Still, the underlying mechanisms involved in the pathogenesis of IR and β-cell disorders are not fully understood. The discovery of increased circulating inflammatory factors such as CRP, chemokines, and cytokines in T2DM patients, and increased levels of TNF-α in adipose tissue, which is associated with the incidence of infrared radiation and islets related to obesity, ushering in a new era of understanding the Pathophysiology of T2DM and shedding light on the pathogenic role of inflammation.(18).

Obesity is one of the most important risk factors for developing T2DM because it is a large endocrine organ. Abdominal adipose tissue is therefore filled with various types of immune cells, such as macrophages and T and B cells. (19). This is because the number and inflammatory activity are related to the degree of obesity and the severity of IR. (20, 21).

Infiltrated in the visceral adipose tissue, macrophages are the leading producers of the pro-inflammatory molecule TNF-α. Moreover, in a state of overnutrition, visceral adipose tissue, liver, and pancreatic islets also secrete different inflammatory factors like interleukin-1β (IL-1β), IL-6, CRP, and various chemokines. Elevated levels of these inflammatory mediators reflect chronic low-grade tissue destruction associated with obesity and may represent a predictive factor for the development of T2DM(22, 23).

Cytokines are a large family of cellular messenger molecules driving the inflammatory responses by regulating the balance between proinflammatory and anti-inflammatory signals. To date, various cytokines are targets for the biological treatment of autoinflammatory and autoimmune diseases, and anti-cytokine agents are broadly used as disease modifying drugs in patients with rheumatic conditions. Additionally, some of these cytokines are involved in glucose metabolism as well.

Diabetes Mellitus with Cardiovascular disease (CVD)

There are several mechanisms that are likely to contributed to accelerated atherosclerosis and increased cardiovascular disease risk are noted in diabetes. The patients with T2DM are recognized as a high-risk group. Although a consistent association between glycemic control and cardiovascular disorder has been noted in

epidemiological studies, the effect of tight glycemic control did not seem to reduce the risk of CVD in clinical trial. Hyperglycemia can lead to vascular complications by numerous mechanisms. One possible mechanism is that high glucose level can stimulate nuclear factor κB (NF-κB), which can increase the expression of various genes in many cell types such as endothelial cells, monocyte-derived macrophages, and vascular smooth-muscle cells. Advanced glycation end-product, cells, monocyte-derived called AGEs, consist of protein cross-links, fluorophores, and other low molecular- weight residue that are formed by sustained exposure of proteins and lipids to high concentration of glucose generating reactive oxygen species (ROS). Ligation processes of AGEs to specific cell surface receptors can regulate gene expression in vessel-well cells. Glucose can increase oxidative stress by auto-oxidation of glucose leading to the formation of ROS (e.g., superoxide anion), which can oxidize LDL. Indirect observation suggests that lipoprotein oxidation might be increased in patients with T2DM and is related to glycemic control.

Atherosclerosis

Atherosclerosis is the most common pathological process leading to CVD, which is disease of arteries characterized by formation of atherosclerosis plagues consisting of necrotic cores, calcified regions, accumulated modified lipids, inflamed smooth muscle cells, endothelial cells, leukocytes and foam cells. Atherosclerosis mainly asymptomatic for decades, eventually produces two main problems. Firstly, the atheromatous plagues, though long compensated for by artery enlargement, lead to plague ruptures and stark inside the artery lumen over the ruptures. Thus, an insufficient blood supply to the tissues and organ it feeds. Second, the compensating artery enlargement process is excessive, and an aneurysm then occurs. The complications of atherosclerosis are slowly progressive and cumulative as shown in Figure 2 (24). Soft plague suddenly ruptures causing the thrombus formation that will rapidly slow or stop blood flow, leading to death of the tissues in approximately 5 minutes because of an insufficient blood. One of the common scenarios is located in coronary artery, also known as coronary thrombosis, causing myocardial infarction or heart attack. Another in this symptom is an artery in brain, referred to as stroke, being the same process. In addition, scenario is also typically located in legs, called

claudication. Because atherosclerosis is a body-wide process, similar events occur also in the arteries to the brain, intestines, kidneys and leg(25).

According to possible cause of atherosclerosis, oxidized LDL (OxLDL) plays an important role through the induction of foam cell formation, alternative of nitric oxide signaling, initiation of endothelial stimulation, and expression of adhesion molecules that accelerate leukocyte seeding to the site of atherosclerosis. LDL, the major lipid carrier in blood circulation, consists of cholesteryl ester, phospholipids, free cholesterol, triglyceride, and apolipoprotein B100 (apoB100). ApoB100 (500 kDa) is single peptide chain synthesized in liver. During LDL oxidation, both the lipids and apoB100 presented in LDL are modified by reactive oxygen species (ROS). ApoB100 is fragmented in range of 14 - 500 kDA. The polyunsaturated fatty acids in cholesteryl esters, phospholipids, and triglycerides are also induced by ROS to yield a broad array of smaller fragments (26-28).

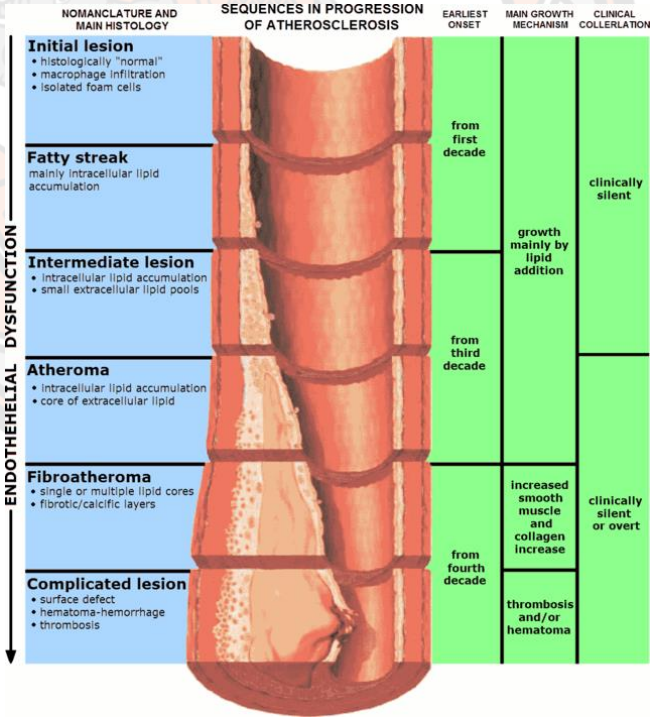

Figure 2 Sequences in progression of atherosclerosis

Source: https://en.wikipedia.org/wiki/Atherosclerosis

There is convincing evidence that OXLDL is demonstrated in the atherosclerosis lesions of both human and experiment of the lesion is still a matter of

contention. It is usually accepted that the oxidation of LDL locates in the subendothelial space of the arteries, not in the circulation. It is believed that OXLDL may have a very short half-life in the plasma because it looks like it to be eliminated quietly from the circulation by the reticuloendothelial system. However, small amount of OxLDL is immunologically detectable in plasma, and are increased significantly in numerous disease states including coronary heart disease, diabetes, and renal disease. LDL oxidation could take place at the site of inflammation because of the infiltration of neutrophils and monocytes / macrophages, and because of the increased vascular permeability and consequent increase in LDL concentration in the tissues at the sites of inflammation as demonstrated in Figure 3. The free radicals are also generated by free transition metals commonly used for in vitro oxidation of LDL, but are not significantly observed OXLDL *in vivo*.

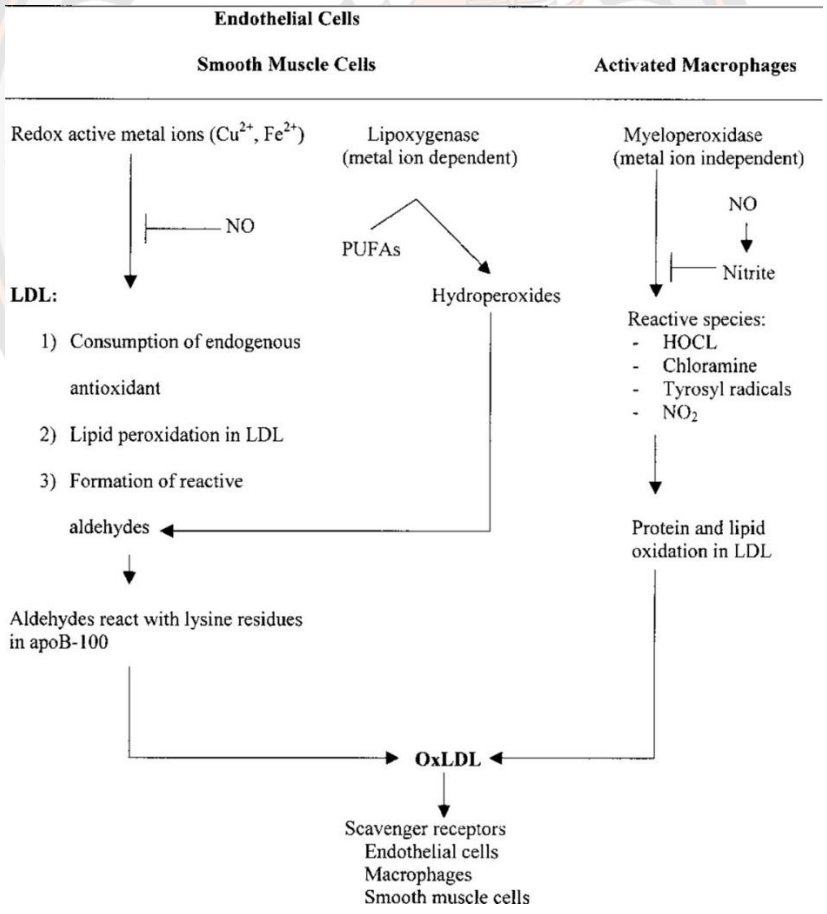

Figure 3 Mechanisms of LDL oxidation(29)

Mechanisms of LDL oxidation and macrophage foam cell formation in the artery wall. LDL that enters artery wall may be oxidized by vascular cells (endothelial cells, smooth muscle cells, and macrophages) with oxidizing enzyme including lipoxygenase and myeloperoxidase in the presence or absence of transition metal ions (iron or copper). Minimally oxidized LDL has a low affinity to macrophages scavenger receptors, and thereby, minimally oxidized LDL can be recycled into blood circulation and can be detected as a serum oxidized LDL. Such the minimally oxidized LDL stimulates adhesion molecules and chemokines. Extensively oxidized LDL can be taken up by macrophages through the scavenger receptors, leading to the formation of foam cells. These extensively oxidized LDL and minimally oxidized LDL enhance macrophage scavenger receptors with various modulations of cytokines as demonstrated in Figure 4 (30).

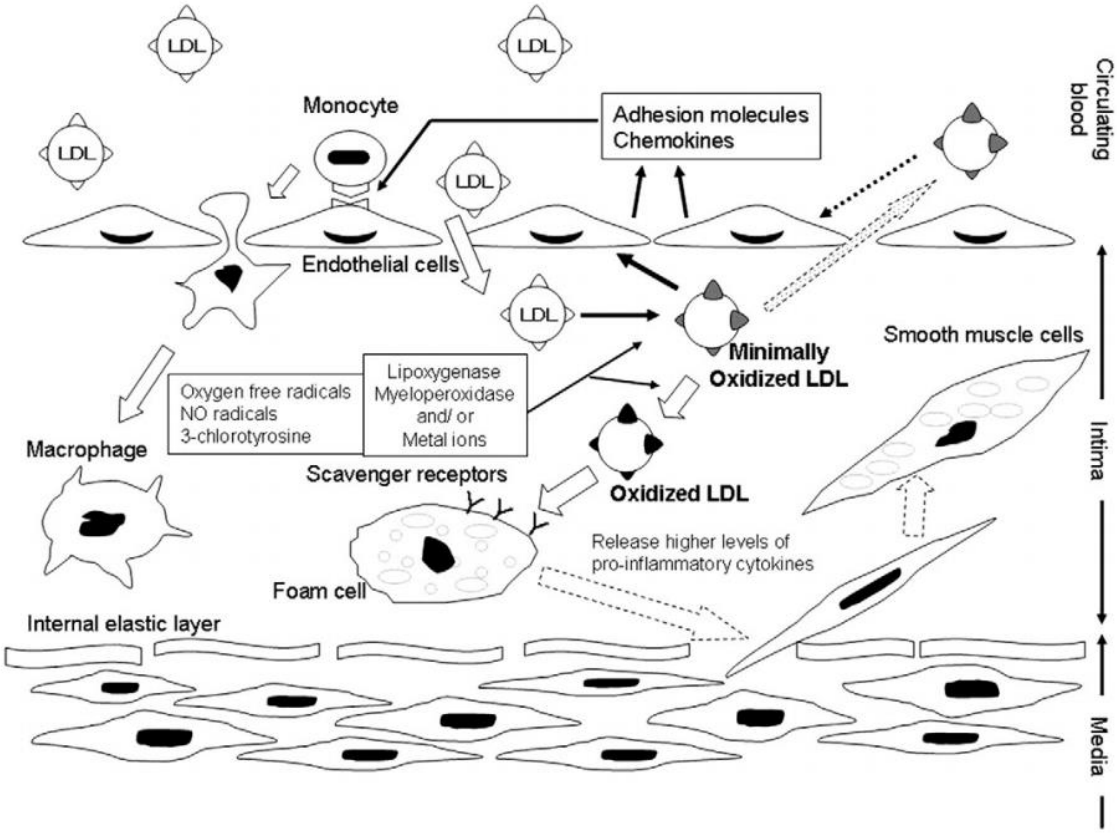

Figure 4 Mechanisms of LDL oxidation and macrophage foam cell formation in the artery wall (30)

In vitro oxidation of LDL by metal ions occurs in three phases: an initial lag phase (consumption of endogenous antioxidant), a propagation phase (rapid oxidation of unsaturated fatty acids to lipid hydroperoxides), and a decomposition phase (formation of reactive aldehydes). These aldehydes respond with lysine residues in apoB-100, the resulted in oxidized LDL. NO inhibits copper-mediated oxidation. The metal ion-dependent enzyme lipoxygenase converts polyunsaturated fatty acids into lipid hydroperoxides and thereby oxidizes LDL. Activated macrophages secrete myeloperoxidase, which generates reactive species, thereby oxidizing protein and lipid moieties of LDL. NO is converted under aerobic conditions to nitrite. Nitrite inhibits the myeloperoxidase-mediated oxidation of LDL. Finally, oxidized LDL is interacting with scavenger receptors present on endothelial cells, macrophages, and smooth muscle cells(31).

Oxidative stress and diabetic cardiovascular complications

Oxidative stress is caused by an imbalance between the production of ROS and physiological ability to immediately eliminate the reactive intermediates or easily repair the resulting damage. There are many molecules that contain one or more unpaired electrons. Table 1 lists important radical and non-radical reactive species according to reactivity towards polyunsaturated fatty acids(32).

Table 1 Reactive oxygen species

Type of free radical	
Reactive oxygen species	H_2O_2 ozone O_3
Superoxide anion $O_2^{\bullet-}$	Hypobromous acid, HOBr
Hydroxyl, $HO_2^{\bullet}$	Hypochlorous acid, HOCl
Peroxyl, $RO_2^{\bullet}$	Singlet oxygen
Alkoxyl, $RO^{\bullet}$	Organic peroxides, ROOH

There is increasing evidence in both experimental and clinical studies suggesting that oxidative stress play a pivotal role in the pathogenesis of both type of diabetes mellitus. Free radicals are produced excessively in diabetes via glucose

oxidation, non-enzymatic glycation of proteins and subsequent oxidative degradation of glycoproteins. Uncontrolled processes of antioxidant defense and abnormally high levels of free radicals can be responsible for physiological damages such as damage of cellular organelles and enzymes, lipid peroxidation, and development of insulin resistance.

In its enediol form, glucose is oxidized in a transition metal-dependent reaction to enediol anion radicals that is converted into reactive ketoaldehydes and to superoxide anion radicals. The superoxide radicals are dismutated by superoxide dismutase (SOD) to hydrogen peroxide, which can catalyze free transition metals leading to production of harmfully reactive hydroxyl radicals if hydrogen peroxide is not eliminated by catalase or glutathione peroxidase. Superoxide anion can also react with nitric oxide to form reactive peroxynitrite radicals. By superoxide dependent pathway, extremely lipid peroxidation of LDL has been observed in the patients with hyperglycemia. Free or non-esterified fatty acids (FFA) are elevated in diabetic patients. Excess FFA enters the citric acid cycle and generates acetyl-CoA to produce excess NADH, which increases mitochondrial superoxide production. In humans, acute infusion of FFA has been shown to cause elevations in isoprostanes, which are the induction of lipid peroxidation.

Another source of free radicals in diabetes is the interaction of glucose with proteins, which can be responsible for the formation of an Amadori product and then advanced glycation end-products (AGEs). These AGEs result the inactivation of enzymes, the induction of free radical formation, and inhibition of antiproliferative effect of nitric oxide. AGEs also stimulate the transcription factor (NF-κB), which enhances increased nitric oxide. This result is believed to be a mediator of islet beta cell damage. Additionally, oxidative stress in diabetes is also associated with decreased glutathione levels and depletion of NADPH levels. Alternatively, increased sorbital dehydrogenase activity is linked to NAD levels leading to protein modification by nonenzymatic glycosylation of lens proteins. Mechanisms of the changes in diabetes neuropathy and the induction in sorbitol pathway are not completely clear. One possible mechanism, metabolic imbalances in the neural

tissues, has been implicated in impaired neurotropism, neurotransmission changes, Schwann cell injury, and axonopathy(33).

Summary of mechanisms of diabetes-induced oxidative stress and their potential roles in atherosclerosis is presented in Figure 3. Oxidative stress, as an important key, leads to many proatherogenic events such as LDL oxidation, endothelial dysfunction, and vascular smooth muscle proliferation and migration.

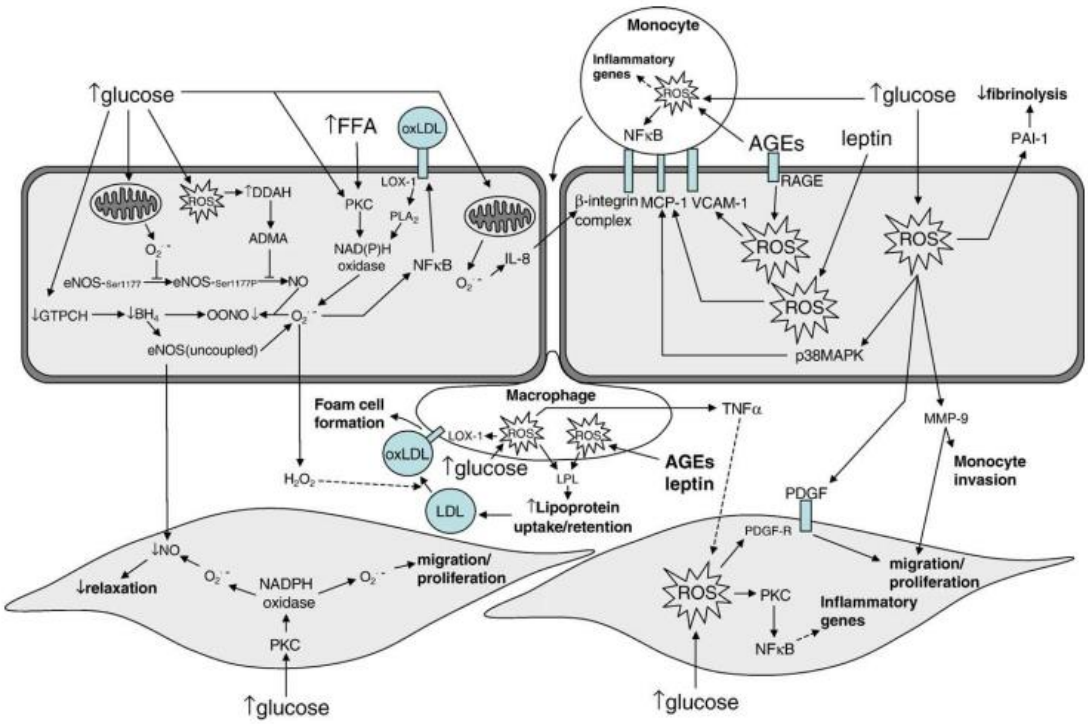

Figure 5 Consequences of oxidative stress-induced signaling mechanisms in diabetes.(34)

ROS, reactive oxygen species; $NO^{\bullet}$, nitric oxide, $O_2^{\bullet-}$, superoxide, eNOS, endothelial nitric oxide synthase; NF-κB, nuclear factor κB, FFA, free fatty acids, AGEs, advanced glycation end-products, RAGE, receptor for AGE; PDGF, platelet derived growth factor, PDGR-R, PDGF receptor, ADMA, asymmetric dimethyl arginine, DDAH, dimethylarginine dimethylaminohydrolase; PKC, protein kinase C; PLA_2. phospholipase A_2: BH_4, tetrahydrobiopterin, GTPCH, GTP-cyclohydrolase I; MMP-9, matrix metalloproteinase-9; p38MAPK, p38 mitogen-activated kinase; IL-8, interleukin-8; OxLDL, oxidized LDL; LOX-1, lectin-like OxLDL receptor-1; MCP-1,

monocyte chemoattractant protein-1; VCAM-1, vascular cellular adhesion molecule-1; TNF-α, tumor necrosis factor α(34).

Endothelial cell dysfunction

Alterations in endothelial cell function are proposed to play an important role in atherogenesis. These perturbations include the loss of endothelial cell-directed vasodilatation, the increased expression of cellular adhesion molecules such as vascular cell adhesion molecule-1 (VCAM-1) and intercellular cell adhesion molecule-1, increased permeability so circulating lipoproteins (notably LDL), and increased retention of these lipoproteins. A number of studies have shown that patients with either type 1 or type 2 diabetes exhibit endothelial dysfunction. Furthermore, the endothelial function in diabetic patients can be improved with antioxidants, suggesting that oxidative stress plays an important role in the pathogenesis of endothelial dysfunction in diabetes(35-38)

The major contributor to endothelial oxidative stress is the increased production of superoxide. This seems to occur via two principal sources: NADPH oxidases and uncoupled eNOS. Hyperglycemia, AGE, FFA, and OxLDL have been shown to increase endothelial NADPH oxidase activity. The activation of NADPH oxidases by hyperglycemia and FFA has been shown to be mediated by PKC. Vessels isolated from diabetic patients exhibit increased superoxide production that is inhibited by diphenylene iodonium, and demonstrate increased expression of several NADPH oxidases subunits (p22phox, p47phox, and p67phox) (39), suggesting that NADPH oxidases are more active in diabetes. Not only does excess superoxide itself cause increased oxidative stress, but it can also react with nitric oxide ($NO^{\bullet}$) to produce peroxynitrite, which, in turn, can oxidize tetrahydrobiopterin (BH_4), thus reducing its availability to eNOS. In the presence of reduced concentrations of BH_4, eNOS becomes uncoupled and transfers electrons to molecular oxygen instead of l-arginine to produce superoxide rather than NOS. The presence of uncoupled eNOS in the diabetic vasculature is supported by a study in which diabetic vessels were found to produce less superoxide when incubated with the $NO^{\bullet}$ synthase inhibitor *NG*-nitro-l- arginine methyl ester. BH_4 availability may also be decreased by a reduction of its synthesis. The expression of GTP-cyclohydrolase I (GTPCH), the rate-limiting

enzyme for de novo BH_4 synthesis, is reduced in diabetic rats, indicating that uncoupled eNOS plays a role in diabetic endothelial. Furthermore, transgenic mice overexpressing GTPCH treated with streptozotocin (STZ) are able to maintain endothelial via two principal sources: NADPH oxidases and uncoupled eNOS(40).

The oxidative stress caused by diabetes leads to the decreased bioavailability of $NO^{\bullet}$ and subsequent impairment of endothelial-directed vasodilation. As noted above, superoxide can react with $NO^{\bullet}$. There is also evidence for several mechanisms that lead to the inactivation of eNOS itself. Hyperglycemia causes O-linked *N*-acetylglucosamine modification of serine 1177 on eNOS, the Akt activation site. This modification prevents its phosphorylation and is caused by hyperglycemia-induced mitochondrial superoxide production and activation of the hexosamine pathway(41). The oxidative stress produced by diabetes may also inhibit Akt activity. It has been demonstrated that oxidative stress induces serine phosphorylation of insulin receptor substrate-1 (IRS-1) and targets it for degradation. The decrease in IRS-1 leads to the impaired activation of the phosphatidylinositol 3-kinase/Akt pathway. Hyperglycemia also seems to result in the accumulation of asymmetric dimethylarginine (ADMA), an inhibitor of eNOS. In STZ-treated rats, the activity of dimethylarginine dimethylaminohydrolase (DDAH, an enzyme which catabolizes ADMA) is decreased, resulting in an increase in ADMA. This decreased DDAH activity also seems to be caused by oxidative stress, as polyethylene glycol- conjugated superoxide dismutase was able to reverse the effects of hyperglycemia-induced DDAH inactivation(42, 43). Together, these findings suggest that oxidative stress can inhibit eNOS activity in diabetic patients through multiple mechanisms.

Elevated concentrations of glucose, FFA, leptin and the presence of AGE can cause a multitude of proatherogenic consequences that are mediated by ROS in endothelial cells. Hyperglycemia can increase monocyte adhesion by the increased expression of MCP-1 via p38 mitogen-activated kinase and through the activation of β1-integrin by interleukin-8 and ROS from a mitochondrial source. Monocyte invasion and vascular smooth muscle cell (VSMC) migration may be facilitated by the ROS-mediated expression of MMP-9, which has been shown to be induced by glucose. Glucose induced ROS also increases the secretion of platelet derived growth

factor (PDGF), a known smooth muscle cell mitogen, and plasminogen activator-1. ROS produced by leptin have been shown to activate the transcription factors NF-κB and activated protein 1 (AP-1) as well as increasing MCP-1 expression. FFA induced ROS also increase NF- κB binding. AGE cause increases in VCAM-1 expression and vascular permeability through ROS. In vivo studies have demonstrated that the increased levels of soluble adhesion molecules found in diabetics can be decreased through the administration of antioxidants. Furthermore, FFA induced endothelial dysfunction produced in healthy volunteers is improved by co-administration of vitamin C. These findings demonstrate the central role of oxidative stress in many aspects of the endothelial contribution to atherosclerosis(44-47).

Effect of Exercise on Lipid Metabolism and Insulin Sensitivity

Immediately There are several approaches to treating T2DM, including insulin therapy. The best way to prevent obesity and related metabolic disorders is through lifestyle modifications, improving nutrition and physical activity or exercise behaviors. In addition to a healthy diet, physical activity looks like to play a key role. It is well known that regular exercise improves blood glucose control, which can prevent, or prolong for T2DM. It also improves quality of life, has a positive effect on lipid metabolic, blood pressure, cardiovascular incidence. Physical activity and exercise that improves glucose homeostasis can be divided into two types: aerobic exercise and anaerobic exercise (strength/ resistance training). Aerobic training is imposed as an activity involving multiple muscle groups and a duration of continuous and rhythmic action such as dancing, cycling, jogging or long-distance running walking and swimming. This type of training is completely dependent on oxygen availability. Because this type of exercise muscles need oxygen to produce energy in the form of adenosine triphosphate (ATP) from fatty acids, carbohydrates, and amino acids. Insulin sensitivity is enhanced by exercise by increasing translocation of glucose transporters to the plasma membrane. Improve the pathophysiological pathways associated with insulin resistance. (reduction of adipokines in response to inflammatory and oxidative stress), and improving insulin signal transduction through various molecular pathways.

In contrast to aerobic exercise is anaerobic exercise, which is meant to be short and fast or high-intensity exercise. The mechanisms underlying cause the positive effects of resistance exercise training on blood glucose homeostasis and cellular response to insulin (insulin sensitivity) are like to be those in aerobic training. Resistance exercise training is effective in the treatment of diabetes in the population of elderly people with the high-risk factors of T2DM. This type of training significantly improved glycemic or blood glucose control and increases muscle mass whilst reducing abdominal obesity. As if aerobic exercise, anaerobic exercises have been shown to have an influence positively on the parameters associated with metabolic syndromes, such as glucose intolerance, hyperinsulinemia, hypertension, and hypertriglyceridemia. The rate of insulin-stimulated glucose uptake was increased with both types of exercise. It is worth noting that the increase in muscle mass is independent of the improvement in glucose transport after resistance training. This means that neither of these exercises need to increase skeletal muscle mass to improve glucose metabolism. Another type of exercise training that seems to be recognized as a good way to combat insulin resistance is high-intensity interval training (HIIT). This type of training is performed at maximum intensity for a short period of time. HIIT can be used as an effective alternative to traditional endurance training. In healthy and diseased populations, this exercise could be used to effectively induce similar changes in the physiological, performance, and various signs related to health. HIIT benefits improve heart function, blood pressure, metabolism of lipid, oxidative stress, and destructive markers. Recent studies have shown that HIIT appears to be effective in improving insulin sensitivity too, especially in people at risk for T2DM. However, data on insulin sensitization efficacy are inconsistent and the molecular mechanisms involved in the effectiveness of HIIT on skeletal muscle in individuals with insulin resistance (IR) have not been thoroughly investigated. In all probability, the impact of HIIT on IR is caused by higher skeletal muscle mitochondrial function. HIIT has shown that it has been being a potent activator of upstream signals to mitochondrial biogenesis such as mitochondrial transcription factor A (TFAM) and peroxisome proliferator-activated receptor-gamma coactivator 1 alpha (PGC1-α).

Effect of Physical Activity on Insulin Signaling Pathway

There are three main reasons why exercise plays such an important role in improving insulin sensitivity. First of all, exercising increased capillary blood supply, which leads to an increase in the absorption of glucose in the muscles. Second, it increases the transport of sarcolemma and t-tubular glucose from the interstitial to the muscle. This is supported by an increased content of glucose transporter 4 (GLUT4) in cell membranes increased by physical activity. Thirdly, physical activity or exercise activates molecular mechanisms that lead to GLUT4 translocation to the plasma membrane. Animal model studies have shown that aerobic exercise training improves insulin sensitivity as evidenced by a decrease in the value of the homeostatic model assessment of insulin resistance (HOMA-IR) or the Lee index in trained animals compared to the reduced sedentary group showed similar results in research involving humans. The results of these studies confirmed that aerobic exercise training increased insulin sensitivity. Existing data also suggest that improved glucose tolerance and whole-body insulin sensitivity may be due to short-term aerobic exercise training. Based on the available data, that physical activity benefit is beneficial for several proteins in the insulin pathway. Physical exercise training increases the muscle uptake of insulin-stimulated glucose through increased expression and/or activity of proteins involved in the intracellular insulin signaling pathway It has been shown to increase both the content and phosphorylation of exercise-induced insulin receptors. Apart from that, it is well-known that phosphorylation of tyrosine residues in the IR allows for proper signal transduction of insulin, in the event that phosphorylation of serine residues inhibits the insulin pathway. Da Silva's studies have found that even a single physical exercise training improved insulin signaling by inhibiting phosphorylation of serine residues and increasing phosphorylation of tyrosine residues in insulin receptor substrate 1. Moreover, performed studies display those physical exercises training also increase mRNA level of phosphoinositide 3-kinase (PI3K). PI3K through Akt/PKB signaling pathway, not only affects the increase of glucose uptake but also the increase in glycogen synthesis. It was monitored that the uptake of glucose into the skeletal muscle was greatly increased. This will persist for several hours after a single workout. The muscle contraction promotes glucose transporter 4 (GLUT4)

translocation from intracellular sources to the sarcolemma and T tubules, this increases the number of sites where glucose can be transported into the muscles. Besides, it has been shown that increasing GLUT4 translocation to the cell membrane in addition to exercises, likewise leads to an increase in the intracellular level of this protein. Resistance training leads to an increase in GLUT4 expression in both human and animal skeletal muscles. Moreover, it has been demonstrated that aerobic exercise training is a potent inducer for GLUT4 enhancer factor (GEF), resulting in improving glycemic control and increased GLUT4 expression. It has been found, that a single bout of exercise also increases the Akt substrate regulating GLUT4 (AS160 level) and Akt/PKB threonine phosphorylation and serine phosphorylation of this protein in rat skeletal muscle. This leads to the enhancement of insulin-stimulated glucose transport by increasing GLUT4 translocation to the plasma membrane. Furthermore, studies showed the beneficial effect of three-week exercise on the increased expression and activity/phosphorylation of Akt and AS160 conducted on healthy young men. Glycogen synthesis with decreased regulation of glycogen synthesis (GS) activity was increased through physical activity in addition to increased glucose uptake. Studies in humans have shown that in both healthy and T2DM subjects physical exercise training significantly increases GS activity. During exercise, GS activity is affected by both stimulatory and inhibitory factors, consequently, the result of the relative strength of various stimuli from the effect of exercise on GS activity. In conclusion, physical exercise training increases glucose uptake, as well as that glycogen synthesis in the skeletal muscle with no change in glycogen synthase expression. Also revealed that low-intensity strength training leads to increase insulin receptors and an increase in the content of GLUT4 protein. Improvement in insulin stimulating glucose transport in aerobic exercise and resistance training animals results from, among other things, an increase in the basic isoform of insulin-sensitive glucose transporter (GLUT4). Yaspelkis et al, found in their studies that the level of GLUT4 protein in aerobic exercise training animals was increased in lower leg muscles, which are mainly used for running (i.e., soleus muscles, plantar muscle, red gastrocnemius muscle). In turn, in animals after resistance exercise training, the GLUT4 content was higher in the muscles of the upper limb that are needed to perform a squat. Brought

together, these pieces of information confirm that the mechanisms of action of different forms of exercise training in improving glucose homeostasis are similar.

Physical Activity and Lipid Metabolism

The effect of exercise on an increase in insulin sensitivity is largely caused by an improvement in the metabolism of lipids. One of them the main effects of exercise or physical activity was the reduction of fat mass, particularly in the visceral region, associated with a significant reduction in obesity. This improves metabolic disorders associated with obesity, including insulin resistance. Both types of exercises, resistance exercise and aerobic exercise, cause of reduced visceral adipose tissue and subcutaneous. Exercise or physical activity inducing improvements in body composition has a positive effect on inflammation associated with obesity. It was found that the levels of circulating blood mediators from adipose tissue, particularly TNFα-1 and IL-6, were decreased with exercise which could result in weight loss. It is worth noting that in obesity, weight loss has a positive effect on hormonal balance. A study by Milan et al. It was proved that weight loss in obese rats increased adiponectin expression in visceral adipose tissue. All these changes were accompanied by higher glucose uptake caused by improved insulin sensitivity. The improvement in insulin sensitivity appears to be due to the reduction of inflammation or the normalization of hormone balance as a result of prolonged exercise and is also associated with weight loss. All the same, studies have shown that physical activity or exercise could induce insulin sensitivity independent of weight loss and fat distribution. Moreover, studies by Koh et al. have shown that inflammation can be reduced by physical activity or aerobic exercise training without a total fat mass being reduced. Despite this, physical activity or aerobic exercise training has also been shown to statistically reduce TNF-α concentration while keeping body weight the same at baseline. An interesting result was presented by Nassis et al. who showed that even with 12 weeks of aerobic exercise, girls who were overweight or obese had significantly increased insulin sensitivity. However, what is more important, these changes occurred while keeping body weight the same at baseline, the same percentage of fat, and the unchanged concentration of circulating adiponectin, IL-6, CRP, and other inflammation markers. The information presented here is

recommended that increased physical activity or aerobic exercise training may improve the metabolic disturbances associated with obesity. The phenomenon of interest, associated with regular physical activity, is called the athlete's paradox. T2DM and insulin resistance are associated with increased intramuscular lipids content. Since in endurance athletes the higher the amount of these lipids, the higher the oxidation capacity and the increased insulin sensitivity. It has been shown that physical activity or aerobic exercise training increases the expression of the genes responsible for triacylglycerols synthesis, which in turn leads to the accumulation of triacylglycerol (TAG) in the muscles. The higher level of intramuscular TAG in athletes acts as adaptive responsiveness to endurance exercise training. During prolonged exercise, it improves for a greater contribution of the lipid pool as a substrate source. A study that also had similar results by Dube et.al studied previously obese or overweight, insulin-resistant older subjects and found that the effect of exercise training on intramuscular lipid levels, muscle oxidative capacity, and insulin sensitivity. The data provided by these researchers showed that training significantly increased levels of intramuscular lipid. However, it decreases the content of diacylglycerol and ceramide at the same time.

In other studies that comparing the effects of treadmills based on high-intensity interval training (HIIT) or moderate-intensity continuous training (MICT) on markers of oxidative stress inflammation in patients with T2DM, the main findings were that there were no effects of either training intensity on circulating redox homeostasis or inflammatory biomarker over the initial 12-week intervention period and a decrease in total antioxidant capacity in the MICT group from baseline to 1 year(48).

Also, other studies were an attempt to assess the effects of aerobic exercise upon fatigue symptoms associated with markers of systemic inflammation in obese patients with T2DM. Experimental design of this study's obese patients with T2DM were divided the experimental group. Into 2 subgroups; group (A) received treadmill aerobic exercise training on treadmill and group (B) received no exercise training. All participants received an examination of the inflammation parameters and fatigue symptoms were measured by the completion of the Multidimensional Fatigue

Inventory (MFI). The results show that significant associations were found between fatigue symptom dimensions and circulating levels of inflammatory markers in obese patients with T2DM, the involvement of the inflammatory process in the development of fatigue associated with T2DM. It has been shown that treadmill walking exercise training with an intensity 60-70% of maximum heart rate for three months is an effective treatment policy to improve symptoms of fatigue related to inflammatory cytokines in obese patients with T2DM.

CHAPTER III
REASEARCH METHODOLOGY

Materials and methods

Subjects

One hundred and fifty-one women from the seven sub-districts of Sai Ngam district, Kamphaeng Phet Province (February 2011–January 2013) were selected from the total of 428 abdominal obesity subjects who participated in a Project of Health Survey for Protection of Hypertension and T2DM (age ≥ 40 years). All eligible participants were apparently healthy with no clinical signs of associated pathologies, no antihypertensive and antihyperglycemic medication, no history of coronary, cerebrovascular atherosclerotic disease, end stage renal failure, cancer, infection and any life-threatening diseases. They all agreed to participate a two months aerobic dance exercise (45-60 minutes) in the present study. All women were subjected to physical and medical examination. All participants gave written informed consent and they all agreed to participate and to provide blood sample for their health check before and after study period. The experimental designs were approved by Naresuan University Institutional Review Board (The certificate number 0319/62) and were conducted in accordance with the Declaration of Helsinki.

Aerobic dance exercise

All 151 women were participated the aerobic dance exercise in each center of the seven sub-districts of Sai Ngam district, Kamphaeng Phet Province. This aerobic dance exercise session proceeded for 45-60 minutes/day, 5 days/week on the 2 months. This aerobic exercise was performed between 5:00 and 6:00 pm, participants were recommended to do 8-minute warm-up routine, which stretches and strengthens the muscles of the hips, thighs, and ankles before start into an aerobic dance exercise. After warm-up, participants will begin with a fast music (K-pop, hip-hop, pop) for bounce, bending the knees and moving the shoulders. Step one foot out to the right for a double bounce, bring it back in and repeat to the left. Next step to the side for a single bounce and do the same on the other side. Keep the shoulders moving to this dance workout and pick up the rhythm with some quicker side steps. Move the arms

even more for a total-body workout taken from the dance floor (field). Bounce the body as continue the dance workout with forward steps. Really pop those hips and raise the elbows. Follow along with this fun aerobic dance exercise workout to dance away the weight and shake out the stress.

Anthropometric and Blood Pressure Measurement

Subjects' height, weight, and blood pressure (BP) were measured and body mass index (BMI) was calculated. Waist circumference (WC) was measured at the midpoint between the both of rib cage and the top of lateral border of iliac crest during minimal respiration. Abdominal obesity defined as WC ≥ 80 cm or 31.5 inches (female)(49). BP was measured after the participants seated and rested for 5 minutes as the mean value of at least two measurements of these participants on the same day with a Terumo digital BP monitor (ES-P110). Hypertension was defined as an average BP ≥ 140/90 mmHg or if the participant was taking antihypertensive medications or had been diagnosed with hypertension (HT)(50).

Blood Sample Collection and Biochemical Determination

Venous blood samples were collected without stasis after 12 h fast and a 30 min rest in a supine position. Blood specimens were processed and assayed at the central laboratory of Department of Medical Technology, Faculty of Allied Health Sciences on the same day, both in before and after study period. Fasting plasma glucose (Glu), blood urea nitrogen (BUN), uric acid (UA), total cholesterol (TC), triglycerides (TG), high density lipoprotein cholesterol (HDL-C) were assayed on the Hitachi 912 auto-analyzer (Roche Diagnostic, Switzerland) and low-density lipoprotein cholesterol (LDL-C) was calculated by Friedewald's equation, which was valided for TG values less than or equal to 400 mg/dl.

Insulin Assay

Fasting insulin levels were measured based on micro-particle enzyme immunoassay technology using Abbott reagents with Axsym system (Abbott laboratories, Illinois, USA). All participants underwent evaluation of Homeostasis model assessment (HOMA)-formula for insulin resistance index (HOMA-IR), HOMA%B [as beta cell function (insulin activity)] and Quantitative Insulin

Sensitivity Check Index (QUICKI; as insulin sensitivity)(51-53). HOMA-IR was defined using the following formula: fasting glucose (mmol/l) × fasting insulin (lU/ml)/22.5. HOMA %B as formula: [20 × insulin (lU/ml)]/[glucose (mmol/l) – 3.5]. QUICKI as formula: 1/[LOG (insulin (lU/ml)] + LOG [glucose (mmol/l)].

Malondialdehyde (MDA) Assay

The method is based on the formation of red (pink) chromophore following the reaction of thiobarbituric acid (TBA) with MDA and the other breakdown products of peroxidized lipids called thiobarbituric acid reactive substance. One molecule of MDA reacts with two molecules of TBA to yield a pink pigment with maximum absorption at 532 nm. This was measured by spectrophotometry using 1,1,3,3-tetraethoxypropane as standard as described previously(54). The final results were expressed as μmol of MDA formed per liters of serum. Intra-assay and Inter-assay imprecision were 3.24 and 5.78 %, respectively. The normal range of MDA was < 3.5 μmol/L.

Total Antioxidant (TAC) Status

The method is based on formation of the $ABTS^{\bullet+}$ cation [2, 20-azinobis (3-ethylbenzothiazoline-6-sulfonic acid)] and its scavenging by antioxidant sample constituents (serum) measured by spectrophotometry at 600 nm decay of green/blue color absorption is inversely associated with antioxidant sample content and the control antioxidant is Trolox, a hydrophilic vitamin E analog(55).

Systemic Inflammation Assays

The concentrations of IL-6 and TNF-α determined using by the ELISA assay kits which purchased from Invitrogen (Carlsbad, CA). Standard curves were constructed for determination of each analyte concentration according to the manufacturers' instructions. In accordance with standard practice, a protocol provided by Invitrogen for custom assays was used with no modifications. High sensitivity CRP (hs-CRP) concentrations were determined by using latex-enhanced immunonephelometric assay on the Hitachi 912 auto-analyzer (Roche Diagnostic, Switzerland) that has been standardized against the World Health Organization reference. The normal range of hs-CRP was <3.0 mg/l.

Statistical analysis

The distributions of variables were expressed in median and interquartile range. Wilcoxon signed ranks tests (2-tailed non-parametric tests) were used to assess the differences between before and after of the study period. *P*-values less than 0.05 were considered statistically significant. All analysis was performed using the SPSS computer program version 13.0 (SPSS, Chicago, IL).

CHAPTER IV
RESULT AND DISCUSSION

One hundred and fifty-one obese women from the seven sub-districts of Sai Ngam district, Kamphaeng Phet Province only were carried out the two months period of continuous aerobic dance exercise without any adverse events. Physical and biochemical parameters were measured before and after exercise for two months. General clinical characteristics at the beginning of these obese women showed median aged of participants at 48.0 years (Q1-3= 41 – 56) and demonstrated the values of median and interquartile systolic blood pressure, diastolic blood pressure, Body Mass Index and waist circumference being about 126.0 (116.0 – 140.0) mmHg, 80 (71.0 – 85.0) mmHg, 26.2 (23.4 – 29.1) kg/m^2, and 86.0 (81.0 – 94.0), respectively (Table 2).

Table 2 The participant's characteristics testing at baseline (n=151)

Parameter	Median	Range (Q1-Q3)
Age (years)	48.0	41.0 - 56.0
Systolic blood pressure (mmHg)	126.0	116.0 - 140.0
Diastolic blood pressure (mmHg)	80.0	71.0 - 85.0
Body Mass Index (kg/m^2)	26.2	23.4 - 29.1
Waist circumference (cm)	86.0	81.0 - 94.0

Table 3 showed the comparison of anthropometric, blood pressure and clinical markers of participants before and after aerobic dance exercise study. After aerobic dance exercise period, we found that Glu, BUN, CT, UA, TC, TG and LDL-C levels were significantly decreased (p<0.05), while eGFR and HDL-C levels were significantly increased (p<0.05).

Table 3 Effect of aerobic dance exercise on physical and chemical parameters of AO subjects before and after training.

Parameter	Before		After		*p*-value
	Median	Range (Q1-Q3)	Median	Range (Q1-Q3)	
Age (years)	48.0	41.0 - 56.0	48.0	41.0 - 56.0	
Systolic blood pressure (mmHg)	126.0	114.0 - 138.0	126.0	116.0 - 140.0	0.336
Diastolic blood pressure (mmHg)	79.0	72.0 - 85.0	80.0	71.0 - 85.0	0.450
Body Mass Index (kg/m^2)	26.2	23.4 - 29.1	25.7	23.8 - 28.8	0.054
Waist circumference (cm)	86.0	81.0 - 94.0	87.0	80.0 - 94.0	0.372
Glu (mmol/L)	5.28	4.95 - 6.05	4.95	4.51 - 5.72	<0.001
BUN (mmol/L)	4.64	3.57 - 5.71	3.92	3.21 - 4.64	<0.001
CT (μmmol/L)	79.56	70.72 - 79.56	79.56	70.72 - 88.40	<0.001
UA (mmol/L)	339.2	261.8 - 428.4	315.4	267.8 - 392.7	0.002
eGFR (ml/min/1.73 m^2)	80.24	64.58 - 96.50	84.62	69.68 - 104.76	0.033
TC (mmol/L)	5.57	2.97 - 6.27	5.24	4.64 - 6.19	0.005
TG (mmol/L)	1.89	1.29 - 2.98	1.66	1.13 - 2.31	<0.001
HDL-C (mmol/L)	1.45	1.25 - 1.79	1.50	1.32 - 1.75	<0.001
LDL-C (mmol/L)	3.07	2.42 - 2.68	2.94	2.29 - 3.56	0.033

Note: Glu, Glucose; BUN, blood urea nitrogen; CT, creatinine; UA, uric acid; eGFR, Estimated glomerular filtration rate; TC, total cholesterol; TG, triglyceride; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol

The results of insulin resistance and low-grade inflammation demonstrated in Table 4. After aerobic dance exercise, we found that Glu, Insulin, HOMA-IR, MDA, hs-CRP, TNF-α, and IL-6 levels were significantly decreased (p<0.05), while TAC, HOMA%β (β-cell function) and QUCKI (insulin sensitivity) were significantly increased (p<0.05).

Table 4 The effect of aerobic dance exercise on insulin resistance and low-grade inflammation between before and after aerobic dance exercise study

Parameter	Before		After		*p*-value
	Median	Range (Q1-Q3)	Median	Range (Q1-Q3)	
Glu (mmol/L)	5.28	4.95 - 6.05	4.95	4.51 - 5.72	<0.001
Insulin (µU/ml)	6.00	4.00 - 9.50	5.50	3.70 - 8.30	0.008
HOMA-IR	0.80	0.50 - 1.30	0.70	0.50 - 1.10	0.009
HOMA%B	69.2	46.4 - 95.1	75.0	53.3 - 105.9	0.006
QUICKI	123.8	75.7 - 189.3	143.4	89.8 - 205.0	0.002
MDA (µmol/l)	4.67	3.82 - 5.78	4.50	3.66 - 5.50	0.007
TAC (µmolTroloxEquiv/L)	547.0	407.4 - 774.2	564.0	423.0 - 787.0	0.006
hs-CRP (mg/L)	2.36	0.95 - 5.84	2.16	0.97 - 4.26	<0.001
TNF-α (pg/ml)	3.58	2.21 - 4.98	3.14	2.13 - 4.58	0.004
IL-6 (pg/ml)	2.78	1.21 - 3.74	2.01	1.12 - 3.00	<0.001

Note: Glu, Glucose; HOMA-IR, homeostatic model assessments of insulin resistance; HOMA%B, homeostatic model assessment of beta-cell function;
MDA, Malondialdehyde; TAC, total antioxidant capacity; hs-CRP, high sensitivity C-reactive protein; TNF-α, Tumor necrosis factor (TNF)-alpha; IL-6, interleukin-6

Discussion

In the 21st century, when obesity is recognized as a civilization-related, economic, and social burden and the numbers of obese and overweight individuals still increase, we need new strategies to prevent and treat those conditions. Since excess body weight results from an imbalance between energy intake and energy expenditure, one way to maintain correct body weight is to stimulate lipid catabolism through increased physical activity. Increased physical activity is the best way to maintain good health. During exercise, triacylglycerols, an energy reservoir in adipose tissue, are hydrolyzed to free fatty acids which are then released into the circulation, providing fuel for working muscles. Thus, regular physical activity leads to a reduction of adipose tissue mass and improves metabolism. However, the reduction of lipid reservoirs is also associated with many other interesting changes in adipose tissue fatty acids metabolism. For example, prolonged exercise contributes to a decrease in lipoprotein lipase activity and the resultant reduction of fatty acids uptake. This results in the improvement of mitochondrial function and upregulation of enzymes involved in the metabolism of polyunsaturated fatty acids. The exercise-induced changes in adipocyte metabolism are associated with modifications of fatty acid composition. The modifications are adipose tissue depot-specific and follow different patterns in visceral and subcutaneous adipose tissue. Moreover, exercise affects adipokine release from adipose tissue, thus, reducing inflammation and improving insulin sensitivity.

Abdominal obesity (AO) may indicate an individual has visceral adipose tissue around the stomach and abdomen. Also known as central obesity, may indicate an individual's visceral adipose tissue is a calorie surplus resulting from excess energy intake and/or reduced energy expenditure(56). AO is the one major risk factor of metabolic syndrome (MetS), which is a cluster of cardiovascular risk factors characterized by visceral obesity, dyslipidemia (low levels of HDL-C and elevated TG levels), hypertension, glucose intolerance and also demonstrated by insulin resistance and low-grade inflammation with increased adipokine production(56). Our study demonstrated that baseline of AO women showed elevate results in BP, BMI, WC, Glu, TG, LDL-C, insulin, insulin resistance, MDA, TNF-α, IL-6, hs-CRP, and

decreased in HDL-C, insulin sensitivity (QUICKI), β-cell function (HOMA %B) and TAC.

Cardiovascular diseases are the public health problem and leading cause of mortality in the world. The most common forms of CVDs are composed with ischemic heart disease, stroke and arterial hypertension. The cardiovascular risk is continuous during the life and depends on the many factors such as age, sex, smoking, diet habits, high blood pressure and hyperlipidemia.

Oxidative stress results from an imbalance between oxidizing compounds and antioxidant and more recently as a disruption of redox signaling and control. An improper activation of oxidative processes can be chronically present in pathological conditions such as arterial hypertension and diabetes mellitus, contributing to the oxidative damage. Vasorelaxant molecules, nitric oxide (NO), hydrogen sulfide (H2S), and prostaglandin I2 (PGI2), play a fundamental role in the regulation of vascular tone and are especially damaged by excessive oxidative stress production.

More important of ROS elevation may cause damage of macromolecules and produce cytotoxic end products (57, 58). Vascular oxidative stress caused activation of systemic inflammatory pathways which play an important role in the pathogenesis of CVD. Total antioxidant status is a measure of the net balance of the interactions between ROS and antioxidants in circulation, assessing the ability of the antioxidants to inhibit the specific radial formation (59). This method provides an overall measure of antioxidant status and does not give information on the specific species of antioxidants. OS or increased free radical generation leads to inflammation, lipid peroxidation and macro-molecules damage, which are associated with the onset of various pathological conditions, such as cardiovascular disease (CVD), diabetes mellitus, cancer and obstructive pulmonary disease (60, 61).

Characterized by low-grade inflammation with abnormal adipokine product. Adipose tissue produces numerous adipokines such as adiponectin, leptin, and cytokines such as TNF-α and IL-6. High sensitivity-CRP is a sensitive general marker of low-grade tissue inflammation that is not only associated with features of insulin resistance but has also independently predicted the development of hypertension, MetS, T2DM, and CVD. IL-6 has been suggested to promote hs-CRP production by

the liver as a component of the sub-clinical inflammation related to obesity. Malondialdehyde (MDA) is the end product of the degradation of unsaturated lipids causing oxidative stress and represent. a lipid peroxidation marker which results from increased oxidative stress in AO subjects (16). Total antioxidant status is a measure of the net effect of the interactions between ROS and antioxidants in circulation, assessing the ability of the antioxidants to inhibit the formation of a specific radial. This method allows for the assessment of the status of the antioxidant ability to work in synergism to reduce the potential ROS damage. Although this method does not give information on specific antioxidants, it provides an overall measure of antioxidant status. Epidemiological evidence and the present study demonstrated that elevated inflammatory markers such as TNF-α, IL-6, and hs-CRP predict the development of T2DM and glucose disorder. TNF-α is a multifunction regulatory cytokine that changes the expression of several adipocyte-secreted factors including adiponectin and IL-6. In addition, it has been considered an important link to obesity and insulin resistance, which were also elevated in these AO women subjects. TNF-α is known to impair insulin receptor signaling. TNF-α also inhibits lipoprotein lipase (LPL) and stimulates lipolysis in adipocytes, and the resulting increase in circulating non-esterified fatty acids would be expected to contribute to insulin resistance.

Adipose tissue produces numbers of adipokines and cytokines such as adiponectin, leptin, TNF-α and IL-6. IL-6 has been suggested to promote hs-CRP production from the liver as a biomarker of the sub-clinical inflammation related to obesity(62). Hs-CRP is a sensitive marker of low-grade inflammation that is not only associated with insulin resistance, but also predicted the development of MetS, T2DM, hypertension and CVD(63, 64). Furthermore, cardiovascular morbidity and mortality is increased in patients with elevated CRP levels(65).

After 2 months period of aerobic dance exercise, these AO women were demonstrated decreased in GLU, UA, TC, TG, LDL-C, MDA, TNF-α, IL-6, hs-CRP, insulin, insulin resistance level while increased in HDL-C, insulin sensitivity (QUICKI), β-cell function (HOMA %B) and TAC without weight loss. Physical activity and exercise training increase energy expenditure and reduce body fat and visceral fat, even with/without weight loss(66, 67), and caused the reduction of IL-6

and TNF-α (68-70), as in the same of present study (shown in Table 3 and 4). Moreover, exercise or physical activity also induces adiponectin production from adipose tissues (71-73). It exerts antiapoptotic, anti-inflammatory, and antioxidative activities (74, 75).

To our knowledge, this report shows the effect of regular aerobic exercise on systemic inflammatory biomarkers. Notably, AO subjects with continuous two months aerobic dance exercise showed the significantly decrease of hs-CRP and IL-6 levels. On the other hand, many studies on interventional and randomized controlled trials demonstrate did not significantly affect from the regular aerobic exercise on systemic inflammatory biomarkers in adults(76-78) and the regular aerobic exercise did not reduce CRP levels(79). The effects of physical exercise may depend on the type of activity (aerobic/resistance), intensity (mild/moderate/intense/exhaustive), and frequency (sessions per day/week/month) of the physical exercise and may also on the individual's characteristic (age, endurance capacity, and health status).

CHAPTER V
CONCLUSION

Our finding indicated the benefits of aerobic dance exercise on various physiological benefits through its energy expenditure, Glucose, lipid profiles, antioxidant and anti-inflammatory actions. The inflammatory actions of exercise are mainly exerted on adipose tissue. Then regular aerobic dance exercise exerts the most substantial anti-inflammatory, antioxidant, energy expenditure effects in individuals having high risk in these biomarkers particularly AO subjects.

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