CHAPTER II

LITERATURE REVIEW

Introduction

Diabetes mellitus (DM) is one of major chronic diseases causing health care financial difficulties. There were about 171 million worldwide people with DM in 2000. By 2030, the numbers of individuals with DM are estimated about 366 million (24).

In Thailand, the estimated prevalence of all types of DM in adult (≥ 35 yrs.) is 9.6% or 2.4 million people. The prevalence of DM in men is similar to women. Additionally, old individuals have greater prevalence than young counterparts (2).

DM is a group of chronic metabolic disease characterized by chronic hyperglycemia resulting in defects in either insulin secretion or action. According to American Diabetes Association (1997), DM is classified into four types based on its etiology: 1) Type 1 DM or insulin-dependent diabetes mellitus (IDDM) describes as an absolute deficiency of insulin production caused by a reduction in insulin secreting beta cells of pancreas; 2) Type 2 DM or non insulin-dependent diabetes mellitus (NIDDM), which usually occurs after age of 35 (25) with a main feature of insulin resistance; 3) Gestational diabetes mellitus, a type of glucose intolerance during pregnancy; and 4) Other specific types of diabetes mellitus caused by genetic syndrome, infection, surgery, drugs, malnutrition and other illnesses (1).

Only type 2 DM is described in this review because it accounts for approximately 90 % of all cases (24). Since type 2 DM is a chronic disease, rehabilitation in these populations is necessarily required. A common conceptual

framework used in rehabilitation is disable model. The disable model is the association among pathology, impairment, functional limitation, and disability reflecting the defects at cellular, systematic, functional, and social levels, respectively (26). This review was covered the effects of type 2 DM on: pathology, impairment, and functional limitation.

Pathology of type 2 DM

The risk of developing type 2 DM increases with age, obesity, physical inactivity and family history of diabetes. It occurs more frequently in women pregnant with is named as gestational diabetes mellitus and in individuals with hypertension or dyslipidemia (1, 27).

Type 2 DM is developed due to insulin resistance combining with a failure of insulin secretion. These result in relative insulin deficiency. However, the specific etiology of type 2 DM is not known (27-29).

Insulin resistance is the inability of insulin to produce its normal biological effect on tissues. Insulin resistance typically occurs in early stage of type 2 DM. In order to compensate insulin resistance, increment of insulin secretion occurs. This results in hyperinsulinemia, glucose intolerance, and eventually complete β-cells failure (30). Additionally, other metabolic disorder is more pronounced such as increased low-density lipoprotein (LDL) cholesterol, elevated triglyceride and decreased high-density lipoprotein (HDL) cholesterol (31).

The consequences of insulin resistance include endothelial dysfunction and increased risk of thrombosis (31). Long term complications of type 2 DM are cardiovascular diseases considering macrovascular disease (1, 27). Also,

microvascular diseases such as nephropathy, retinopathy and neuropathy are commonly occurred. About 20 percent of patients with type 2 DM develops nephropathy. The earliest clinical evidence of diabetic nephropathy is the appearance of microalbuminuria. Nephropathy is a major cause of renal disease in these patients (32, 33). Retinopathy is the major cause of blindness in patients with type 2 DM. The characteristic lesions of retinopathy are non-proliferative and proliferative retinopathy. The progression of retinopathy depends on diabetes duration (32, 33). Neuropathy is commonly found in long-term DM. Electrophysiologic studies demonstrate subclinical abnormalities including slow motor and sensory nerve conduction in most type 2 DM individuals after 5 to 10 years of the onset of the disease. Peripheral neuropathy is the most common form of diabetic neuropathy and is associated with diabetic foot problems. There are many tests for neuropathy diagnosis. However, these tests require the experts and the expensive equipments (32, 33).

Type 2 DM and impairments

In this review, cardiovascular, respiratory, and musculoskeletal impairments in patients with type 2 DM are focused.

Cardiovascular impairment

The major cause of type 2 DM morbidity and mortality is cardiovascular impairment. It is known that individuals with type 2 DM have two to four times higher risk of coronary, cerebral, and peripheral vascular diseases than normal subjects (3-5).

Hypertension or high blood pressure is commonly found in these populations. According to the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC VII), severity of hypertension can be classified into 3 stages based on blood pressure level: 1) Prehypertension SBP 120–139 or DBP 80–89 mmHg; 2) Hypertension, Stage 1 SBP 140–159 or DBP 90–99 mmHg; 3) Hypertension, Stage 2 SBP ≥160 or ≥ DBP 100 mmHg.

Recent evidence found that patients with type 2 DM exhibit change in cardiac structure resulting in cardiac pump dysfunction (6). The clinical manifestation is the inability of heart to pump blood out off the heart due to the impairment of cardiac contractility (4, 6). These cardiovascular impairments can limit functional ability in patients with type 2 DM.

Respiratory impairment

The two main functions of respiratory system are ventilatory pump and gas exchange (21). The ventilatory pump is referred to the mechanical process of moving atmospheric air into and out of the lungs. Ventilatory pump function can be evaluated via volume, flow and pressure generated during respiratory cycle. Standardized spirometry test has been established by American Thoracic Society (ATS) (34). This test measures the volume of air that an individual inhales or exhales as a function of time. The test results are interpreted by comparison with reference values based on age, height, gender and race (21, 34, 35). Therefore, the spirometry values can reflect the ventilatory pump impairment of respiratory system whether it is restrictive or obstructive type. The gas exchange function refers to the diffusion of gases (O_2 and CO_2) between capillary and alveolar membrane in the lungs. The impairment of gas

exchange can be indicated by the deviation of normal diffusing capacity achieved by carbon monoxide breathing method (DLco) (35).

Recent studies found that lung might be one of the affected organs in type 2 DM populations. It was found that percentage-predicted pulmonary functions (forced vital capacity (FVC), forced expiratory volume in 1 second (FEV_1), vital capacity (VC), and peak expiratory flow (PEF)) were significantly decreased in these patients. As the results, it is not clear whether the respiratory pump defect is obstructive or restrictive types (7). In contrast, the results showed that spirometric values in these populations were preserved (8, 9). Thus, the evidences are still questionable whether the impairment of ventilatory pump exists in patients with type 2 DM. The other impairment of respiratory function is gas exchange. Research related to gas exchange impairment in type 2 DM is limited. Benbassat et al (2001) (8) reported that there were no defects in diffusing capacity in patients with type 2 DM.

Musculoskeletal impairment

One of the major sites of insulin resistance is in skeletal muscles. This is because this tissue is a predominant site of glucose disposal. Insulin resistance in skeletal muscle is impaired by reduction of insulin receptor substrate-1 (IRS-1) and phosphatidylinositol 3-kinase (PI3-K) activation and impairment of glucose transporter-4 (GLUT-4) translocation. These defects can inhibit insulin-stimulated glucose transport and glycogen synthesis (36).

Skeletal muscle is a main site of insulin action. The difference of insulin action depended on type of muscle fibers and density of capillary. Type I fiber or red fiber, rich in capillary density, is the high insulin sensitive fiber type. In contrast,

Type II fiber or white fiber, low in capillary density, is the low insulin sensitive fiber type (10).

Individuals with type 2 DM showed typical characteristics of muscle morphology. Their skeletal muscles had low percentage of type I fibers and capillary density, but high percentage of type IIb fibers comparing to healthy normal individuals (10, 11, 37, 38). Thus, for therapeutic purpose, type I fibers are more favorable than type II fibers.

Muscle strength is the maximum force that can be generated by a muscle or muscle group. Isokinetic strength testing is one of muscle strength assessments which is commonly used in clinical and laboratory settings during rehabilitation (21). Isokinetic testing has been accepted as a reliable method for muscle strength (ICC ~ 0.70-0.90) (21, 39-41).

The reduction of muscle strength has been linked to loss of muscle mass (42, 43), which reflects an impairment of muscular system. Andersen et al (12) found that maximal isokinetic muscle strength of knee and ankle muscle in patients with type 2 DM was significantly reduced as compared with control subjects. However, very few studies are being investigated with the effect of DM on upper extremity muscle.

The onset of DM occurs at the middle age. Therefore, aging may contribute to muscle strength reduction secondary to loss of muscle mass in these populations. It was found that age-related loss of muscle mass was 10% in the age of 25 to 50 years and increased to 40% from in the age of 50 to 80 years (21). Additionally, disused atrophy may partially be responsible for loss of muscle mass and eventually muscle strength reduction.

Type 2 Diabetes mellitus and functional limitation

In order to provide energy to the body at rest and during performing long term task, respiratory, cardiovascular, and musculoskeletal systems have to work in concert. The energy that body consumed can be indirectly measured in term of oxygen uptake ($\dot{V}O_2$). Therefore, the oxygen uptake can infer the whole body metabolic demand.

Most studies reported that individuals with type 2 DM had reduced cardiorespiratory fitness compare with control group (18, 19, 44, 45). It is obvious that musculoskeletal system is involved since it is the final system initiating the action of the movement. Therefore, low cardiorespiratory fitness can indirectly be inferred to the combined impairment of pulmonary, cardiovascular, and musculoskeletal systems.

Normally, patients with type 2 DM are clinically presented with the limitation of functional capacity, negatively impacting execution normal daily activities. Study showed that individuals with type 2 DM were associated with the reduction in functional exercise capacity (13). Moreover, the comparisons of functional activities between healthy and type 2 DM individuals have been made (14-17). The results revealed that functional activities of healthy individuals were greater than individuals with type 2 DM. Additionally, physical dimension of type 2 DM patients, related to quality of life on lower extremity functions (such as walking, stair climbing and etc.) is lower than the healthy persons. Therefore, locomotion in these pathologic populations is limited. As a result, the assessment of functional exercise capacity in patients with type 2 DM is importance.

Physical training in type 2 DM patients

Like other chronic diseases, exercise training has been introduced in rehabilitation for type 2 DM in order to delayed muscle atrophy, regain functional ability, and improve quality of life. Studies have shown that strength training can delay muscle atrophy and improve strength in both healthy elderly and diabetic patients (46-49). Therefore, muscle strength reduction in patients with type 2 DM, more likely due to loss of muscle mass, aging, and disused atrophy, can be delayed using exercise training.

Physical testing in type 2 DM patients

The six minute walk test or 6MWT is the combined work of pulmonary, cardiovascular, and musculoskeletal system, which can indirectly determine submaximal functional capacity of an individual (22). During the test, patients will be asked to walk at adjusted speed as far as they can. The distance covered within 6-minute period is recorded.

It is commonly used in clinical setting due to its practicability, economics, and safety (22, 23). The objective of the test is to reflect changes in physical activity caused by progression of disease, medical intervention, and rehabilitation.

The 6MWT is normally applied to assess functional capacity in various populations such as elderly (50, 51), chronic obstructive pulmonary disease (COPD) (52), heart failure (53, 54), and fibromyalgia patients (55). Those studies showed the high test-retest reliability (ICC > 0.90; $P<0.05$) of the 6MWT (23, 50, 51, 53-56). Additionally, the positive correlations among the 6-minute walk distance (6MWD) and workloads, heart rate and oxygen consumption have been found ($P<0.05$) (22, 23,

53, 56-58). Thus, the 6MWT is valid in these populations. However, the 6MWT test-retest reliability and validity is not identified in patients with type 2 DM.

The 6MWT-standardized procedure is already established (22). Basically, it is suggested that the test should be performed in hallway. The floor should be flat, hard, and straight (30 meters in length) (22). The use of a treadmill to obtain the 6MWD may save space and allow constant monitoring during the test (59). However, the distance between these two different modalities is not comparable. Therefore, treadmill use is not recommended for the 6MWT (22).

The 6MWT may be performed in outdoor if the temperature between indoor and outdoor is similar. Brooks et al (2003) (60) showed that there was no significant difference between indoor (~ 25 °C) and outdoor setting (~21 °C) on walking distance. However, the outdoor temperature in tropical zone is normally greater than 25 °C. Therefore, this result may not be directly applied when the outdoor test is conducted in a tropical zone.

Previous studies found that gender and anthropometric factors such as age, weight, height, and body mass index (BMI) could confound the 6MWD (22, 50, 51, 58, 61). The distance was shorter in women than men. Moreover, the distance tended to increase with increasing height, but reduce with increasing age, weight and BMI (22, 50, 51, 58, 61).

Familiarization and time of day affect the 6MWD. When familiarization was not obtained, the distance increased with the second test and generally reached plateau after two trials (61). It was explained that the familiarization might improve coordination, obtain optimal stride length, and reduce anxiety (22, 61). This effect was prolonged for two month period (61). Kervio et al (2004) (56) found that the

6MWD did not differ between morning and afternoon. However, cardiovascular parameters such as heart rate and VO_2 were higher during the afternoon test. Therefore, the 6MWT should be tested at the same time of the day if the cardiovascular parameters are considered.

Recently, Lord et al (2002) (62) investigated the relative contributions of a range of physiologic, psychologic and health factors on 6MWD in older subjects. They found that 6MWD was significantly associated with a wide range of physiologic, psychologic and health factors in elderly. Interestingly, the study found that lower extremity strength is one of the specific factors which are significant and independent predictors of 6MWD.

For the rehabilitation purpose, improvement in functional limitation and consequently quality of life are desired. It would be great if the contribution of cardiovascular, pulmonary, and musculoskeletal to functional limitation could be quantified. Consequently, proper management on each particular system could be done. Thus, the treatment in these particular populations would eventually be much more efficient. Unfortunately, it is currently not known how much impairment of these three systems contributed to the reduction of functional capacity indicated by 6MWT in patients with type 2 DM.