CHAPTER 2

Literature Review

2.1 Chronic kidney disease

Chronic kidney disease (CKD) is a disease that increases mortality and morbidity worldwide (1). Incidence is now as high as 200 cases per million per year in many countries around the world (1). Similarly, the prevalence of CKD in Thailand is increasing. Annual reports from the Nephrology Society of Thailand in 2005 showed that the prevalence rate of end stage renal failure with hemodialysis treatment was 275.29 per million (19). However, it is well-recognized that the number of patients with end-stage renal disease (ESRD) may reach 2.24 million by 2030 (2, 20). CKD is characterized by kidney damage that shows albuminuria or reduced kidney function with a glomerular filtration rate (GFR) less than 60 mL/min per 1.73 m^2 for three months or more (21). The causes of CKD may include kidney damage or inflammation due to glomerular and tubulointerstitial diseases, infections and exposure to drugs and toxins, or other factors such as old age, diabetes, hypertension, obesity, cardiovascular diseases, and diabetic mellitus (20). A diagnosis of CKD is classified into five stages on the basis of GFR as follows (21):

Stage 1 GFR more than 90 mL/min per 1.73 m^2
Stage 2 GFR 60-89 mL/min per 1.73 m^2
Stage 3 GFR 30-59 mL/min per 1.73 m^2
Stage 4 GFR 15-29 mL/min per 1.73m^2
Stage 5 GFR less than 15 mL/min per1.73m^2

However, the complications of CKD can occur at any stage, often lead to death with no progression to kidney failure, and can arise from the adverse effects of intervention to prevent or treat the disease (1, 20). Stage 5 of CKD, which includes a GFR less than 15

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mL/min per 1.73 m^2, is the kidney function failure stage, called ESRD (21). In this stage, patients need to be treated with renal replacement therapy (RRT), which is dialysis or transplantation. Dialysis treated includes hemodialysis and peritoneal dialysis technique.

2.2 Complications of chronic kidney disease

CKD patients have complications from the disease. Common complications are listed below.

2.2.1 Uremic manifestations are the result of accumulated toxins and disrupted excretory and hormonal functions (22). The symptoms from uremia are fatigue, weakness, frailty, and decreased health-related quality of life (1).

2.2.2 Hypertension is the most common complication seen in renal failure patients. Hypertension is attributed to salt retention and an increase of vascular tone due to a failure to suppress the sympathetic nervous system and renin-angiotensin system, inhibition of sodium-potassium adenosine triphosphate (ATPase), and nitric-oxide deficiency (1). Expanded extracellular fluid volume from fluid overload associated with sodium retention is the most prevalent cause; there is also an increased risk of cardiovascular morbidity in this patient group (23). The optimum level of blood pressure and selection of antihypertensive agents to reduce the risk of cardiovascular disease is still controversial (1).

2.2.3. Anemia is the most common and severe hematologic defect in CKD patients. The causes of anemia in ESRD patients include the failure to produce or an inhibition of the action of erythropoietin, a hormone produced by the kidney that stimulates the bone marrow to produce red blood cells; a shortened life span of the red blood cells; impaired intake of iron; blood loss caused by platelet abnormalities; blood loss related to a dialysis procedure; elevated levels of parathyroid hormone (PTH), which has a suppressive effect on erythropoiesis in the bone marrow; and poor nutrition and diet (23). The effects of anemia are fatigue, pallor, shortness of breath, and poor exercise tolerance (23). The treatment of anemia with exogenous erythrocyte

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stimulating agents (ESA) raises hemoglobin, which reduces the need for transfusions and improves quality of life and exercise capacity (1). However, treatment with ESA for target hemoglobin concentrations of 130 g/L or more (achieved mean concentrations > 110 g/L or 120 g/L) has been consistently associated with high rates of cardiovascular disease, especially in patients who are ESA-hyporesponsive (1).

2.2.4. Minerals and bone disorders are characterized by abnormalities in serum concentrations of calcium, phosphorus, 1, 25-dihydroxycholecalciferol, and parathyroid hormone. Abnormalities in bone morphology such as osteomalacia, osteitis fibrosa, osteoporosis, osteosclerosis, growth retardation (in children), metastatic calcification, and osteodystrophy were found in CKD patients (21). Phosphate retention and deficiency of 1, 25-dihydroxycholecalciferol are causes of hyperparathyroidism and hypocalcaemia (1). Fibroblast growth factor (FGF)-23, a bone-derived phosphaturic hormone, is secreted in response to phosphorus intake and inhibits production of 1, 25-dihydroxycholecalciferol, which is associated with cardiovascular diseases (1).

2.2.5. Malnutrition and inflammation frequently coexist in chronic kidney disease patients (1). Decreased energy intake is an important causal factor, but dietary interventions are usually not sufficient to increase intake (1). Inflammation might be partly a result of underlying systemic vascular disease and a way to retain solutes (1). Infection is the second most common cause of death in ESRD patients (23).

2.2.6 Neurological complications occur in CKD patients. Both the central nervous system (CNS) and the peripheral nervous system (PNS) are affected by CKD (24). Retained toxins are thought to have a role in these disorders, and intensive dialysis has been linked with amelioration (24). Peripheral neuropathy causes patients to have weakness and disability (24). The signs of PNS and CNS disorders include peripheral neuropathy, RLS, sleep disorders, and cognitive impairment. However, these signs can improve after renal transplantation (24).

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2.3 Management of chronic kidney disease

Disease management is based on clinical diagnosis and stage according to GFR and albuminuria level (1). The disease stage can be used to guide non-specific therapies to slow progression and reduce the risk of complications (1, 20). Renal replacement therapy (RRT) is a treatment for CKD patients in stage 5 or ESRD. RRT consists of dialysis and transplantation treatments (1, 20).

Kidney transplantation has become the preferred treatment of ESRD, as it improves the patient's quality of life. All recipients require lifelong treatment with immunosuppressive drugs, which has associated risks of infection and malignancy in transplantation patients (20).

Dialysis treatment includes peritoneal dialysis and hemodialysis. It is the process that removes waste products such as uremia toxins, excess extracellular fluid, and electrolytes (sodium and potassium) by equilibrating the patient in terms of blood to dialysate fluid through a semi-permeable membrane (20).

Peritoneal dialysis uses the peritoneum of patients as a semi-permeable membrane. A dialyzer is inserted into the peritoneal cavity to pass a catheter and is left to equilibrate with the blood before it is drained out and replaced with fresh fluid. The osmolality of the dialysate can be changed by concentration in the glucose. It can control the quantity of extra fluid for drainage. Peritoneal dialysis can be performed manually or with machines, to which the patient is attached overnight. Peritoneal dialysis carries the risk of infection such as peritonitis as a result of the contamination of the fluid during the exchange procedure, usually by a Staphylococcus species (20).

Hemodialysis is a highly successful life-saving and life-sustaining therapy. With its complementary treatments, peritoneal dialysis, and renal transplantation, it has revolutionized the outlook for patients with ESRD (25). Approximately 91.9 % of patients diagnosed with ESRD receive maintenance hemodialysis (26). Hemodialysis treatment requires around 4 hours to complete and must be performed several times per week according to the severity of the kidney disease (27).

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The basis of hemodialysis is the movement of solutes and water across semi-permeable membranes by diffusion and convection. Diffusion is the movement of solutes across a semi-permeable membrane down a concentration gradient. Diffusive clearance of a solute depends on its molecular weight, electrical charge, the blood dialysis fluid concentration gradient, blood and dialysis flow rates, and on the membrane's characteristics (diffusion coefficient). Smaller molecules such as urea are cleared well, whereas larger molecules such as albumin cannot pass through the membrane. The clearance of mid-sized molecules such as b2-microglobulin can be improved by using high-flux membranes, which have pores of sufficient size to allow the passage of such molecules. Convection refers to the movement of solvents and dissolved solutes across a semi-permeable membrane and down a hydrostatic pressure gradient. Convection improves a mid-sized molecule's clearance. Ultrafiltration is the convective movement of water across a membrane. The ultrafiltration rate depends on the hydrostatic pressure difference across the membrane and on its permeability to water (ultrafiltration coefficient) (25). The dialyzers consist of semi-permeable membranes arranged to form separate adjacent paths for blood and dialysis fluid, which flow on opposite sides of the membrane in opposite directions to maximize diffusion gradients. Dialyzers are classified by their designed geometry, membrane composition, surface area, permeability characteristics (diffusion and ultrafiltration coefficient), and biocompatibility characteristics. Currently, hollow fiber dialyzers are the most commonly used type (25).

Complications during intradialytic include dialysis disequilibrium syndrome, hypotension, and cardiac arrhythmias (25). Although dialysis therapy is life sustaining, patients still have complications from the dialysis treatment, including hypotension, cramping, problems with bleeding, and fatigue (28). Studies have shown that the ability to perform physical exercise in ESRD patients who are treated with dialysis was reduced by 30-40% when compared with healthy individuals of the same age (27, 29). Moreover, patients who had dialysis treatment were found to have the aerobic peak power or VO_2peak of only half of that expected for normal subjects of the same age (30-32). In addition, patients with ESRD have very low self-reported levels of physical

functioning and low scores in quality of life measured with the SF-36 questionnaire (33).

In conclusion, chronic kidney disease patients have complications in many systems, including cardiovascular, musculoskeletal, and neurological systems. The main cause of these complications was uremia. According to the severity of CKD, patients have to endure the deterioration of physical status and health. Although dialysis therapy is a life-sustaining treatment, patients still experience complications from the treatment. Deterioration of physical health causes a loss of mobility, resulting in higher rates of hospitalization, morbidity, and mortality in CKD patients. Therefore, an evaluation of the physical performance of CKD patients who experience complications from uremia could be used as primitive data for planning therapeutic treatment and could help to promote physical well-being in this group of patients.

2.4 Restless legs syndrome (RLS)

RLS is a neurological disorder characterized by sensorimotor symptoms such as paresthesia and restlessness that mainly affect the lower limbs. It occurs during rest, especially in the evenings or overnight, and symptoms are relieved by movement (34). The prevalence varies with nationality. For example, the prevalence of RLS was 5.8% in Swedish men (13), 11.5% in Norway and Denmark (13), and 8.5% (women 10.8%, men 5.8%) in France (13). The prevalence of RLS in hemodialysis patients in Thailand is 45.5% (35).

The causes of RLS are still unknown. However, the primary cause of RLS may an inherited disorder (idiopathic RLS), and the secondary cause of RLS may be other diseases processes such as spinal cord or peripheral nerve lesions, iron deficiency, pregnancy, ESRD, and side effects from medications (34).

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2.4.1 Pathophysiology

RLS may be related to three conditions, which are dopaminergic dysfunction, impaired iron homeostasis, and a genetic mechanism. The pathophysiology of RLS is described below.

2.4.1.1 Dopamine dysfunction

Dopamine plays a role in the CNS, which regulates both sensory and motor functions (36). A previous study postulated that RLS is caused by the dysfunction of dopamine cells in the nigro-striatal areas of the brain (34). According to dopaminergic pathways, the A11 dopaminergic system may play a role in the development of RLS (37). The A11 system has a connection to the suprachiasmatic nucleus of the hypothalamus, which is related to the regulation of circadian rhythms (38). Therefore, the symptoms of RLS are activated in the same period of time. Moreover, A11 cell bodies connect into the dorsal horns and intermediolateral tracts of the spinal cord that might be involved in sensory suppression (37), which relates to discomfort in the legs. A positron emission tomography (PET) study found abnormal dopamine receptor binding, which decreased the amount of dopamine D2 receptor binding in the striatum of RLS patients (39). Moreover, they found hypoactive dopaminergic neurotransmission and suggest that both striatal and extrastriatal brain regions are involved in RLS patients (39).

2.4.1.2 Iron insufficiency

Iron is a necessary cofactor for the synthesis of dopamine and the regulation of dopamine receptors in the brain and thus for the amount of dopamine available in the synapse. Previous studies (40, 41) found that iron and ferritin were at low levels in the cerebrospinal fluid in RLS patients. A magnetic resonance imaging (MRI) study showed reduced iron stores in the striatum and red nuclei effects that were more marked in patients with early-onset RLS (<45 years) (42, 43). In addition, nigral iron concentration was shown to be inversely correlated with the severity of the disease. Thus, patients with lower iron levels in the brain showed more severe RLS symptom

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(42). The effects of insufficiency of iron in the brain may reduce dopaminergic function by decreasing the activity of tyrosine hydroxylase. Thus, decreased activity of tyrosine hydroxylase could cause the reduction of dopamine synthesis and affect the amount of dopamine binding to post-synaptic receptors (44). ESRD patients and pregnancy with RLS were found to have inadequate iron supplies (45).

However, it is still hypothesized that other substances for signal transmission in the brain, such as those inside the endogenous opioid system, may exert their effect by altering dopamine function and may indirectly induce therapeutic effects for RLS (46).

2.4.1.3 Genetics

The incidence of RLS related to family history occurred in approximately 60% of cases (47, 48); moreover, more than 80% of the identical twins of patients with RLS also had the disease (49). A family history of RLS is suggested from an autosomal-dominant transmission (50). Gene investigations showed associations with chromosomes 12q, 14q, 9p, 2q, 20p, and 16p (50).

2.4.2 Symptoms of restless legs syndrome

The severity of symptoms varies widely both in the general population and in patients (51). The main characteristic of the syndrome is an urge to move the legs (34). These symptoms are usually associated with very unpleasant sensations felt mostly deep inside the limbs, occurring unilaterally or bilaterally, affecting the ankle, knee, or the entire lower limb (34). An involvement of the arms has been described in up to 48% of patients with a progressive form of the disease (34). In some patients, pain dominates the picture and can lead to the syndrome being misdiagnosed as a chronic pain problem (34). Sensory symptoms occur during wakefulness, mostly when the patient is sitting or lying down, and at night (34). Movement brings about at least temporary and partial relief of the discomfort, especially walking, stretching, or bending the legs (34).

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2.4.3 Diagnosis of restless legs syndrome

The clinical diagnosis criteria for RLS were established by the International Restless Legs Syndrome Study Group (IRLSSG). The workshop participants and executive committee of the IRLSSG developed standardized criteria for the diagnosis of restless legs syndrome in 1995 and in 2003 (51, 52).

The essential criteria are as follows:

- An urge to move the legs, usually accompanied by uncomfortable or unpleasant sensations in the legs.
- Unpleasant sensations or the urge to move begins or worsens during periods of rest or inactivity such as lying or sitting.
- Unpleasant sensations or the urge to move are partly or totally relieved by movements such as walking, bending, and stretching, at least for as long as the activity continues.
- Unpleasant sensations or the urge to move are worse in the evening or at night than during the day, or only occur in the evening or night.

All four essential criteria must be met for a positive diagnosis. However, there are three supportive criteria, which are 1) has a family history, 2) responds to dopaminergic therapy, and 3) has periodic limb movements (during wakefulness or sleep), that are used for a differential diagnosis (51). Moreover, there are three associated criteria for RLS, which are 1) a natural clinical course, 2) sleep disturbance, and 3) medical evaluation/physical examination with responses to medicine and testing (53).

There are some diagnostic instrumental examinations that can confirm the suspected cases or help the physician make a differential diagnosis. The three instrumental tools are polysomnography (PSG), the suggested immobilization test (SIT), and actigraphy. The PSG is used to detect the presence of periodic leg movements (PLMs) during sleep, which are found in 80-90% of RLS patients (54). PSG is measured by using surface

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electromyograms (EMGs) to detect the contractions of muscles (e.g., anterior tibialis muscles). The suggested immobilization test is one method to confirm RLS. The purpose of the suggested immobilization test (SIT) was to induce the sensory symptoms and motor signs of RLS by immobility (55). The patient sits or lies on a bed for 60 minutes and is instructed not to move and not to fall asleep (55). The periodic leg movement in wakefulness (PLMW) is recorded by surface EMG derived from bilateral anterior tibialis muscles (56), whereas sensory leg discomfort is rated using a visual analog scale by the patient every 5 minutes (57, 58). The number of leg movements per hour was recorded as the SIT index. The previous study reported a difference between the first and the second night for the SIT PLM index. They used a cut-off value of 12 for the SIT, PLM index and suggested that this index has a sensitivity and specificity high enough to confirm RLS (59). However, a study by Montplaisir et al. suggested that in 80% of cases, an SIT index higher than 40 per hour has been shown to differentiate between patients with and without RLS (55). Actigraphy is employed to monitor motor activity at night over long periods of time. It also used to assess sleep quality and duration in insomnia patients. Moreover, it is used to assess sleep-wake patterns in patients with circadian disturbances (60). The method of actigraphy used a miniaturized computerized wristwatch-like device to monitor and collect data generated by movements that most actigraphs include in their analog systems.

2.4.4 Treatment of restless legs syndrome

Management of RLS is conducted by using medications and modifying life style. Medications such as dopaminergic agents, opiates, benzodiazepines receptors agonists, and antiepileptics were utilized to treat RLS patients (5). Dopaminaergic treatment with levodopa and dopamine agonists is the first choice in idiopathic RLS, but augmentation and rebound should be monitored in long-term treatment. In addition, modifying the patient's life style by increasing physical activity, i.e., exercise, massage, and hot baths, was beneficial for RLS patients (5).

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The physical therapy treatments in RLS patients are as follows.

1. Aerobic and resistance exercise can ameliorate RLS symptoms. A previous study (61) found that 6 weeks of exercise can reduce symptoms of RLS both in the general population and in hemodialysis patients. Moreover, it can improve quality of life in hemodialysis patients with RLS (62).

2. A previous study (63) showed that massages helps to relieve the symptoms of RLS. Massage techniques including myofascial release, trigger point therapy, deep tissue, and sport massage decreased lower extremity discomfort and increased quality of life (63).

2.4.5 Factors related to restless legs syndrome

RLS can develop at any age. However, the prevalence of RLS increases with age (53). RLS is more prevalent in adults than in younger subjects (64). Being female also seems to be a risk factor for RLS (53).

There are others factors related to RLS. RLS patients have been found to be less fit, heavier, have a higher body mass index (BMI), and have a history of smoking. In addition, patients who have hypercholesterolemia, low HDL, a lower HDL/LDL cholesterol ratio, high fasting glucose concentrations, and reduce renal function were found to have a high incidence of RLS (18).

2.4.6 Restless legs syndrome in hemodialysis patients

RLS has been found in ESRD patients who are undergoing hemodialysis treatment. The prevalence of RLS symptoms ranges from 6.6% to 83% (65, 66), which was higher than the general population (5 to 15%). RLS can occur both before and after dialysis treatment; however, it can be treated after renal transplantation (67).

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2.5 Physical performance

Physical performance has been defined as the ability of a person to perform an activity (68). Physical performance can be evaluated with both direct and indirect methods. A direct method of evaluation is measuring the maximal oxygen uptake (VO_2max), which is usually performed using a cycle ergometer or a treadmill and gas analysis (69). Indirect methods evaluate the peak point of oxygen consumption reached and plateaus or increases to some extent in response to an increase in work rate that usually measures HR and speed. Indirect methods for the measurement of physical performance are the gait speed test, 6-minute walk test (6MWT), step test, and sit-to-stand-to-sit test (STS) (69). Physical performance can be used to assess health status and predict the risk of diseases (70).

The health-related components of physical fitness consist of cardiopulmonary fitness, muscular endurance, muscular strength, flexibility, and body composition (68, 71, 72). Cardiopulmonary fitness is called aerobic fitness, which involves blood flow from the heart bringing oxygen to active muscles during an exercise period. Cardiopulmonary fitness indicates the ability of muscle to use oxygen to produce energy for exercise. Common physical performance tests for the cardiopulmonary system are the run/walk test, step test, swimming test, and bicycle test. Muscle endurance is the ability of a muscle to repeat force or sustain a submaximal muscle contraction repeatedly over a period of time to perform a daily task (71-73).

Muscle strength is the maximum single muscle contraction or the capacity of a muscle or muscle groups to affect a one-time maximal force against resistance through a full range of motion. Examples of a muscle strength test are the 1-RM (repetition maximum) test and the handgrip test (71, 73).

Flexibility is the ability to freely move a joint throughout a range of motion, unrestricted by a joint or series of joints. People who lack muscle flexibility might be at risk of injury of a muscle or tendon during or after performing an activity, such as muscles in the back. Flexibility tests include the trunk flexion test (sit and reach test), trunk extension test, shoulder reach test, and total body rotation test (71, 73).

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Body composition is defined as the percentage of body fat and lean body mass of the total of muscle, bone, fat, and other elements that comprise the body. An excess of fat in the body is unhealthy and carries a high risk of diseases such as obesity and cardiovascular diseases. Body composition can be assessed by using hydrostatic or underwater weighing, skinfold thickness, girth measurement, bioelectrical impedance, and air displacement methods (71, 73).

The main problem in hemodialysis patients is poor ability to perform physical function along with limited physical activity according to the severity of the disease (74). Dialysis patients have a reduced exercise capacity and live a sedentary life style (31, 75-78). Previous studies found that dialysis patients had weakness in the proximal and distal muscle groups and had muscle atrophy that was associated with reduce physical performance (12, 79). Moreover, a previous study showed that hemodialysis patients with RLS had low levels of the quality of life and experienced muscle atrophy (14). Lower quality of life and higher muscle atrophy increase the patient's mortality rate (14).

Currently, physical performance in hemodialysis patients with RLS has only been investigated in one report that showed evidence of thigh muscle atrophy, impaired sleep quality, depression, and decreased quality of life, but this study did not find differences in physical performance between patients with and without RLS. The result was not clear. Therefore, this study is interested in investigating physical performance in hemodialysis patients with RLS in terms of muscle strength, muscle endurance and cardiopulmonary fitness. The physical performance tests that employed in this study were the sit-to-stand-to-sit 10 repetitions, sit-to-stand-to-sit 60 seconds and 6MWT.

The sit-to-stand-to-sit (STS-10) test is used to assess lower extremity muscle strength (80-83). This test is associated with the activities of daily life and can be used to predict the mortality rate. This test measures the time required to perform 10 repetitions of fully standing up from sitting down in a chair (81, 82). The time in which the participant can perform this task will be recorded in seconds. Participants will be instructed to sit and stand as quickly as possible for 10 consecutive repetitions, while

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folding their arms across the chest (81, 82). The standard chair height is 44.5 cm, the standard depth is 38 cm, and the chair has a back but no arm rests (82). The sit-to-stand-to-sit (STS-60) test was used to assess lower-extremity muscle endurance (82). This test measures the number of repetitions that the patient can perform of fully standing up from sitting on the chair within 60 seconds (82).

Factors affecting sit-to-stand-to-sit include are chair (high, seat), age, gender, muscle force, speed and position (84). A previous study reported the interclass correlation coefficient (ICC 2, 1) for STS-10 was 0.78-0.94 and for STS-60 was 0.94-0.98 (82). Therefore, those tests have high reliability. Moreover, those tests also had high test-retest reliability in patients who were undergoing hemodialysis treatment. The minimal detectable change (MDC) score at 90% confidence intervals was 8.4 seconds for the STS-10 and 4 repetitions of the STS-60 (82).

The 6-minute walk test (6MWT) was utilized to assess the functional capacity or the ability to perform daily activities (85-87). Participants will be asked to walk along a 20-meter walkway as far as possible within 6 minutes, but not run or jog. Most studies have used a 30-meter walking distance, but there was no significant difference between the length of the walkway and the participant's walk distance (82, 85). The 6-minute walk distance (6MWD) was associated with age, sex, height, gender, and BMI (85).

The factors that reduce the 6MWD include shortness, old age, higher body weight, being female, impaired cognition, a shorter corridor, pulmonary disease, cardiovascular disease, and musculoskeletal disorders (85). The factors that increase the 6MWD include being tall, being male, height, motivation, previously performing the test, medication for a disabling disease taken just before the test, and oxygen supplementation in patients with exercise-induced hypoxemia (85). The interclass correlation coefficient (ICC 2,1) was 0.94 in hemodialysis patients, which indicated high test-retest reliability (82).

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