CHAPTER I

INTRODUCTION

Throughout the world, chronic kidney disease (CKD) is a growing health concern because of its increasing prevalence and incidence rates and dismal outcomes. Despite technical advances in dialysis and transplantation, the prognosis of kidney failure remains poor. The U.S. Renal Data System provides statistics on individuals with end-stage renal disease (ESRD), which include individuals with kidney failure who are receiving dialysis, as well as kidney transplant recipients at all stages of CKD. This U.S. registry reported more than 76,500 deaths in patients with ESRD in 2001, an annual mortality rate in excess of 20% *(1)*. By 2010, there will be a projected 160,000 new dialysis-dependent patients/year, double the current rate *(2)*. The average life span of a patient entering a long-term dialysis program is 20-25 years less than that of the normal age-sex-race-matched U.S. population over the age of 45 *(3)*. Among many factors, including treatment characteristics and co-morbid conditions, protein and calorie malnutrition has been shown to be a major risk factor for increased mortality in the ESRD patient population *(4)*. Many studies found 20-40% of patients on maintenance hemodialysis suffer from malnutrition *(5, 6)*. It has been suggested that patients with serum albumin less than 3.5 gram per deciliter (g/dL) had 10% higher in-hospital mortality as compared to patients with serum albumin higher than 3.5 g/dL *(7)*. Moreover, the risk of death in patients with serum albumin concentration below 2.5 g/dL was close to 20-fold compared to patients with serum albumin of 4.0 to 4.5 g/dL *(7)*, which is considered to be the reference range. Also, the largest hemodialysis study by Rocco and his coworkers reported at least 29% of the patients undergoing hemodialysis to have serum albumin concentration less than 3.5 g/dL *(8)*. It has been reported that malnutrition and sarcopenia are commonly seen in patients with ESRD, especially chronic intermittent hemodialysis which has been implicated as a catabolic process that worsens the nutritional status of the ESRD patients treated with this modality. Chronic hemodialysis causes negative protein and calorie balance by the inevitable loss of amino acids and increased energy expenditure during hemodialysis *(9-11)*. Parenteral nutrition has been used to improve the nutritional status of these patients, however, it has been proven to be ineffective *(12)*.

Therapies designed to improve the nutritional status of dialysis patients might therefore be expected to improve outcome. Anabolic-androgenic steroids, megestrol acetate, and growth hormones are currently in use *(13-15)*. However, therapy with megestrol acetate typically results in an increase in fat mass *(16-18)*, whereas growth hormone use is associated with high cost and some untoward side effects *(12, 19)*, such as hyperglycemia, arthralgia, myalgia, fluid accumulation in extremities, fat distribution abnormalities and glucose intolerance *(12, 13, 19)*. The use of insulin-like growth factor-1 (IGF-1) has been limited by the hypoglycemic effects of excess free IGF-1 temporomandibular pain *(19)*. Anabolic-androgenic steroid therapy, thus, appears to be an exciting alternative for treatment of cachexia in chronic illness. It might be expected to accomplish some of the same anabolic effects of human growth hormones without leading to hyperglycemia. The study by Johansen et al.*(13)* in a previous double blind, placebo-controlled trial, patients were randomized to either

placebo or intramuscular androgenic steroid injection, nandrolone decanoate, for 6 months. Lean body mass and serum creatinine were significantly greater in the nandrolone group ($p<0.001$ and $p=0.02$, respectively), also patients performed much better in functional tests such as timed walking and stair-climbing ($p=0.05$)[13]. However, there were several reports related to subjects who developed a hematoma at the injection site and some encountered infectious complications due to injection [13, 20].

Oxymetholone overcomes this limitation by orally, and exhibits higher anabolic activity and lower androgenic activity compared to nandrolone decanoate [21, 22]. There have been a few studies that show the improvement of body mass in patients obtaining oxymetholone [23-26]. The result led to a significant weight gain in the HIV-wasting patients taking oxymetholone 50 milligrams (mg) twice daily or three times daily for 16 weeks ($p<0.05$) [24]. Significant improvements were noted in appetite and food intake, increased well-being, and were reduced weakness [24]. However, the most important adverse event was liver-associated toxicity [27-29]. Additionally, the study of short course oxymetholone in continuous ambulatory peritoneal dialysis (CAPD) patients for lean body mass improvement has obviously increased the efficacy as well [26]. More interestingly, the study by Suttiwan showed a significant nutritional improvement in 66.7% of the CAPD patients receiving oxymetholone [30]. However, oxymetholone results in androgenic side effects such as acne (13%), hirsutism and oily skin (3%) [24]. Yet, the most severe adverse event is liver-associated toxicity, particularly aminotransferase elevation which can be seen in the range of 14-43%, depending on the dose of oxymetholone [31, 32]. In 100-mg oxymetholone group, 25% of patients had a greater than 5 times baseline increase for aminotransferase enzymes and 43% of patients in 150-mg oxymetholone group [31]. Additonally, peliosis hepatic, an unusual cystic lesion of the liver, is a rare life-threatening adverse effect associated with oxymetholone use [27, 29]. However, these adverse effects have not been found in CAPD trial [30]. Furthermore, dyslipidemia has been reported after 5 weeks of oxymetholone therapy in a patient receiving long-term hemodialysis, which were increase of cholesterol and triglyceride while decrease of high-density lipoprotein cholesterol (HDL-C), but not statistically significant compared to placebo [33, 34]. However, these adverse events recover after discontinuation [27, 29, 30].

Previous studies have revealed that the kidney is an important organ of glucose hemeostasis [35-37]. When renal function fails, it alters glucose metabolism [38, 39]. The study by DeFronzo et al. found that insulin-stimulated glucose uptakes has been diminished in uremic patients [39, 40]. Impaired carbohydrate metabolism, therefore, can be commonly found in renal failure [40]. The most prominent abnormality is insulin resistance, which leads to glucose intolerance [41]. In addition, insulin resistance associated with renal failure results from post-receptor defects in insulin action in muscle, adipose and liver tissues. These defects are primarily restricted to glucose uptake and metabolism by these insulin-sensitive tissues [42]. The existence of insulin resistance in many non-diabetic individuals is also an important prognostic indicator for cardiovascular disease, which is mainly associated with the development of metabolic syndrome [43]. It is well established that non-diabetic patients with insulin resistance exhibit high concentration of serum triglyceride and low concentration of HDL-cholesterol [44]. Association between androgen and insulin resistance is well recognized in previous evidences [45, 46].

Volpi and her colleagues have conducted research in women diagnosed of hyperandrogenism showing that after surgical correction of hypertestosteronemia, lean body mass decreases and fat gains, particularly abdominal fat *(45)*. In addition, the result of this research suggested that testosterone withdrawal worsened insulin sensitivity *(45)*. Nonetheless, this study is not unequivocally convincing, and other confounding factors may influence the response of glucose to testosterone, thus it should underscore the need for further investigations in this area.

The study of association between insulin resistance and body fat in chronic kidney disease patients has been conducted. Lee et al. and Satirapoj et al. revealed that insulin resistance assessed by using the hemeostasis model assessment of insulin resistance (HOMA-IR) was positively correlated with phase angle ($r=0.35$, $p<0.01$), percentage of total body fat ($r=0.27$, $p<0.01$), and body mass index ($r=0.48$, $p<0.01$) *(47, 48)*. Likewise, the study by Schroeder reported that using the dosage of 100-mg oxymetholone significantly decreased total fat mass and trunk fat which resulted in improved insulin sensitivity *(49)*. However, there were too few subjects in each study group to detect significant changes ($p=0.84$) *(49)*.

According to all above mentioned, this present study is undertaken to determine whether a 6-month course of oxymetholone could improve lean body mass in end-stage renal disease patients on maintenance hemodialysis and the change of lean body mass is expected to improve insulin resistance.

Objectives
To assess:
1. Efficacy of an oral anabolic steroid, oxymetholone, on lean body mass in end-stage renal disease patients on maintenance hemodialysis;
2. The relationship of change in lean body mass and insulin resistance in end-stage renal disease patients on maintenance hemodialysis;
3. The adverse effects of oxymetholone in short term use in end-stage renal disease patients on maintenance hemodialysis.

Study design
This study is a double-blind, placebo-controlled design, with determined patients undergoing hemodialysis at Hemodialysis unit, The Kidney Foundation of Thailand at Kalayaniwattana building, Priest hospital. The period of this study was during June 20th 2006 to Feb 20th 2007. The method of this study has been approved by Ethical Committee on Human Research at Phramongkutklao hospital on February 20th 2006.

Hypothesis
Oxymetholone, an anabolic androgenic steroid, has the potential to be an effective therapy for improving lean body mass and decreasing abdominal fat. This change may result in the improvement of insulin resistance in end-stage renal disease patients on maintenance hemodialysis.

Operational definitions

1. Insulin resistance means a state in which greater-than-normal amounts of insulin are required to elicit a quantitatively normal response. Insulin resistance is determined by using homeostasis model assessment *(50)*, which calculated by:

$$\text{Insulin resistance} = \frac{\text{fasting serum insulin } (\mu U/mL) \times \text{fasting plasma glucose (mg/dL)}}{405}$$

2. Efficacy means the capability of enhancing lean body mass, and albumin level from baseline. In this study, the efficacy will be evaluated after the patient has taken oxymetholone for 6 months. The efficacy in enhancing lean body mass and albumin level are assessed by the changes from baseline.

3. Safety means rates of adverse events from oxymetholone e.g., cholestatic jaundice, more than 3 times the upper limit of normal of AST and ALT, and dyslipidemia. Safety is evaluated throughout the study period by adverse event report, patient interview, physical examinations, and laboratory tests.

4. Body mass index (BMI) is calculated as weight in kilograms divided by the square of height in meters (kg/m^2)

$$\text{Body Mass Index } (kg/m^2) = \frac{\text{weight (kg)}}{\text{height}^2 \text{ (meter)}}$$

5. Dual energy x-ray absorptiometry scan (DEXA scan) is the most reliable noninvasive method using low dose radiation to measure body composition including total body mass, total body fat and bone mass.

Advantage

1. To determine relationship between increased lean body mass and insulin resistance in hemodialysis patients.

2. To evaluate a short-term safety of oxymetholone in end-stage renal disease maintenance hemodialysis.

3. Used for therapeutic decision making process between risk and benefit for using oxymetholone for lean body mass improvement.