CHAPTER IV

RESULTS AND DISCUSSIONS

This study was a double-blind, randomized, placebo-controlled trial. The purpose of the study was to evaluate the efficacy and safety of oxymetholone 50 milligram twice daily in terms of: (1) lean body mass alteration, (2) the adverse event rates, and (3) to investigate the relationship between change in lean body mass and insulin resistance. The results are demonstrated in 4 parts:

(1) Baseline patient demographic, which are baseline patient demographics, biochemical laboratory data, and body composition,
(2) Efficacy evaluation including the efficacy of oxymetholone 50 mg twice daily on lean body mass, dry weight, serum albumin, serum creatinine, which changed from baseline,
(3) The relationship of change in lean body mass and insulin resistance,
(4) Safety assessment.

1. Baseline Patient Characteristics

1.1 Baseline patient demographics

A total of 423 patients were accessible and screened for possible study enrollment. All subjects who met the entry criteria were asked to participate. However, only 87 patients on maintenance hemodialysis at hemodialysis unit, The Kidney Foundation of Thailand at Kalayaniwattana building, Priest hospital were eligible according to the entry criteria. One patient was excluded due to low ventricular function. Twenty-seven patients who were eligible declined to participate in the study. The most frequent reasons for decline are not being interested and afraid of side effects. Sixteen patients decided not to participate after providing informed consent, and not receiving study therapy. Therefore, only 43 patient profiles were reviewed for collecting general information, past medical history, medication history, and current medication.

All patients undergoing maintenance hemodialysis at the hemodialysis unit between June 2006 and February 2007 were studied. Forty-three hemodialysis patients were enrolled in the study and randomly assigned. Characteristics of the study population are shown in Table 15. Subjects were 25 males (58%) and 18 females (42%). Twenty-two of 43 patients were in the control group, and 21 in the oxymetholone group. One patient who received oxymetholone therapy decided not to participate in the study after taking study therapy for one month owing to being scared of gaining weight (Figure 7). Thereafter, one patient (4.76%) from the oxymetholone group had to be withdrawn from the study as a result of presenting icteric sclera and elevated both total bilirubin and direct bilirubin after taking oxymetholone for five months. The remaining 41 patients completed the study. All of them were adherent based on pill counts.

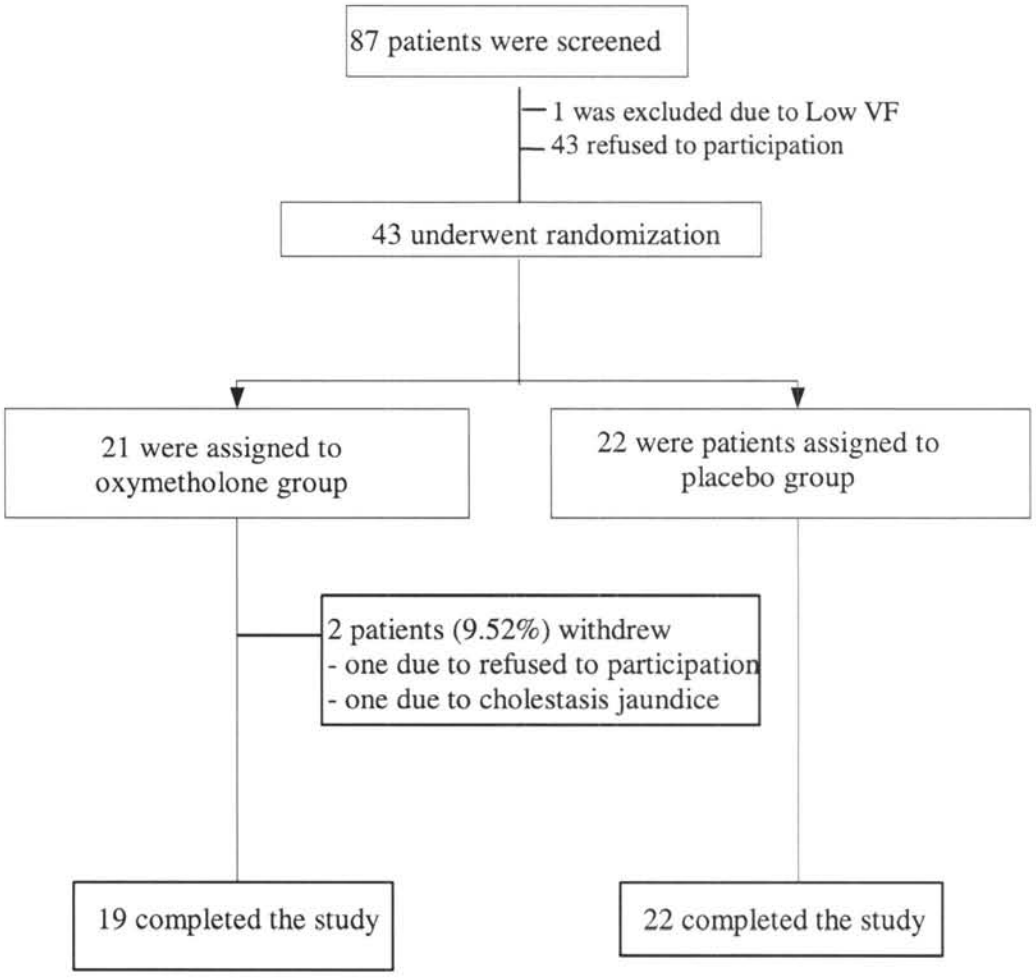

Figure 7 Flow diagram of the study

Of these 43 patients, the etiologies of end-stage renal disease were diagnosed by physician; it was reported in their profiles when the patients firstly registered to the kidney foundation that 14 patients (32.59%) were chronic glomerulonephritis causing ESRD, followed by hypertension secondary to ESRD found in 6 patients (13.95%), 14 subjects (32.59%) were undetermined, and . All patients underwent hemodialysis session three times a week as maintenance hemodialysis. The mean age of patient (mean±SD) was 43.49±9.90 years (ranging from 20-64 years). The average weight was 55.23±8.89 kg (ranging from 39.05 to 73.94 kg). The mean duration on dialysis was 92.84±37.83 months (ranging from 27 to 184 months). The mean body mass index was 21.26±3.29 kg/m^2 (ranging from 14.79 to 27.58 kg/m^2). However, the average age, body weights after each dialysis session (so-called edema-free or dry weight), duration on dialysis, and body mass index of both groups were not statistically significantly different (p=0.282; p=0.245; p=0.631, and p=0.842, respectively). For assessing blood pressure by using a 2-week average predialysis blood pressure *(142)*, it showed that there was no significant difference in predialysis systolic blood pressure and predialysis diastolic blood pressure between both groups (p=0.968, p=0.591, respectively). The descriptive features of the patient population

are shown in Table 15. Most of the co-morbid conditions that found among these subjects were hypertension, which presented in 22 patients (51.16%).

Table 15 Baseline characteristics of the study population.

Data	Oxymetholone (n=21)	Placebo (n=22)	*p*-value[a]
Age (years±SD)	41.81±11.13	45.09±8.51	0.282
Sex (n [%])			
Female	11 (52.38)	7 (31.82)	0.172[a]
Male	10 (47.62)	15 (68.18)	
Etiologies of ESRD (n [%])			
CGN	8 (38.10)	6 (27.27)	
Hypertension	3 (14.29)	3 (13.64)	0.820[b]
Ig A nephropathy	1 (4.76)	3 (13.64)	
Undefined	6 (28.57)	8 (36.36)	
Others	3 (14.29)	2 (9.09)	
Comorbidities (n [%])			
Hypertension	11 (52.38)	11 (50.00)	
Congestive heart failure	2 (9.52)	0 (0.00)	0.362[b]
Gout	0 (0.00)	1 (4.55)	
None	8 (38.10)	10 (45.45)	
Dry weight (kg±SD)	53.61±8.79	56.79±8.91	0.245
Duration on dialysis (months±SD)	89.95±36.19	95.59±39.98	0.631
Body mass index (kg/m^2±SD)	21.36±3.19	21.16±3.47	0.842
Predialysis SBP (mmHg)	139.95±16.05	139±10.38	0.968
Predialysis DBP (mmHg)	78.54±8.08	79.62±4.33	0.591

[a] using independent *t*-test to compare mean of the control group with the study group
[b] using Chi-square test to compare the number of patients in the control group with the study group

According to weight status by using body mass index, the patients' status was assessed by WHO classification for Asian-pacific region *(143)* ranged Table 16:

Table 16 Weight classification by WHO for Asian-pacific region

Status	BMI (kg/m^2)	Oxymetholone (n=21)	Placebo (n=22)	*p*-value[a]
Underweight	<18.5	5	7	
Normal	18.5-22.9	16	15	
Overweight	23-24.9	0	0	0.558
Obese	25-29.9	0	0	
Extremely obese	>30	0	0	

[a] using Chi-square test to compare the number of patients in the control group with the study group

As seen in Table 16, the mean value of body mass index (BMI) was classified as normal in both groups. Nonetheless, there were 12 patients (27.91%), whose BMI were less than 18.5 kg/m^2. Of these 12 patients, 5 of them were in the oxymetholone group. This finding is consistent with the previous studies which showed that hemodialysis patients (20.5%) had lower body mass index than healthy subjects *(92, 93)*. Although this BMI value does not directly represent body composition, it is the favored measure to estimate relative risk of disease since it is simple, rapid, and inexpensive measure that can be applied generally for clinical use *(81)*.

Regarding to medication taken by the subjects, the result showed that most of the patients (81.39%) were currently receiving blood pressure lowering treatment. These medications were categorized by pharmacological mechanisms. Such medications are beta-adrenergic antagonists, alpha-adrenergic antagonists, calcium channel blockers (CCBs), angiotensin-converting enzyme inhibitors (ACEIs), Angiotension II receptor blockers (ARBs), and diuretics. The classifications by functional class of medication are shown in Table 17. Both study groups had a similar proportion of patients who received antihypertensive medications; however, the difference in the use of antihypertensive medications did not show statistical significance between the two groups (Table 17). The number of patients who received each type of concurrent drug was not significantly different between the control and the study groups (all $p>0.05$) except simvastatin taken by the patients in oxymetholone group, which were much more than patients in placebo group statistically significant ($p=0.046$).

Table 17 Comparison of the use of concurrent drugs in the control group with the study group

Medications by pharmacological mechanism	Number of patients		*p*-value[†]
	Oxymetholone (n=21)	Placebo (n=22)	
• ***No. of patients on antihypertensive drugs***	18	17	0.689
• ***Beta-adrenergic antagonists***			
- Atenolol	4	4	1.000
- Metoprolol	3	4	1.000
• ***Alpha-adrenergic antagonists***			
- prazocin	6	2	0.132
- doxazocin	1	0	0.488
- clonidine	1	1	1.000
• ***Calcium channel blockers***			
- Nifedipine	6	8	0.586[ŧ]
- Amlodipine	3	3	1.000
- Manidipine	2	1	0.607
- Felodipine	1	0	0.488
• ***Angiotencin-converting enzyme inhibitors***	7	5	0.438[ŧ]
- Enalapril			
• ***Angiotensin II receptor blockers***			
- Telmisartan	0	1	1.000

Table 17 Comparison of the use of concurrent drugs in the control group with the study group (continued)

Medications by pharmacological mechanism	Number of patients		*p*-value†
	Oxymetholone (n=21)	Placebo (n=22)	
• ***Diurectics***			
- Furosemide	2	4	0.664
• Iron supplement	20	22	1.000
• Folic acid	20	20	1.000
• Simvastatin	6	1	0.046*
• ***Phosphate binding agent***			
- Calcium carbonate	18	17	0.698
- Aluminium hydroxide	3	8	0.097♆
• 1-alpha calciferol	11	15	0.289♆
• Isosorbide-dinitrate	1	1	1.000
• Aspirin gr I	0	3	0.233
• Recombinant human erythropoietin	19	18	0.413
• Mean of recombinant human erythropoietin (unit/kg/week); mean±SD	68.33 ±30.16	67.87 ±24.99	0.959[a]

[a] using independent *t*-test to compare mean of the control group with the study group

♆ using Chi-square test to compare the number of patients taking the drug and not taking that drug in the control with the study group

† using Fisher's exact test to compare the number of patients taking the drug and not taking that drug in the control with the study group

* having a significant difference at α=0.05

1.2 Baseline laboratory data

Baseline clinical laboratory data is presented in Table 18. Independent *t*-test was used to determine baseline clinical laboratory data between the control and study groups. This result showed that most of variables were not statistically significantly different (p>0.05) except total cholesterol, LDL-C levels, and fasting plasma insulin, which were significantly different between placebo and oxymetholone groups (p=0.037, p=0.033, and p=0.013, respectively).

The overall mean baseline of serum albumin level was 3.88±0.27 g/dL (ranging from 3.3 to 4.3 g/dL). Mean baseline albumin in the placebo group was slightly higher than those in the oxymetholone group. However, there was no difference (p=0.374). Mean baseline predialysis BUN was 59.65±13.27 mg/dL, ranging from 34 to 90 mg/dL). The mean baseline predialysis BUN in the placebo group (62.68±14.13 mg/dL, ranging from 41 to 90 mg/dL) did not differ significantly from that in the oxymetholone group (56.48±11.81 mg/dL, ranging from 34 to 83 mg/dL, p=0.127). Similarly, the average predialysis serum creatinine in both groups was 11.29±2.09 mg/dL (ranging from 6.6-14.9 mg/dL). The average of serum creatinine in the oxymetholone group and placebo group were 11.09±2.60 (ranging from 6.6-14.9 mg/dL) and 11.48±1.49 (ranging from 8.9-14.3), respectively

(p=0.553).With regard to hemoglobin and hematocrit baselines, both groups were quite similar, with total mean of 10.11±1.32 g/dL and 31.71±3.42%. Mean hemoglobin in the oxymetholone group was 10.17±1.37 g/dL, which was not significantly different from that of the placebo group, which was 10.04±1.30 g/dL (p=0.750). For the hematocrit baseline, both groups did not vary (p=0.942). The hematocrit value in the oxymetholone group was 31.67±3.36% (range from 28.92 to 41.0%), while that of the placebo group was 31.75±3.55% (ranging from 28.92 to 40.23%). These values were lower than the target level that recommended in K/DOQI, which recommends a hemoglobin target level of 11.0-12.0 g/dL, while hematocrit should be 33% to 36% *(144)*. For fasting blood sugar, the overall mean was 77.83±10.07 mg/dL (ranging from 65 to 125 mg/dL). Mean fasting blood sugar in the oxymetholone group was 78.08±6.67 mg/dL (ranging from 70 to 94 mg/dL), while that in the placebo group was 77.59±12.67 mg/dL (ranging from 65 to 125 mg/dL). The differences were not statistically significant (p=0.872).

Regarding the lipid profile baseline including total cholesterol (TC), triglyceride, Low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C), triglyceride and HDL-C were not statistically different (both p>0.05), where as TC and LDL-C statistically differed (p<0.05 for both variables). Mean of total cholesterol variable was significantly greater in the placebo group (190.86±22.69 mg/dL, ranging from 146 to 232 mg/dL) than that of in the oxymetholone group (173.90±28.59 mg/dL, ranging from 136 to 246 mg/dL) with a significance at p=0.037. The overall total cholesterol of study participants was 182.58±26.83 mg/dL with a range of 136 to 245 mg/dL. For triglyceride baseline, there was no statistically significant difference between the oxymetholone group and the placebo group (p=0.330). Mean baseline triglyceride in the oxymetholone group and the placebo groups were 115.14±71.71 mg/dL (ranging from 49 to 308 mg/dL) and 96.81±48.35 mg/dL (ranging from 40 to 226 mg/dL). Mean baseline triglyceride for all patients was 105.77±60.86 mg/dL (ranging from 40 to 308 mg/dL). For LDL-C baseline, the overall mean was 117.79±26.54 mg/dL (ranging from 80 to 199 mg/dL). There was a significant difference between the oxymetholone group and the placebo group (109.04±26.14 mg/dL, ranging from 80 to 199 mg/dL and 126.13±24.67 mg/dL, ranging from 80 to 182 mg/dL, respectively) with a significance at p=0.033. For HDL-C baseline, the overall mean was 57.81±14.13 mg/dL (ranging from 32 to 88 mg/dL). There was no statistical difference between two group (p=0.450), which the LDL-C mean of the oxymetholone group was 56.19±15.15 mg/dL (ranging from 32 to 88 mg/dL), and that of the placebo group was 59.36±13.25 mg/dL (ranging from 38 to 80 mg/dL).

Additionally, the laboratory parameters for safety profile were assessed as liver function test. Thus, AST and ALT were assessed for baseline. The overall mean of AST and ALT was 15.02±5.79 U/L (ranging from 6 to 33 U/L) and 13.69±5.70 U/L (ranging from 8 to 34 U/L), respectively. The mean AST of patients in the oxymetholone group was 16.28±6.45 U/L with a range of 8 to 33 U/L, while that of patients in the placebo group was 13.82±4.92 U/L with a range of 6 to 23 U/L. However, this difference did not reach statistically significant (p=0.165). Also, there was no difference between the ALT mean of the oxymetholone group (14.38±6.41 U/L, ranging from 8 to 34 U/L) and the placebo group (13.04±4.99 U/L, ranging from 8 to 30 U/L); p=0.450. In addition, total bilirubin, and direct bilirubin were assessed

for baseline. The mean total bilirubin of patients in the oxymetholone group was 0.31±0.11 mg/dL with a range of 0.1 to 0.52 mg/dL, while that of patients in the placebo group was 0.33±0.09 mg/dL with a range of 0.17 to 0.54 mg/dL. However, this difference did not reach statistically significant (p=0.526). For direct bilirubin, the mean direct bilirubin of patients in the oxymetholone group was 0.10 mg/dL while that of patients in the placebo group was 0.10±0.02 mg/dL with a range of 0.1 to 0.2 mg/dL. However, this difference did not reach statistically significant (p=0.335). Considering the fasting plasma insulin, mean baseline value demonstrated that fasting plasma insulin level in the oxymetholone group was significantly different from that in the placebo group (61.30±52.28 μU/mL *vs.* 28.24±28.45 μU/mL, p=0.013).

Table 18 Baseline laboratory data

Laboratory parameters	Mean ±SD			*p*-value[a]
	Oxymetholone (n=21)	Placebo (n=22)	Total (n=43)	
Hemoglobin (g/dL)	10.17±1.37	10.04±1.30	10.11±1.32	0.750
Hematocrit (%)	31.67±3.36	31.75±3.55	31.71±3.42	0.942
FBS (mg/dL)	78.09±6.67	77.59±12.67	77.83±10.07	0.872
Fasting plasma insulin (μU/mL)	61.30±52.28	28.24±28.45	44.38±44.57	0.013*
BUN (mg/dL)	56.48±11.82	62.68±14.13	59.65±13.27	0.127
serum creatinine (mg/dL)	11.09±2.60	11.48±1.49	11.29±2.09	0.553
Serum albumin (g/dL)	3.84±0.30	3.92±0.24	3.88±0.27	0.374
Kt/V (per week)	1.79±0.46	1.74±0.37	1.77±0.41	0.715
AST (U/L)	16.28±6.45	13.82±4.92	15.02±5.79	0.165
ALT (U/L)	14.38±6.41	13.04±4.99	13.69±5.70	0.450
TB (mg/dL)	0.31±0.11	0.33±0.09	0.32±0.09	0.526
DB (mg/dL)	0.10±0.00	0.10±0.02	0.10±0.02	0.335
TC (mg/dL)	173.90±28.59	190.86±22.69	182.58±26.83	0.037*
TG (mg/dL)	115.14±71.71	96.81±48.35	105.77±60.86	0.330
LDL-C (mg/dL)	109.04±26.14	126.13±24.67	117.79±26.54	0.033*
HDL-C (mg/dL)	56.19±15.15	59.36±13.25	57.81±14.13	0.450

[a] using independent *t*-test to compare mean of the control group with the study group

* having a significant difference at $\alpha < 0.05$

1.3 Baseline body composition and nutrient intake

Body composition of both groups was evaluated by using dual-energy x-ray absorptiometry (DEXA) scan as shown in Table 19. All body composition data are reported in gram, but each value is normalized by individual weight. Thus, all these values are presented in gram per kg (g/kg). Patients in both groups did not have significant difference in lean body mass (LBM; g/kg) and fat mass (g/kg) at baseline (all variables $p>0.05$). Considering LBM, the average LBM of the oxymetholone group and the placebo group were not statistically significantly different ($p=0.231$). Likewise, the comparison of fat mass was not significantly different between both groups ($p=0.344$).

Nutrient intake data were evaluated by a dietitian (Table 19). All obtained measurements were not statistically significantly different between both groups (all variables $p>0.05$). For nutrient intake data, there was no statistical difference in both groups as well (all $p>0.05$).

Table 19 Baseline body composition and nutrient intake

Data	Mean ±SD			*p*-value[a]
	Oxymetholone (n=21)	Placebo (n=22)	Total (n=43)	
Body composition				
LBM (g/kg)	712.75±91.59	745.99±87.63	729.76±90.09	0.231
Fat mass (g/kg)	245.74±108.59	216.27±93.00	230.66±100.81	0.344
Nutrient intake data[b]				
Energy intake (kcal/kg/day)	22.19±6.44	19.06±6.11	20.58±6.39	0.110
Protein intake (g/kg/day)	0.96±0.39	0.77±0.21	0.87±0.33	0.062

[a] using independent *t*-test to compare mean of the control group with the study group
[b] using Inmucal® software for assessment from 3-day dietary records

Moreover, quality of life was assessed by SF-36, a short-form quality of life (QOL) scoring system with 36 items. It is a self-administered questionnaire, with 35 of all items compressed into eight multi-item scales. Of these scales, physical functioning is the scale used in this study to evaluate the ability to deal with the physical requirement of life, such as attending to personal needs, walking, and flexibility. In SF36 scoring system, a score between 0 and 100 is calculated, with a higher score indicating a better state of health *(145)*.

Table 20 shows baseline quality of life assessed by SF-36 questionnaire. The result showed that there was no difference in physical functioning, and total scores between two groups (p=0.593, and p=0.371, respectively).

Table 20 Baseline short form-36 (SF-36)[b]

Data	Mean ±SD			p-value[a]
	Oxymetholone (n=21)	Placebo (n=22)	Total (n=43)	
SF-36 Physical Functioning	71.90±17.71	74.77±17.21	73.37±17.31	0.593
SF-36 total score	63.19±17.99	68.35±19.74	65.86±18.86	0.371

[a] using independent t-test to compare mean of the control group with the study group
[b] using Microsoft Excel 2002 for SF-36 scoring of the scales, and scoring scale was developed by Kalartar-Zadeh

2. Efficacy Evaluation

Of 21 patients in the oxymetholone group, one patient (4.76%) withdrew from the study after first month of the study, and another one (4.76%) in the oxymetholone group had to discontinue after taking the medication for 5 months. The latter was due to icteric sclera, which was caused clinically by elevation of bilirubin. Also, her liver function enzymes were higher than the upper limit of normal; however, these not more than three times the upper limit of normal. Intention-to-treat analysis, therefore, was performed to determine the efficacy of all patients, which were 21 patients in oxymetholone group and 22 patients in placebo group. The missing data were replaced by series mean.

2.1 Efficacy on body weight and body composition changing from baseline

There were a number of indicators which were used to assess nutritional status. However, body weight, body mass index and body composition measured by dual energy x-ray absorptiometry (DEXA) were used for nutritional assessment in this study.

2.1.1 Body weight

Regarding average body weight, Table 21 presents the average body weight over period of the study. In the oxymetholone group, the values progressively increased over period. When comparing within group, the evaluation was performed by using one-way repeated ANOVA for each period (4 weeks). For the oxymetholone group, a repeated measures one-way ANOVA revealed that there were significant differences in mean body weight between the times of measurements (Table 22), ($F_{1.19,23.88}$ = 11.84, p=0.001). Interestingly, when comparing all means, pairwise comparisons also revealed that mean body weight at week 0 was significantly different from that at week 4. Also, the differences were found between week 0 and week 8, week 0 and week 12, week 0 and week 16, week 0 and week 20, and week 0 and week 24 (all p<0.05; Appendix L). Additionally, mean body weight at week 4 significantly differed from that at week 8. Also, there were significant differences in mean body weight in week 4 compared to week 12, and week 4 compared to week 16 (all p<0.05; Appendix L). Ultimately, the difference between mean body weight at

week 8 and week 12 is statistically significant as well ($p<0.05$; Appendix L). In contrast, there was no significant difference in mean body weight between any periods of measurement in the placebo group ($F_{1.6,34.07}=2.86$, $p=0.081$; Appendix M). When comparing average weight between two groups by using one-way ANOVA, the outcome showed that there was no significant difference in mean body weight between the oxymetholone and the placebo group during 24-week peroid ($F_{1,41}=0.842$, $p=0.364$). Figure 8 depicts average body weight during the 24-week treatment period.

Table 21 Average body weight over period of the study

Time point	Body weight (kg)	
	Oxymetholone* (n=21)	Placebo (n=22)
	Mean ± SD	Mean ± SD
Week 0	53.61±8.79	56.79±8.91
Week 4	54.03±8.74	56.95±8.87
Week 8	54.48±8.66	57.07±8.76
Week 12	55.09±8.42	57.19±8.72
Week 16	55.29±8.33	57.21±8.63
Week 20	55.32±8.16	57.26±8.69
Week 24	55.15±8.25	57.31±8.71

* intention-to-treat analysis was used in data at week 24 and missing data were replaced by series mean

Table 22 ANOVA summary table for the change in average weight following oxymetholone and placebo

Dependent variable: weight

Source	Sum of squares	Df	Mean squares	F-ratio	p-value
Between subjects					
Group	8.82	1	435.67	0.842	0.364
Residual between	21218.75	41	517.53		
Within subjects					
Time	58.35	1.19	48.86	11.84	0.001*
Residual within	98.61	23.88	4.12		

* having a significant difference at $\alpha=0.05$

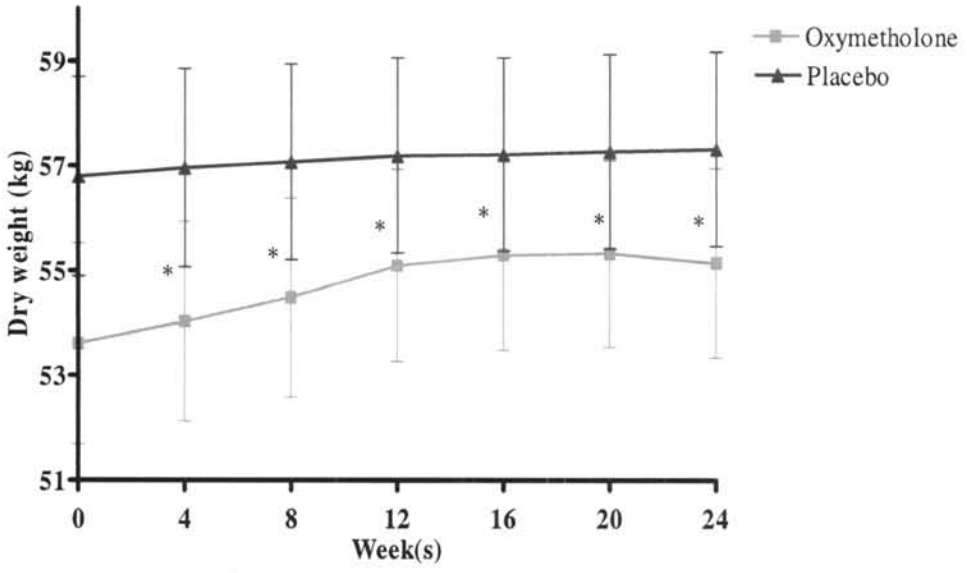

Figure 8 Relative increases in average weight between two groups in comparison with baseline values by repeated one-way ANOVA. The values are expressed as mean±SE. Asterisks indicate statistical significance ($p<0.05$) compared to baseline.

For determination of the changes of body weight through 24 weeks, independent *t*-test was applied to compare the difference between two groups (Table 23). The results showed that either subject in oxymetholone or in placebo had progressive weight gain. However, a statistically significant increase occurred as early as 4 weeks after baseline for the oxymetholone group ($p=0.030$). Figure 9 displays the efficacy of oxymetholone and placebo on weight gain. This findings are consistent with the result determined by Hengge et al.*(24)*, they concluded that the onset of weight gain occurred within 4 weeks after starting oxymetholone.

Table 23 Mean changes in body weight from baseline assessed at each 4 weeks compared between oxymetholone and placebo (between group).

Difference during period time	Changes in body weight (kg) Mean±SD		*p*-value[a] (between group)
	Oxymetholone* (n=21)	Placebo (n=22)	
0 to 4	0.42±0.43	0.16±0.33	0.030**
0 to 8	0.87±0.58	0.28±0.68	0.004**
0 to 12	1.49±1.15	0.39±0.89	0.001**
0 to 16	1.69±1.60	0.42±0.96	0.003**
0 to 20	1.71±1.94	0.47±1.12	0.013**
0 to 24	1.54±1.98	0.52±1.21	0.048**

* intention-to-treat analysis was used in data at each 4-week and missing data were replaced by series mean

[a] using independent *t*-test to compare change in body weight from baseline at each time point of study (weeks 4, 8, 12, 16, 20, and 24) between the oxymetholone group and placebo group

** having a significant difference at $\alpha = 0.05$

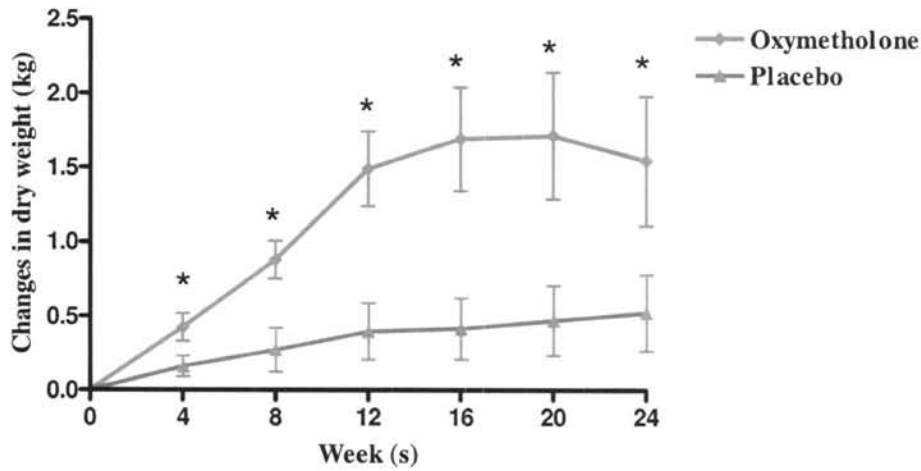

Figure 9 Average body weight gain during the 24-week treatment period. Mean change in weight from baseline at each time point is shown. The values are expressed as mean±SE. Asterisks indicate statistical significance compared between groups by independent *t*-test ($p<0.05$).

As shown in Figure 9, there was a gain of 0.52±1.21 kg on placebo while a gain of 1.54±1.98 kg on oxymetholone during 24 weeks. When using independent *t*-test to compare the differences between both groups, it was found that weight gain on oxymetholone was statistically significant difference from weight gain on placebo ($p=0.048$ *vs.* placebo at week 24).

2.1.2 Body mass index

Furthermore, body mass index is one of the anthropometry parameter used for nutritional assessment. The result showed in Table 24 indicating that body mass index in the oxymetholone group progressively increased compared to baseline, while there had been negligible difference in body mass index in the placebo group. Regarding average body mass index, Table 24 presents the average body mass index over period of the study. In the oxymetholone group, the values progressively increased over period. When comparing within group, the evaluation was performed by using one-way repeated ANOVA for the average BMI of each period (4 weeks). A repeated measures one-way ANOVA indicated in Table 25 that means of body mass index were significantly different between the times of measurements ($F_{1.21,\ 24.29} = 9.88$, $p=0.003$). Pairwise comparisons revealed that average BMI at week 0 was significantly different from that at week 4, also between week 0 and week 8, week 0 and week 12, week 0 and week 16, week 0 and week 20, and week 0 and week 24 (all $p<0.05$; Appendix N). Additionally, the pairwise comparisons also detailed the mean BMI, which were significantly different between week 4 and week 8, week 4 and week 12, week4 and week 16, and week 4 and week 20 (all $p<0.05$; Appendix N). Ultimately, the differences between week 8 and week 12, week 8 and week 16, and week 8 and week 20 were statistically significant (all $p<0.05$; Appendix N). In contrast, there was no significant difference in body mass index over time in the placebo group ($F_{1.59,33.39}=2.87$, $p=0.082$;) and between any periods of measurement in the placebo group (Appendix O). When comparing average body mass index between two groups by using one-way ANOVA, the outcome indicated that there was no significantly difference between the oxymetholone and the placebo groups during 24-

week period ($F_{1,41}$=0.265, p=0.609). After all, assessed by WHO classification for Asian-pacific region (Table 26), average BMI in both groups were classified as normal status. However, one patient in the oxymetholone group (4.76%) was classified as underweight, while there were 6 patients in the placebo group (27.27%). When comparing the number of patients between groups with Chi-square test, the result showed that there was a significant difference between groups (p=0.046)

Table 24 Average body mass index over period of the study

Time point	Body mass index (kg/m^2)	
	Oxymetholone* (n=21)	Placebo (n=22)
	Mean ± SD	Mean ± SD
Week 0	21.36±3.18	21.16±3.47
Week 4	21.54±3.19	21.22±3.50
Week 8	21.73±3.15	21.26±3.46
Week 12	21.96±3.01	21.31±3.46
Week 16	22.03±2.93	21.36±3.44
Week 20	22.04±2.86	21.34±3.48
Week 24	21.92±2.87	21.30±3.52

* intention-to-treat analysis was used in data at each 4-week and missing data were replaced by series mean,

Table 25 ANOVA summary table for the change in average body mass index following oxymetholone and placebo

Dependent variable: body mass index

Source	Sum of squares	df	Mean squares	F-ratio	p-value
Between subjects					
Group	19.69	1	19.69	0.265	0.609
Residual between	3042.03	41	74.19		
Within subjects					
Time	8.82	1.21	7.26	9.882	0.003*
Residual within	17.85	24.29	0.735		

* having a significance difference at α=0.05

Table 26 Comparison of number of patients according to weight status classified by WHO for Asian-pacific region between the oxymetholone and the placebo group at the end of the study (week 24)

Status	BMI (kg/m^2)	Oxymetholone (n=21)	Placebo (n=22)	p-value[a]
Underweight	<18.5	1	6	
Normal	18.5-22.9	20	16	
Overweight	23-24.9	0	0	0.046*
Obese	25-29.9	0	0	
Extremely obese	>30	0	0	

[a] using Chi-square test to compare the number of patients between groups

* having a significant difference at $\alpha < 0.05$

Regarding percent changes in body mass index (Table 27), the finding showed remarkable statistical difference in increased body mass index on oxymetholone compared to placebo. Independent *t*-test was used to compare the differences.

Table 27 Percent change in body mass index from baseline assessed at each 4 weeks compared between oxymetholone and placebo (between groups)

Difference during period time	Percent change in body mass index (%) (Mean±SD)		*p*-value[a] (between group)
	Oxymetholone* (n=21)	Placebo (n=22)	
0 to 4	0.83±0.88	0.31±0.57	0.026**
0 to 8	1.72±1.21	0.54±1.11	0.002**
0 to 12	2.98±2.39	0.76±1.41	0.001**
0 to 16	3.41±3.23	0.83±1.56	0.003**
0 to 20	3.52±3.88	0.91±1.75	0.009**
0 to 24	3.17±3.89	0.99±1.94	0.029**

* intention-to-treat analysis was used in data at week 24 and missing data were replaced by series mean

[a] using independent *t*-test to compare percent change in body mass index from baseline at each time point of study (weeks 4, 8, 12, 16, 20, and 24) between the oxymetholone group and placebo group

** having a significant difference at $\alpha = 0.05$

However, the use of body mass index for measuring body composition has a foible because body mass index is unlikely to distinguish fat and lean masses *(146)*. Thus, dual energy x-ray absorptiometry (DEXA) was performed to determine body composition. This method was recommended for monitoring nutritional status of maintenance dialysis patients *(147)*. In addition, it was proven to be a valid and clinically useful technique for assessing nutritional status and less influenced by the abnormalities in hydration status, which is common in hemodialysis patients *(148)*. Table 28 shows the assessment of body composition investigated by DEXA scanner. This method provided the main components of body composition such as fat mass and fat-free mass or lean body mass.

2.1.3 Lean body mass and fat mass

For measuring body composition by DEXA (Table 28), mean LBM in the oxymetholone group was statistically superior compared to baseline (769.06±99.67 g/kg *vs.* 712.75±91.59 g/kg, $p<0.0001$) whereas mean fat mass statistically significantly diminished compared to baseline (211.36±88.41 *vs.* 245.74±108.59, $p=0.006$). When assessing body composition in the placebo group, there was statistically significant change in total fat mass compared to baseline (206.54±92.39 *vs.* 216.27±93.00 g/kg, $p=0.011$); however, total LBM gained not significantly compared to baseline (750.66±86.39 *vs.* 745.99±87.63 g/kg, $p=0.206$). Total LBM increased by 56.30±60.69 g/kg after 24-week treatment ($p=0.001$) with oxymetholone, which was greater than the result from the placebo group (4.67±16.79 g/kg) as shown in Table 29 and Figure 10. Furthermore, although two subjects in the oxymetholone group had experienced on average 5 % to 10% weight loss, their LBM significantly increased at the end of the study.

Table 28 Comparison of body composition measured by dual energy x-ray absorptiometry between week 0 and week 24 within patient group and between two groups at week 24

Variable	Body composition measure by DEXA (g/kg) (Mean ± SD)				*p*-value[b] (between group)
	Oxymetholone* (n=21)	*p*-value[a] (within group)	Placebo (n=22)	*p*-value[a] (within group)	
LBM Week 0	712.75±91.59	-	745.99±87.63	-	0.231
Week 24	769.06±99.67	<0.0001**	750.66±86.39	0.206	0.521
Fat Mass Week 0	245.74±108.59	-	216.27±93.00	-	0.344
Week 24	211.36±88.41	0.006**	206.54±92.39	0.011**	0.862

* intention-to-treat analysis was used in data at week 24 and missing data were replaced by series mean

[a] using paired *t*-test to compare mean at the study initiation (week 0) to the end of study (week 24) for each group

[b] using independent *t*-test to compare mean at the end of study (week 24) between two groups

** having a significantly difference at $\alpha = 0.05$

Table 29 Mean changes in body composition measured by dual energy x-ray absorptiometry (DEXA) from baseline assessed at the end of the study (week 24)

Variable	Change in body composition (Mean±SD)		*p*-value[a] (between groups)
	Oxymetholone* (n=21)	Placebo (n=22)	
LBM (g/kg)	56.30±60.69	4.67±16.79	0.001**
Fat mass (g/kg)	-34.38±50.77	-9.73±16.48	0.045**

* intention-to-treat analysis was used in data at week 24 and missing data were replaced by series mean

[a] using independent *t*-test to compare mean changes in body composition from baseline at the end of the study (week 24) between two groups

** having a significant difference at $\alpha = 0.05$

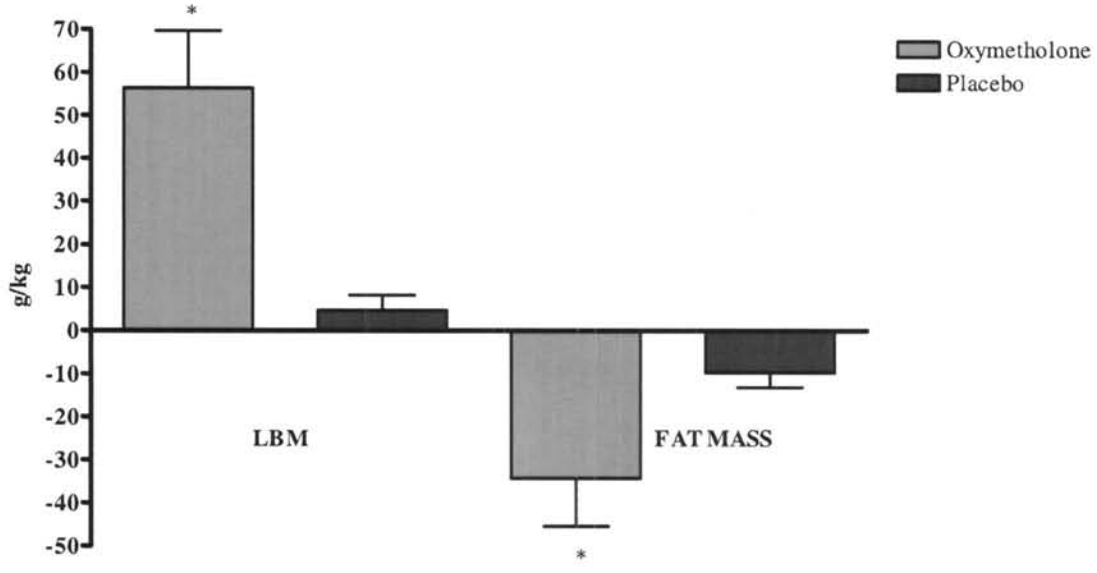

Figure 10 Changes in body composition measured by dual enery x-ray absorptiometry. This figure presents the changes fom the baseline values, which were expressed as mean±SE. Asterisks indicate statistical significance compared between groups by independent *t*-test ($p<0.05$).

2.2 Efficacy on serum albumin and serum creatinine levels

2.2.1 Serum albumin

Serum albumin is a useful measure of protein energy nutritional status in maintenance dialysis patients. It is used as a measure of visceral protein pool size. It is recommened that a predialysis serum albumin equal to or greater than the lower limit of the normal range (approximately 4.0 g/dL) is the outcome goal *(148, 149)*. Table 30 shows predialysis serum albumin levels at baseline (week 0) and the end of study (week 24). Average serum albumin level in the oxymetholone group (3.85±0.30 g/dL) and that in the placebo group (3.92±0.24 g/dL) were not statistically significantly different at the initiation of the study ($p=0.374$). After all, serum albumin levels increased in both groups at the end of the study. There was no difference in mean serum albumin level between groups ($p=0.093$). Also, it did not differ in change of serum albumin between both groups ($p=0.276$). Interestingly, the level in the placebo group was significantly higher than baseline value ($p=0.001$). When the individual's serum albumin level was taken into consideration, it showed that 11 patients (50%) of all patients in the oxymetholone group had increased serum albumin levels whereas 17 of 22 (77.27%) patients in the placebo group had higher serum albumin levels. This was most likely since three patients (14.28%) in the oxymetholone group had acute comorbid conditions at week 20, but these did not related to the study drug. Of these 3 patients, one had tooth extraction, which caused patient to be unable to maintain an adequate dietary. Other two patients had been admitted in the hospital. One of them experienced hypertension crisis secondary to epistaxis, and the other had hydrothorax. All causes resulted in mean serum albumin levels modestly declined at

week 24 in spite of the elevated values before they were ill. Moreover, the previous studies were conducted to determine the relationships among serum albumin and other nutritional variables. The results showed that dietary intake promotes higher albumin concentration *(8, 150)*. Thus, nutritional intake should be taken into account in association with serum albumin levels *(151)*.

Table 30 Comparison of predialysis serum albumin between week 0 and week 24 within patient group and between two groups at week 24

Variable	Predialysis serum albumin (g/dL) (Mean ± SD)				*p*-value[b] (between group)
	Oxymetholone* (n=21)	*p*-value[a] (within group)	Placebo (n=22)	*p*-value[a] (within group)	
Week 0	3.85 ±0.30	-	3.92±0.24	-	0.374
Week 24	3.95±0.28	0.212	4.09±0.25	0.001**	0.093
Change	0.08±0.28	-	0.16±0.20	-	0.276

* intention-to-treat analysis was used in data at week 24 and missing data were replaced by series mean

[a] using paired *t*-test to compare average predialysis serum albumin at baseline (week 0) with the end of the study (weeks 24)

[b] using independent *t*-test to compare the average serum albumin between the control and the study groups

** having a significant difference at $\alpha = 0.05$

2.2.2 Serum creatinine

Furthermore, predialysis serum creatinine level is proportional to dietary protein intake and the somatic (skeletal muscle) mass *(152)*. Likewise, according to K/DOQI guideline*(148)*, the decline of serum creatinine can reflect loss of skeletal muscle. Consequently, the increase in LBM in the oxymetholone group should be accompanied by an increase in predialysis serum creatinine levels. As shown from the mean level of predialysis serum creatinine monitored before and after 24 weeks (Table 31 and Figure 11), for the oxymetholone group, predialysis serum creatinine significantly increased from 11.09±2.61 mg/dL to 12.29±2.81 mg/dL (p=0.004 compared to baseline), whereas the reduction of predialysis serum creatinine from 11.49±1.49 mg/dL to 11.21±1.87 mg/dL were found in the placebo group. In addition, change in serum creatinine in the oxymetholone group was statistically significantly different compared to that in the placebo (p=0.001). The decrease in serum creatinine in the placebo group was suspected on losing of skeletal muscle. This finding was consistent with the previous study by Johansen, which found a significantly positive correlation between the change in serum creatinine levels and the change in LBM (r=0.48, p=0.02) *(13)*. Moreover, the study by Beddhu et al showed that a subject who had an increase in BMI accompanied with high creatinine level inferred low body fat had 15% lower hazard of all-cause and 11% lower hazard of cardiovascular death. In contrast, high BMI with low creatinine level inferred high body fat had 14% higher risk of all-cause and 19% higher risk of cardiovaseculare death *(153)*. Thus, the survival advantage of high BMI was confined to those subjects with normal or high muscle mass. In this study, body composition measurement, DEXA, was performed. The result from DEXA scan showed a significantly improved LBM and

decreased fat mass in the oxymetholone group compared to baseline. Meanwhile, an increased LBM had been found in the placebo group although it did not significantly differ from baseline (p=0.206). However, serum creatinine level was higher in the oxymetholone group. In contrast, a substantial decrease had been found in the placebo group, which was not accompanied by an increase in LBM. Thus, it can probably be summarized that an observed increase in LBM in the placebo group resulting from an expansion in extracellular fluid volume *(13)*.

Table 31 Comparison of predialysis serum creatinine between week 0 and week 24 within patient group and between two groups at week 24

Variable	Predialysis serum creatinine (mg/dL) (Mean ± SD)				p-value[b] (between group)
	Oxymetholone* (n=21)	p-value[a] (within group)	Placebo (n=22)	p-value[a] (within group)	
Week 0	11.09±2.61	-	11.49±1.49	-	0.553
Week 24	12.29±2.81	0.004**	11.21±1.87	0.213	0.150
Change	1.19±1.68	-	-0.27±0.99	-	0.001**

* intention-to-treat analysis was used in data at week 24 and missing data were replaced by series mean

[a] using paired t-test to compare average predialysis serum creatinine at baseline (week 0) and week 24

b using independent t-test to compare the average serum creatinine between the control and the study groups at week 24

** having a significant difference at $\propto$ = 0.05

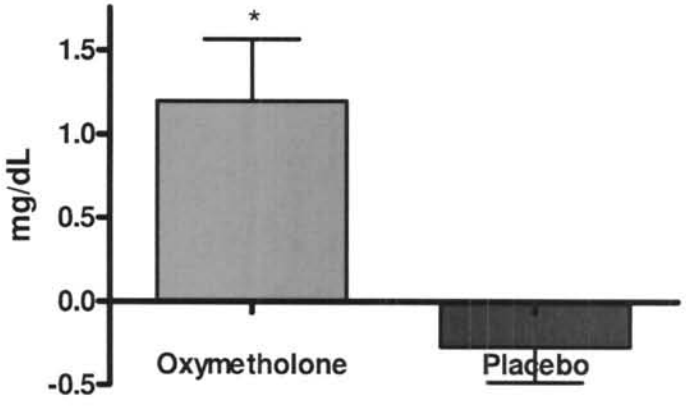

Figure 11 Changes in predialysis serum creatinine between the control and the study groups at week 24 compared by using independent t-test. Asterisk indicates a significance difference at $\propto$ = 0.05.

2.3 Efficacy on dietary intake, quality of life assessment, and handgrip strength

2.3.1 Dietary intake

For estimation protein intake in hemodialysis patients, protein equivalence of nitrogen appearance (PNA) can be applied. This parameter strongly influences serum albumin level *(150)*, and it is closely correlated with dietary protein intake. PNA is usually normalized to body weight, which is expressed as normalized protein equivalence of nitrogen appearance (nPNA). In maintenance hemodialysis patients, the recommended nPNA is 1.2 g/kg/d *(148)*. The assessment of the nPNA can be calculated by the following formula *(148)*.

$$\text{nPNA (mid-week)} = \frac{C_0}{\left[25.8 + \left(\frac{1.15}{\text{spKt/V}}\right) + \left(\frac{56.4}{\text{spKt/V}}\right)\right]} + 0.168$$

Calculate spKt/V

$$\text{spKt/V} = -\ln(R - 0.008 \times t) + (4 - (3.5 \times R)) \times UF/W$$

when nPNA = normalized protein equivalence of nitrogen appearance (g/kg/day)
C_0 = current predialysis BUN (mg/dL)
spKt/V = single-pool Kt/V (per week)
R = previous postdialysis/ previous predialysis BUN ratio
t = dialysis session (hrs)
UF = ultrafiltration volume (L)
W = postdialysis weight (kg)

Regarding protein intake evaluated by normalized protein equivalence of nitrogen appearance (Table 32), the data showed that there was statistically significant difference compared to baseline in the oxymetholone and the control groups (both p=0.003). Besides, mean nPNA at the end of the study did not differ between the oxymetholone and the placebo groups (p=0.981), also there was no difference in change in nPNA between both groups (p=0.362). This can be concluded that there was no variation in protein intake between both groups. Also, due to the fact that serum albumin levels are directly and strongly correlated with dietary protein intake, an increased nPNA, which is used to estimated dietary protein intake *(148)*, can be responsible for increasing in serum albumin level. Yet, serum albumin concentration was lower in the oxymetholone group (compared to the placebo group); it was because few subjects in the oxymetholone group had been affected by acute illness. That resulted in less serum albumin levels in the oxymetholone group than those in the placebo group.

Table 32 Comparison of normalized protein equivalence of nitrogen appearance between week 0 and week 24 within patient group and between two groups at week 24

Variable	Normalized protein equivalence of nitrogen appearance (g/kg/d) (Mean ± SD)				p-value[b] (between group)
	Oxymetholone* (n=21)	p-value[a] (within group)	Placebo (n=22)	p-value[a] (within group)	
Week 0	0.98±0.22	-	1.05±0.24	-	0.327
Week 24	1.20±0.31	0.003**	1.20±0.30	0.003**	0.981
Change	0.22±0.29	-	0.14±0.21	-	0.362

* intention-to-treat analysis was used in data at week 24 and missing data were replaced by series mean

a using paired t-test to compare average nPNA at baseline (week 0) with the end of study (week 24)

b using independent t-test to compare the average nPNA between the control and the study groups at week 24

** having a significant difference at $\alpha = 0.05$

However, since there are limitations to the preciseness with which the nPNA indicates the daily protein intake *(148)*, other measures of protein intake were carried out in addition to nPNA. Three-day dietary records were, therefore, performed to assess nutritional parameters. The records were reported at baseline and week 24, which revealed that there were no statistically significant differences during 24 weeks between the control and the study groups (all variables $p>0.05$; Table 33). For the placebo group, the data showed a significant increase in protein intake was noted in subjects assigned to placebo ($p=0.049$ compared to baseline), while protein intake did not significantly differ in the oxymetholone group. This was not in accord in protein intake measured by nPNA, as well as that from a previous study, which found that protein intake estimated by dietary records was significantly lower than protein intake estimated by nPNA ($p<0.001$); it is because in the catabolic patient nPNA will exceed protein intake to the extent that there is net degradation and metabolism of endogenous protein pools to form urea *(148)*. However, dietary recall is useful method for providing quantitative information concerning intake of energy.

Furthermore, consideration of energy intake, the result showed that there was no significant difference in energy intake in both the oxymetholone and the placebo groups compared to baseline ($p=0.239$, and $p=0.218$, respectively). Although energy intake did not differ between both groups at the end of the study; however, this value was greater in the placebo group than that in the oxymetholone group. According to a previous study of relationship between serum albumin and energy intake, the finding showed that albumin concentration correlated directly with energy intake, which also suggesting the influence of food intake on albumin levels. This increase in energy intake can be responsible for an increased serum albumin in the placebo group as well. However, LBM in the placebo group did not differ from baseline. Thus, it can be assumed that LBM in oxymetholone group remarkably gained regardless of nutritional intake effects.

Neither placebo nor oxymetholone was associated with improvement in quality of life assessed by SF-36 (Table 33). Similarly, there were no significant changes in all parameters as measured by self-reported SF-36. However, self-reported functioning measured by using the physical functioning score of the SF-36 was compared during the study period. It showed that improved self-reported physical functioning was found in the oxymetholone group; however it did not achieve statistically significantly difference (p=0.260 compared to baseline). This is in accord with the recent study by Johansen et al.*(122)*, which showed that even weight and LBM increased in androgenic steroid group over period of the study, there were not different in physical functioning between the study group and placebo (p=0.63*)*. On the other hand, there was significant improvement in patients assigned to exercise (p=0.03).

Regarding muscle strength, handgrip strength was performed, and this method was applied to estimate general muscle strength and functional mobility in hemodialysis patients *(154)*. The study by Heimburger et al. and Wang et al. *(154, 155)* showed strongly relationship between handgrip strength and LBM (r=0.7, p<0.0001). In this study, after six months of treatment, handgrip strength significantly differed from baseline in the oxymetholone group (26.80±8.14 kg *vs* 29.13±9.35 kg, p=0.037), while there was no difference observed from the placebo group (32.39±9.52 kg *vs* 32.09±8.43 kg, p=0.664) as shown in Table 33. The results of handgrip strength can represent the efficacy of oxymetholone in terms of improving muscle strength. Nevertheless, the study by Heimburger et al. *(154)* revealed that serum albumin level was not related to handgrtip strength or LBM (r=0.17, and r=0.07, p>0.05, respectively). This is consistent with this present study because although patients in the placebo group had approaching significantly higher serum albumin level (Table 30) and increased in LBM (Table 19), they did not have handgrip strength improvement at the end of the study (Table 33).

Additionally, comparison of percent changes in nutrient intake data, quality of life sore, presented that there were no differences in percent changes of energy intake and protein intake, physical functioning and total score of SF-36 between the oxymetholone and the placebo group (all p>0.05, Table 34). However, considering muscle strength improvement by handgrip strength, the outcome showed that percent change in handgrip strength in the oxymetholone group was significantly different from the placebo group (p=0.046, Table 34)

Table 33 Comparisons of average dietary intake estimated by 3-day dietary record, quality of life and handgrip strength between week 0 and week 24 within patient group and between two groups at week 24

Data	Oxymetholone (n=21)*			Placebo (n=22)			*p*-value[b] (between group)
	Mean (±SD)		*p*-value[a] (within group)	Mean (±SD)		*p*-value[a] (within group)	
	Week 0	Week 24		Week 0	Week 24		
Nutrient intake data[c]							
Energy intake (kcal/kg/day)	22.19±6.44	19.82±7.61	0.239	19.06 ±6.11	21.28±8.54	0.218	0.557
Protein intake (g/kg/day)	0.96±0.39	0.97±0.52	0.927	0.77±0.21	1.07±0.64	0.049**	0.569
Quality of life[d]							
SF-36 Physical functioning	71.90±17.71	75.71±17.48	0.260	74.77±17.21	75.68±16.71	0.822	0.995
Total score	63.13±17.96	65.92±14.67	0.385	68.35±19.74	73.98±13.47	0.082	0.067
Muscle strength							
Handgrip strength (kg)	26.80±8.14	29.13±9.35	0.037**	32.39±9.52	32.09±8.43	0.664	0.109

* intention-to-treat analysis was used in data at week 24 and missing data were replaced by series mean

[a] using paired *t*-test to compare the difference for each group between week 0 and week 24

[b] using independent *t*-test to compare the difference between the control group and the study group at week 24

[c] using Inmucal® software for assessment from 3-day dietary records

[d] using Microsoft Excel 2002 for SF-36 analysis developed by Kamyar Kalartar-Zadeh

** having a significant difference at α=0.05

Table 34 Comparisons of percent change in dietary intake estimated by 3-day dietary record, quality of life and muscle strength at week 24

Variable	Percent change in nutrient intake, quality of life and handgrip strength (%) (Mean±SD)		*p*-value[a] (between groups)
	Oxymetholone* (n=21)	Placebo (n=22)	
Nutrient intake			
Energy intake (kcal/kg/day)	-4.61±39.82	16.11±50.42	0.144
Protein intake (kcal/kg/day)	10.96±52.41	51.38±140.75	0.223
Quality of life			
SF-36 Physical Functioning	9.57±33.23	5.52±32.12	0.687
Total score	9.98±27.71	17.43±49.26	0.547
Muscle strength			
Handgrip strength	9.35±15.52	0.83±10.99	0.046*

3. The Relationship of Change in Lean Body Mass to Insulin Resistance

3.1 Change in fasting blood sugar, fasting plasma insulin and insulin resistance

Insulin resistance was evaluated by the homeostatic model, based on plasma insulin and glucose at fasting. Considering fasting blood glucose, there was not significantly difference from baseline both oxymetholone group and placebo group (78.09±6.67 mg/dL *vs.* 77.00±8.71 mg/dL and 77.59±12.67 mg/dL *vs.* 83.50±25.90 mg/dL, p=0.619 and p=0.106, respectively). Nonetheless, mean fasting blood sugar did not vary between the oxymetholone and the placebo group at the end of the study (p=0.281). In addition, insulin level and insulin resistance measured by homeostasis assessment model of insulin resistance was analyzed at the end of the study. The findings showed a significant difference for the variation of fasting plasma insulin, and HOMA-IR, which all decreased under oxymetholone treatment. For fasting plasma insulin level, there was a significantly difference compared to baseline (61.30±52.28 µmol/mL *vs.* 13.84±10.41 µmol/mL, p=0.001). Similarly, HOMA-IR in the oxymetholone group significantly improved compared to baseline (8.7±4.87 *vs.* 2.54±1.71, p=0.001). However, HOMA-IR were not significantly different between both groups at week 24 (2.54±1.71 *vs.* 1.69±1.19, p=0.066). All variables mentioned show in Table 37.

This finding is compatible with the effect of androgen on glucose metabolism, which concluded that androgens do not adversely affected glucose metabolism. Another study of effect of AAS in improved insulin resistance was performed by testosterone and dihydrotestosterone administrations. The result assessed by HOMA index showed a statistical significant decrease in HOMA-IR at the end of the study compared to placebo (p<0.01), with the groups treated by AAS. This study provided evidence that androgen treatment improved insulin resistance *(156)*. This was possible that the effect of AAS on changes in body composition and fat mass caused insulin sensitivity. The study by Boden found that a decrease in abdominal fat mass may induce an improvement in insulin sensitivity via a reduction in circulation free fatty acids *(157)*. Furthermore the study by Elbers et al and Zang et al determined effect of testosterone on insulin resistance assessed by HOMA and insulin sensitivity *(158, 159)*. The findings showed that testosterone changes neither fasting glucose nor fasting insulin levels (p>0.05). Similarly, insulin sensitivity was no significant change occurred in testosterone group. Regarding drugs with the potential of confounding the assessment of insulin resistance mention before, all subjects in this study had taken the same type of medication until the study termination.

3.2 Relation between change in LBM and insulin resistance

Using change in HOMA-IR as the dependent variables, the correlation analysis was examined with respect to change in LBM. A significant correlation between change in HOMA-IR and change in LBM persisted. When values for change in HOMA-IR are plotted against change in LBM, the amount of decrease in HOMA-IR had a significantly inversely correlation with the corresponding change in LBM (r=-0.342, p=0.028) as shown in Figure 12.

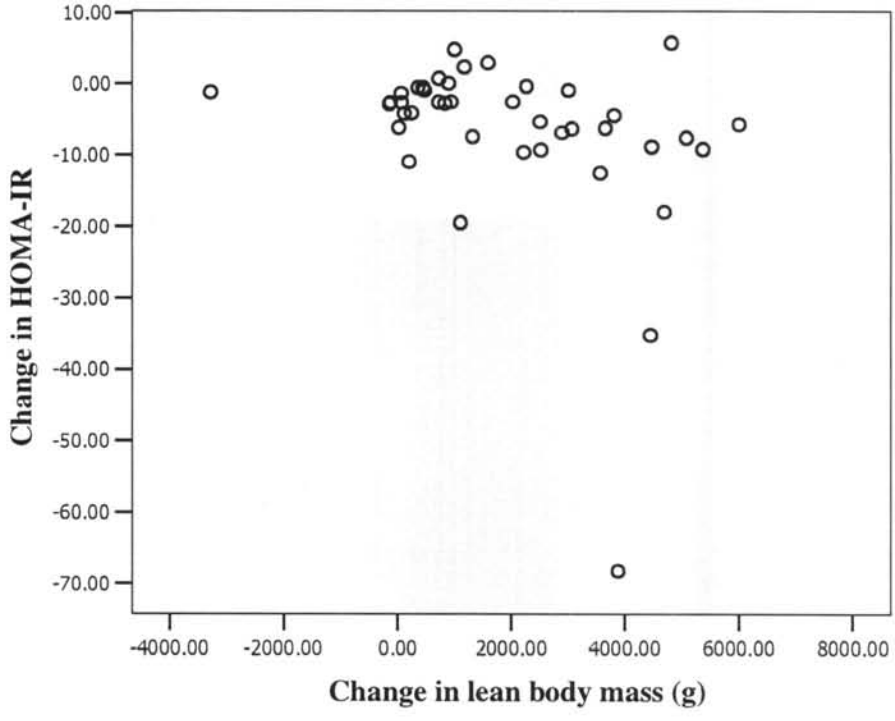

Figure 12 Relation between change in LBM (x-axis) and insulin resistance (y-axis), expressed by HOMA-IR

In contrast, previous studies have concerned that androgen use may be associated with insulin resistance *(158, 160)*, although this relationship has been substantiated in women with polycystic ovary syndrome. However, this present study did not find evidence of worsened insulin resistance in subjects receiving oxymetholone.

4. Safety Evaluation

During the 24-week study period, 2 patients (9.52%) in the oxymetholone group withdrew from the study due to adverse experiences. Of these 2 patients, one voluntarily withdrew because of gaining weight after taking the medication for 4 weeks, while the other one had to be discontinued as a result of the presence of icteric sclera with elevated bilirubin (more than 3 mg/dL) after 20 weeks on medication.

4.1 Effect on liver function enzymes

Overall, there were two patients (9.52%) in the oxymetholone group showing icteric sclera. One of them developed clinical sign after 20-week period of the study, and the other one presented at the end of study. However, after one month of discontinuation, elevated bilirubin returned to normal in both patients. Besides, no clinical sign of icteric sclera had been noticed. The causality assessment by using Naranjo's algorithm showed this adverse event was a probable adverse event due to the study drug. The patient who developed icteric sclera had increased AST and ALT; however these enzymes were lower than three times the upper limit of normal. Also, liver function enzymes and elevatated bilirubins returned to normal after one month of discontinuation. In addition, grade III liver toxicity according to World Health Organization (WHO) liver toxicity classification *(161)* was observed in another patient (4.76%) in the oxymetholone group. He had ALT greater than five times the upper limit of normal (ALT = 297 U/L) in the sixth month of the study.

Table 35 presents the laboratory indicative of liver function enzymes. At the beginning of the study, AST and ALT values were not statistically significantly different between both groups ($p>0.05$). When completing the study (week 24), the AST in the oxymetholone group was 47.81±44.35 U/L, and the ALT in the oxymetholone group was 70.05±69.47 U/L whereas the AST and ALT in the placebo group were 15.32±7.79 U/L and 15.55±7.53 U/L, respectively. However, when reviewing the current medication, it was found that the subject with the highest increase in ALT has been on drug-induced liver toxicity, which is simvastatin. Thus, it was likely that the combination of the study drug and simvastatin resulted in his liver enzyme elevation. According to Table 35, increased AST and ALT were found in oxymetholone group, which had been statistically significantly different from the placebo group since week 4 ($p<0.0001$ for AST and ALT *vs.* placebo). The results of liver-related toxicity within group were analyzed by one-way repeated ANOVA, which found that, within the oxymetholone group, means of AST and ALT statistically significantly varied compared to baseline ($F_{1.88,\ 37.72}=6.25$, $p=0.005$ and $F_{1.82,\ 36.42}=6.23$, $p=0.006$, respectively), while there was no significant difference in mean of AST and ALT compared to baseline in the placebo group ($F_{2.69,53.71}=1.54$, $p=0.217$ and $F_{3.64,72.72}=1.03$, $p=0.392$, respectively). Additionally, when comparing between group, one-way ANOVA showed a significant difference in mean AST and ALT between the oxymetholone and the placebo groups ($F_{1,41}=27.46$, $p<0.0001$ and $F_{1,40}=49.89$, $p<0.0001$, respectively).

Table 35 Comparisons of liver function parameters at each 4-weeks period between the control and the study groups

Week (s)	AST (U/L)		ALT (U/L)	
	Mean (±SD)		Mean (±SD)	
	Oxymetholone* (n=21)	Placebo (n=22)	Oxymetholone (n=21)	Placebo (n=22)
0	16.28 (±6.45)	13.82 (±4.92)	14.38 (±6.41)	13.04 (±4.99)
4	24.26 (±9.69)	13.90 (±5.35)	36.57 (±15.93)	13.23 (±5.96)
8	29.35 (±11.73)	16.00 (±10.36)	44.15 (±25.09)	14.45 (±6.98)
12	28.30 (±12.87)	15.00 (±7.79)	40.30 (±22.75)	13.82 (±7.21)
16	32.00 (±17.22)	13.59 (±5.87)	44.20 (±29.98)	13.73 (±7.62)
20	37.10 (±19.73)	13.86 (±5.52)	49.20 (±2.98)	14.36 (±6.55)
24	47.81 (±44.35)	15.32 (±7.79)	70.05 (±69.47)	15.55 (±7.53)
F	$F_{1.88,37.72}=6.25$	$F_{2.69,53.71}=1.54$	$F_{1.82,36.42}=6.23$	$F_{3.64,72.72}=1.03$
p-value[a]	0.005**	0.217	0.006**	0.392
p-value[b]	$F_{1,40}=27.46$, $p<0.0001$**		$F_{1,40}=49.89$, $p<0.0001$**	

* intention-to-treat analysis was used in data at week 24 and missing data were replaced by series mean

[a] using one-way repeated ANOVA to determine difference of variance within group

[b] using one-way ANOVA to determine difference of variance between group

** having a significant difference at $\alpha = 0.05$

The number of patients who experienced the adverse event associated with liver enzymes was reported in Table 36. There were 2 patients (9.52%) in the oxymetholone group having ALT more than four times the upper limit of normal, which presented at week 24. However, 11 patients (52.38%) in the oxymetholone group had ALT within normal, and 16 patients (76.19%) had normal AST. Conversely, all patients in the placebo group had normal AST and ALT in all period. Regarding the liver-associated adverse event for all period of the study, Table 36 shows the number of patients experiencing abnormality liver function enzymes. The statistically significant difference between the control group and the study at week 24 were determined using Fisher's exact test. The outcome reported that the number of patients experienced elevated ALT (Table 36 and Table 41), which was three times the upper limit of normal, was not statistically higher in the oxymetholone groups than in the placebo group (p=0.233 compared to placebo).

Table 36 The number of patients classified by elevated liver function enzymes measured during 4-week period

Live function enzyme level	Number of patients			
	Oxymetholone		Placebo	
	Week (s)		Week (s)	
	0	24	0	24
ALT (U/L) Normal limit (0-40 U/L)	21	11	22	22
> 1 time ULN (41-80 U/L)	0	7	0	0
> 2 times ULN (81-120 U/L)	0	1	0	0
> 3 times ULN (121-160 U/L)	0	0	0	0
> 4 times ULN (>160 U/L)	0	1	0	0
> 5 times ULN (>200 U/L)	0	1	0	0
AST (U/L) Normal limit (0-37 U/L)	21	16	22	22
> 1 time ULN (38-74 U/L)	0	3	0	0
> 2 times ULN (75-111 U/L)	0	2	0	0
> 3 times ULN (112-148 U/L)	0	0	0	0
> 4 times ULN (>148 U/L)	0	0	0	0
> 5 times ULN (> 185 U/L)	0	0	0	0

Considering liver function profile during week 0 and week 24, the results are shown in Table 37. There were 3 patients (14.28%) experiencing elevated bilirubin. Of these 3 patients, two of them showed clinical cholestatic jaundice. Their bilirubin levels rose up to 3 mg/dL; however, their liver function enzymes did not exceed than three times the upper limit of normal. Moreover, a rise in bilirubin alleviated once drug use was discontinued. This finding is consistent with the review of oxymetholone *(29)* in which a significant elevation in total bilirubin was note in 10% of patients receiving oxymetholone *(29)*. With respect to anabolic androgenic steroid injection, particularly nandrolone decanoate, injectable preparations had not found adverse events associated with liver toxicity *(121, 162)*. In contrast, oral preparations such as oxandrolone and oxymetholone cause more liver toxicity *(24, 27, 130)*.

Besides, changes in liver enzymes were statistically different from baseline, and the values were compared between groups (Table 40). AST and ALT enzymes in patients randomly assigned to oxymetholone immensely significantly elevated from baseline values, and these changes were statistically significantly different between both groups (p=0.004, and p=0.002, for changes in AST and ALT, respectively).

4.2 Effects on serum lipid indexes

Table 37 shows that TC, LDL-C, and TG concentrations with study therapy did not differ between two groups. However, there were significant within-group changes for TC, LDL-C, and HDL-C. For the oxymetholone group, there was a significant decrease in HDL-C level at week 24. Average HDL-C level in oxymetholone group was 34.33±19.27 mg/dL, which was statistically significantly different from baseline (p<0.0001). Moreover, TC and LDL-C levels in the oxymetholone group were also statistically lower than baseline (both p=0.001), but there were no statistical differences between the control and the study groups at the end of the study (p=0.244 and p=0.393 by an analysis of covariance, ANCOVA, using TC and LDL-C at baseline as covariate, respectively), while TG level in the oxymetholone group was not significantly different from baseline (p=0.653). Similarly, TC, LDL-C, and HDL levels in the placebo group were significantly different from baseline (p=0.041, p=0.004, and p=0.005, respectively). Yet, TG level was not statistically different (p=0.246 compared to baseline). Considering lipid indexes between groups, the result in Table 37 demonstrates that there were no differences in TC, TG, and LDL-C (p=0.244, p=0.993, and p=0.393, respectively), while a statistical significant difference in HDL-C was noted in the oxymetholone group (p=0.001)

Based on a previous study, there were some reports revealing an increased incidence of lipid abnormality in patients with chronic renal failure receiving oral androgenic steroids *(33, 34)*. However, such an abnormality was reversible on cessation of androgenic steroids within two months *(34)*. The mechanism of lipid abnormality in androgenic administration is unknown. According to some investigators, they found a markedly increase in TG after taking oxymetholone. They hypothesized that the increased triglyceride might result from the increased hepatic synthesis of endogenous triglycerides or reduced capacity of the liver to produce or release lipoprotein lipase may be responsible *(33, 163)*. Administration of oxymetholone and other oral anabolic androgenic steroids has been associated with significant decreases in plasma HDL-C levels *(130, 133, 164)*. The decreases in HDL-C represent a proatherogenic lipoprotein profile. Greater caution therefore should be exercised in administering androgenic steroids to patients. Serum lipid profiles should be evaluated monthly for the first few months of therapy.

Table 37 Comparison of liver function, lipid profile, fasting blood sugar, insulin resistance between week 0 and week 24 in each patient group and between the control group and the study group at week 24

Data	Oxymetholone* (n=21)			Placebo (n=22)			*p*-value[b] (between group)
	Mean±SD		*p*-value[a] (within group)	Mean±SD		*p*-value[a] (within group)	
	Week 0	Week 24		Week 0	Week 24		
Liver function							
AST (U/L)	16.28±6.45	47.81±44.35	0.003**	13.82±4.92	15.32±7.79	0.279	0.003**
ALT (U/L)	14.38±6.41	70.04±69.47	0.002**	13.05±4.99	15.55±7.53	0.160	0.002**
TB (mg/dL)	0.31±0.11	0.72±0.91	0.045**	0.33±0.09	0.32±0.11	0.629	0.06
DB (mg/dL)	0.1±0.00	0.45±0.72	0.037**	0.1±0.02	0.09±0.06	0.492	0.04**
Lipid profile							
TC (mg/dL)[c]	173.90±28.72	145.38±34.93	0.001**	190.86±22.69	180.64±18.47	0.041**	0.244
TG (mg/dL)	115.14±71.71	122.81±75.19	0.653	96.81±48.35	123.04±103.87	0.246	0.993
LDL-C (mg/dL)[c]	109.04±26.14	84.28±32.14	0.001**	126.13±24.67	112.91±19.07	0.004**	0.393
HDL-C (mg/dL)	56.19±15.15	34.33±19.27	<0.0001**	59.36±13.25	53.36±14.83	0.005**	0.001**
FBS (mg/dL)	78.09±6.67	77.00±8.71	0.619	77.59±12.67	83.50±25.90	0.106	0.281
Fasting plasma insulin (μU/mL)[c]	61.30±52.28	13.84±10.41	0.001**	28.24±28.45	8.30±5.86	0.003**	0.115
HOMA-IR[c]	8.7±4.87	2.54±1.71	0.0001**	4.76±4.52	1.69±1.19	0.005**	0.066

* intention-to-treat analysis was used in data at week 24 and missing data were replaced by series mean

[a] using paired *t*-test to compare the differences of all parameters between week 0 and week 24

[b] using independent *t*-test to compare the differences of all parameter between the control and the study groups at the end of the study (week 24)

[c] using analysis of covariance (ANCOVA) to compare the difference between the control and the study groups at the end of the study (week 24)

** having a statistically significant difference at $\alpha = 0.05$

4.3 Effects on changes in hematologic, fasting blood sugar, insulin resistance and blood pressure

Table 38 presents changes of laboratory parameters indicating the safety of anabolic steroid use in patients. Firstly, the results demonstrated that there was no significant difference in percent change in hemoglobin and hematocrit in the oxymetholone group and the placebo group receiving recombinant human erythropoietin (p=0.401 and p=0.539, respectively). Likewise, it did not differ in percent change of hemoglobin and hematocrit in the patient not receiving recombinant human erythropoietin (p=0.182 and p=0.192, respectively). The recommended hemoglobin and hematocrit levels were not achieved. When considering of individuals' hemoglobin, it was found that 3 patients (14.28%) in the oxymetholone group experienced comorbid conditions affected to hemoglobin and hematocrit levels. As mentioned before, one patient had tooth extraction after which he had to continue regular hemodialysis sessions, which worsened his hemoglobin and hematocrit levels and he did not receiving recombinant erythropoietin. This caused decrease in hemoglobin and hematocrit level. Another patient had been admitted to the hospital because of acute hydrothorax, and the last patient had massive blood loss from dialysis circuit. All these caused rendered decreased hematologic values. Thus, exclusion of the three patients whose hemoglobin and hematocrit levels dropped as a result of all mentioned above, the effect of oxymetholone on hematocrit showed a slightly increase, whereas a decreased hemoglobin was shown. Both variables were not consistent due to the collection of multiple specimens. Hematocrit levels were determined once a week by routine examination at the study site, and an average of 4 values was used, while hemoglobin levels were measured once a month at Phramongkutkloa laboratory for our study. If blood sampling was simultaneously done for routine examination and our study, it would have resulted in lower blood concentration. That caused hemoglobin level not to be related to hematocrit level.

Table 38 Comparison of percent changes in hemoglobin and hematocrit in patients receiving and not receiving recombinant erythropoietin at week 24 between the control group and the study group

Variable		Mean±SD		
		Oxymetholone	Placebo	*p*-value[a]
Hemoglobin	**Receiving rhEPO**	**n=19**	**n=18**	
	Baseline (g/L)	10.06±1.24	9.86±1.13	0.609
	Percent change	-3.75±14.08	0.048±12.33	0.401
	Not receiving rhEPO	**n=2**	**n=4**	
	Baseline (g/L)	11.25±2.75	10.87±1.86	0.848
	Percent change	-10.75±15.21	3.53±7.88	0.182
Hematocrit	**Receiving rhEPO**	**n=19**	**n=18**	
	Baseline (g/L)	31.27±2.60	31.14±2.51	0.877
	Percent change	1.66±10.99	-0.65±10.73	0.539
	Not receiving rhEPO	**n=2**	**n=4**	
	Baseline (g/L)	35.50±8.49	34.5±6.31	0.876
	Percent change	-7.87±12.84	3.31±5.96	0.192

[a] using independent t-test to compare between the control group and the study group at week 24

However, means recombimant human erythropoietin dose (ranging from 2,000-8,000 unit/week) were analyzed for assessing the effect of oxymetholone on hematocrit (Table 39 and Figure 13). The result of the study showed that means of recombinant human erythropoietin dose were not significantly different between two groups at the end of the study (p=0.622). However, mean dose was lower in the oxymetholone group, while that in the placebo group trended toward higher. Although anabolic androgenic steroids have been used to enhance responsiveness to ESA therapy in anemic patients before the availability of erythropoietin therapy *(162, 165-167)*, few previous studies found that there was no statistically difference in hematocrit levels when AAS were administered *(130, 167)*. It was possible that the studies enrolled erythropoietin stimulating agent (ESA) hyporesponsiveness *(167, 168)*. However, the recent K/DOQI guideline, revised in 2006, strongly recommends not to use androgen as an adjuvant to ESA treatment in anemic patients with CKD *(168)*.

Table 39 Comparison of mean of erythropoietin administration (unit/kg/week)

Variable	Week 0	Week 24	p-value[a]
Oxymetholone	68.33±30.16	64.25±26.19	0.267
Placebo	67.87±24.99	68.25±23.33	0.889
p-value[b]	0.959	0.622	

[a] using paired t-test to compare the differences between week 0 and week 24

[b] using independent t-test to compare between the control group and the study group at week 0 and week 24

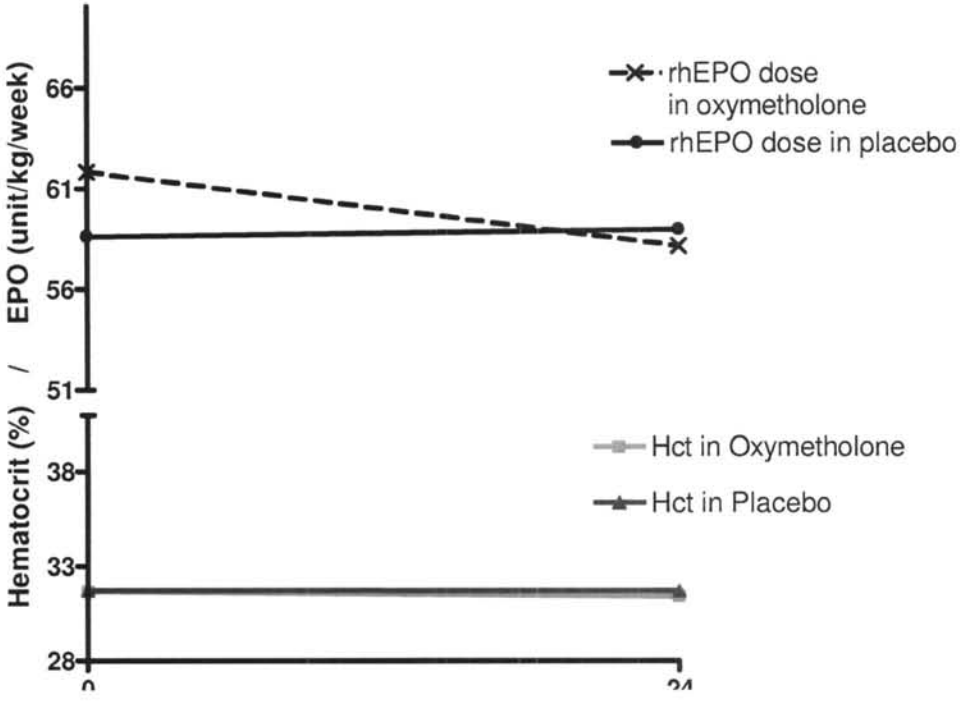

Figure 13 Comparison of recombinant erythropoietin dose (top segment) and hematocrit level (bottom segment) between the oxymetholone and the placebo groups at the initiation of the study (week 0) and the end of the study (week 24)

For percent changes in fasting blood sugar and insulin resistance shown in Table 40, there was no differences between two groups (p=0.097 and p=0.843, respectively). Additionally, blood pressure was evaluated between two groups (Table 40). There were not statistically different in percent changes in SBP and DBP at the end of the study (week 24) in comparison with both groups (both p=0.273, and p=0.393, respectively).

Table 40 Comparison of changes in liver function enzymes and percent changes in fasting blood sugar, insulin resistance assessed by homeostasis model assessment and blood pressure between the control and the oxymetholone groups at week 24

Variable		Mean±SD		
		Oxymetholone* (n=21)	Placebo (n=22)	p-value[a]
AST (U/L)	Baseline	16.28±6.45	13.82±4.92	0.135
	Change week 24	31.52±42.42	1.50±6.34	0.004**
ALT (U/L)	Baseline	14.38±6.41	13.04±4.99	0.450
	Change week 24	55.67±70.29	2.5±8.04	0.002**
FBS	Baseline (mg/dL)	78.09±6.67	77.59±12.67	0.872
	Percent change	-0.90±12.44	6.66±16.37	0.097
HOMA-IR	Baseline	8.7±4.87	4.76±4.52	0.01**
	Percent change	-29.81±125.11	-36.45±82.48	0.843
SBP	Baseline (mmHg)	139.95±16.06	139.79±10.38	0.968
	Percent change	3.31±7.89	0.35±9.46	0.273
DBP	Baseline (mmHg)	78.54±8.08	79.62±4.33	0.585
	Percent change	5.25±8.26	3.26±6.84	0.393

* intention-to-treat analysis was used in data at week 24 and missing data were replaced by series mean

[a] using independent t-test to compare percent changes between the control group and the study group

** having a significant difference at α=0.05

4.4 Hormonal parameters and prostate-specific antigen (PSA)

Table 42 details hormonal parameters. At the end of the study, serum testosterone levels were statistically different between two groups (p<0.0001). This study found that, in the oxymetholone group, serum testosterone levels increased; however the levels did not reach statistical significance in female (p=0.084), while those levels markedly decreased in male (p<0.0001). This is because effects of AAS are gender specific. In male, a negative feedback is responsible for lower testosterone level. Systemically administered testosterone does not raise the testosterone level because it inhibits luteinizing hormone (LH), which exerts testosterone release. Consequently, the net effect of exogenous AAS administration leads to a decrease in testosterone level *(13, 125, 169)*. In turn, the increased level of LH and testosterone were found in female. When excess testosterone appears, a feedback mechanism takes place, which triggers the production of more testosterone *(170)*. Nevertheless, AAS-induced hormonal changes are transient and reversible after discontinuation of AAS. The restoration takes between 3-12 months. However, in females, after AAS

cessation, such a hormone-related effects as a deepening of the voice may represent irreversible *(29, 123, 125)*.

For PSA determination, this study showed that there was not statistically significantly different in subjects receiving oxymetholone compared to baseline (p=0.151). Contrarily, PSA level significantly increased in the placebo group compared to baseline (p=0.004), and there was significantly difference between the oxymetholone and the placebo groups (p=0.007). However, the values were in normal range. This finding is consistent with the study of Snyder et al., who completed 3-year study of testosterone administration *(171)*. Snyder and his co-workers detailed that there was no significant difference in major prostate events between the testosterone and the placebo group *(171)*.

4.5 Side effects-associated with anabolic steroids

Importantly, the incidence of side effects commonly associated with the use of study drug was greater in the oxymetholone group than in the placebo group. In the oxymetholone group, side effects included acne (52.38%), amenorrhea (23.81%), diminished menses (4.76%), alopecia (4.76%), hirsutism (4.76%), and deepening voice (9.52%). Acne (13.64%) and amenorrhea (4.76%) were noted for patients in the placebo group as well. All women experienced menstrual irregularities had spontaneous resumption after discontinuation. Additionally, other hormone-related side effects disappeared after drug discontinuation. All side effects are shown in Table 41.

Table 41 The numbers of patients who experienced adverse events*

Adverse events	Number of patients (%)		p- value[a]
	Oxymetholone (n=21)	Placebo (n=22)	
Acne	11 (52.38)	3 (13.64)	0.01**
Amenorrhea	4 (19.05)	1 (4.55)	0.076
Diminished mense	1 (4.76)	0 (0.0)	0.488
Deepening voice	2 (9.52)	0 (0.0)	0.233
Hirsutism	1 (4.76)	0 (0.0)	0.488
Drowsiness	5 (14.28)	1 (4.55)	0.095
AST >3 times the ULN	0 (0.0)	0 (0.0)	-
ALT >3 times the ULN	2 (9.52)	0 (0.0)	0.233
TB and DB> the ULN	3 (14.28)	0 (0.0)	0.108
Decreased HDL-C[b]	9 (42.85)	0 (0.0)	0.001**

[a] using Fisher's exact test to compare the number of patients in the control with the study group for each event

[b] probable adverse event assessed by using Naranjo's algorithm, and decreased more than 50% of baseline

* one patient could have more than 1 adverse events

** having a statistical significance at $\propto = 0.05$

Table 42 Comparison of hormonal parameter and prostate-specific antigen between week 0 and week 24 within patient group and between two groups at week 24.

Data (Normal range)	Oxymetholone* (n=21)			Placebo (n=22)			*p*-value[b] (between group)
	Mean±SD		*p*-value[a] (within group)	Mean±SD		*p*-value[a] (within group)	
	Week 0	Week 24		Week 0	Week 24		
Testosterone (0.06-28 ng/mL)	3.21.±3.00	1.53±1.57	0.003**	3.90±2.56	4.32±2.78	0.032**	<0.0001**
- Males (8-28 ng/mL)	6.05±1.65	2.17±2.04	<0.0001**	5.28±1.76	5.81±1.90	0.066	<0.0001**
- Females (0.06-0.8 ng/mL)	0.63±0.38	0.95±0.65	0.231	0.95±0.88	1.15±1.16	0.130	0.632
LH (1.7-58.5 mIU/mL)	36.98±73.67	35.47±70.43	0.871	33.24±50.38	33.87±50.58	0.422	0.933
- Males (1.7-8.6 mIU/mL)	13.76±9.97	9.88±15.33	0.458	13.69±8.47	14.62±9.84	0.244	0.184
- Females (2.4-58.5 mIU/mL)	68.72±98.05	66.41±93.95	0.720	75.12±75.58	75.14±76.27	0.993	0.465
PSA (0.00-4 ng/mL)	0.42±0.25	0.31±0.11	0.151	0.50±0.28	0.62±0.33	0.004**	0.007**

* intention-to-treat analysis was used in data at week 24 and missing data were replaced by series mean

[a] using paired *t*-test to compare the differences of all parameters between week 0 and week 24

[b] using independent *t*-test to compare the differences of all parameters between the control and the study groups at the end of the study (week 24)

** having a statistically significant difference at $\alpha = 0.05$

In summary, AAS mostly induce their response at various tissues via a single androgen receptor. At the beginning, AAS pass through the cell membrane of the target tissue and bind to an androgen receptor in the cytosol. The AAS-androgen receptor complex then is transferred to the nucleus and bind to DNA. Ultimately, the stimulation of protein synthesis occurs *(123)*. One of the most orally active AAS preparation is oxymetholone *(29, 125)*. The effect of oxymetholone had profoundly resulted in improving body weight, body mass index, lean body mass, and reducing fat mass in end-stage renal disease patient on maintenance hemodialysis. However, when considering change weight of the oxymetholone group in week 24, the change had trended toward decreased owing to the decreased weight in one patient in the study group. This was due to the patient was under weight control since she was scared of gaining weight. Hence, if this value was excluded, changes in dry weight displays trend toward increase as show in Figure 14.

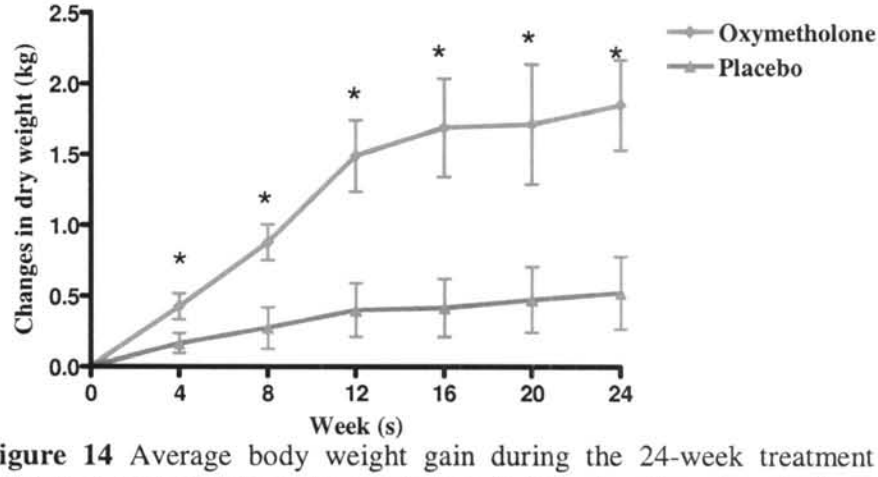

Figure 14 Average body weight gain during the 24-week treatment period (excluded outlier). Mean change in weight from baseline at each time point is shown (**excluded outlier**). The values are expressed as mean±SE. Asterisks indicate statistical significance compared between groups by independent *t*-test ($p<0.05$).

Moreover, all the subjects were advised for walking at least 1 kilometer a day, which was determined by self reporting. However, the most recent study of AAS use in hemodialysis-relating muscle wasting by Johansen *(122)* reported that resistance exercise did not result in a significant increase in LBM, but was associated with a significant increase in body fat mass ($p=0.05$). They concluded that it is because the subjects assigned to resistance exercise group had more energy intake than those in AAS group. Nonetheless, Johansen et al *(122)* also found that an increased LBM in the AAS group was similar to that in the AAS with exercise group (3.3±2.0 and 3.0±2.4 kg, respectively). Interestingly, subjects in the exercise group significantly increased their strength and improved self-reported physical function ($p=0.04$ compared to non-exercise group) *(122)*.

Similar beneficial effects can be achieved in women as in men; however, this study found that androgen-associated adverse effects can be markedly more noticeable in women more than in men (p=0.05 using X^2 test). The adverse events have limited the use of oral AAS because some patients cannot tolerate those side effects. Ultimately, some decided to discontinue the medicine before the end of the study. Nevertheless, many studies already proved the effects of oral AAS in chronic disease-relating to muscle wasting *(23-25, 120, 130)*, and they showed favorable gain in LBM, which was associated with survival rate of those patients *(172)*. Likewise the present study, increased LBM and body weight in the oxymetholone group were significantly higher compared to the placebo group; however, elevated liver function enzymes should be concerned. Hence, oxymetholone can be considered an effective anabolic steroid in ESRD patients on maintenance hemodialysis, but it should be intermittently administered for 3-month period to reduce hepatice side effects. This finding is congruent with a previous study, which suggest an inductive period of 8-10 weeks with 50 mg of oxymetholone twice daily and thereafter maintenance therapy with 50 mg once daily or every other day *(24)*. This regimen has shown sufficient weight and LBM gain while less hepatic side effects in subsequent patients. However, there was a study that demonstrated the effect of AAS to maintain body weight, and there was no change in LBM after 6-month discontinuation *(120)*. Other suggestion may be of benefit, for instance, reducing the dose and duration, which can minimize the risk of side effects or use for cycle *(164)*.

Since anabolic action are not dissociated pharmacologically from the action of testosterone derivatives, subject receiving AAS inevitably accompanied with unwanted side effects. In male, acne results from the stimulation of sebaceous glands, while the use of AAS in female produced a consistent pattern of virilizing side effect. Nevertheless, jaundice is generally the main manifestation of AAS use. It can develop 2-5 months after drug initiation, and is related to individual susceptibility *(173)*. Usually, complete recovery from AAS-induced jaundice and hepatic dysfunction occurs on withdraw of the drug, and does not recur with continued treatment.