COMBINED THERAPY OF OMEGA-3 FATTY ACID AND CHOLECALCIFEROL MODULATES MOLECULES ASSOCIATED WITH CARDIAC HYPERTROPHY AND SARCOPENIA IN 5/6 NEPHRECTOMY RATS

Won Suk An, Su Mi Lee,Young Ki Son, Seong Eun Kim

Internal Medicine, Dong-A University, Busan, Repulbic of Korea

Background

◆ **Cardiac hypertrophy and sarcopenia are common in dialysis patients and result in high probability for morbidity and mortality**

[Wanner C et al, Lancet 2016;388:276-284]
[Isoyama N et al, Clin J Am Nephrol 2014;9:1720-1728]

◆ **Akt-mammalian target of rapamycin (mTOR) axis is related with cardiac hypertrophy and muscle atrophy**

[Sarbassov DD et al, Science 2005;307:1098-1101]
[Glass DJ et al, Int J Biochem Cell Biol 2005;37:1974-1984]
[Gao XM et al, J Hypertens 2006;24:1663-1670]

◆ **Myostatin, a member of TGF-β superfamily, is produced in the skeletal muscle to inhibit myocyte differentiation**

◆ **Myostatin expression is increased in patients with heart failure and chronic kidney disease**

[Heineke J et al, Circulation 2010;121:419-425]
[Verzola D et al, Kidney Int 2011;79:773-782]

◆ **This study aimed to investigate whether omega-3 fatty acid (FA) and cholecalciferol affect on molecules associated with cardiac hypertrophy and sarcopenia in 5/6 nephrectomy (Nx) rats**

Methods

◆ **Male Sprague-Dawley rats were divided into five groups and treated for 6 weeks**

- ✓ **Control group (n = 5) ; rats received saline (1mL/kg/day by gastric gavage)**
- ✓ **5/6 subtotal nephrectomy (Nx) (n = 6) → rats received saline (1mL/kg/day by gastric gavage)**
- ✓ **5/6 Nx treated with vitamin D (n = 6) → rats received cholecalciferol (3000 IU/kg/week by gastric gavage)**
- ✓ **5/6 Nx treated with Omega-3 FA group (n = 6) → rats received omega-3 FA (300 mg/kg/day by gastric gavage)**
- ✓ **5/6 Nx treated with Vitamin D and Omega-3 FA group (n = 6) → rats received both cholecalciferol (3000 IU/kg/week) and omega-3 FA**

◆ **Measurements**

- Expression of myostatin, myogenin, MyoD, Akt, phosphorylated Akt (pAkt), phosphatidylinositol-3 kinase (PI3K), phosphorylated PI3K (pPi3k), P38, phosphorylated P38 (pP38), and mTOR were examined by using western blot

Results

◆ **Serum BUN and creatinine were the lowest in 5/6 Nx group treated with omega-3 FA and vitamin D among other 5/6 Nx groups**

◆ **Compared with control group, 5/6 Nx control group was significantly up-regulated myostatin and down-regulated myogenin and MyoD in both cardiac and skeletal muscle**

◆ **Increased expression of myostatin and decreased dexpression of myogenin and MyoD of cardiac and skeletal muscle were recovered by combined treatment with omega-3 FA and cholecalciferol**

◆ **MyoD of skeletal muscle was dominantly regulated by cholecalciferol supplementation**

◆ **Phosphorylated Akt and mTOR were up-regulated in the cardiac muscle but down-regulated in the skeletal muscle of 5/6 Nx control compared to sham control**

◆ **Combined therapy of omega-3 FA and cholecalciferol decreased pAkt and mTOR expression in cardiac muscle and increased pAkt and mTOR expression in skeletal muscle of 5/6 Nx rats**

Table 1. Laboratory data

	normal control	5/6 Nx	5/6 Nx with vitamin D	5/6 Nx with omega-3 FA	5/6 Nx with omega-3 FA and vitamin D	P value
BUN (mg/dL)	17.7±1.5	77.7±28.4*	75.3±22.1*	63.9±17.0*	51.3±8.7*ab	0.003
Creatinine (mg/dL)	0.4±0.0	1.3±0.6*	1.2±0.3*	1.0±0.3*	0.8±0.1*abc	0.002
Calcium (mg/dL)	6.8±0.3	6.9±0.7	6.5±0.4	7.2±1.0	6.6±0.7	0.502
Phosphorus (mg/dL)	8.4±0.4	9.7±4.0	8.1±0.8	8.2±0.6	7.8±0.5	0.261

Data are expressed as means ± SD
*P value <0.05 (mean values are significantly different from control).
[a]P value <0.05 (mean values are significantly different from 5/6 nephrectomy group).
[b]P value <0.05 (mean values are significantly different from 5/6 nephrectomy c vitamin D group).
[c]P value <0.05 (mean values are significantly different from 5/6 nephrectomy c omega-3 FA group).

Figure 1 Expression of myostatin, myoD and myogenin on skeletal and cardiac muscle in 5/6 Nx rats

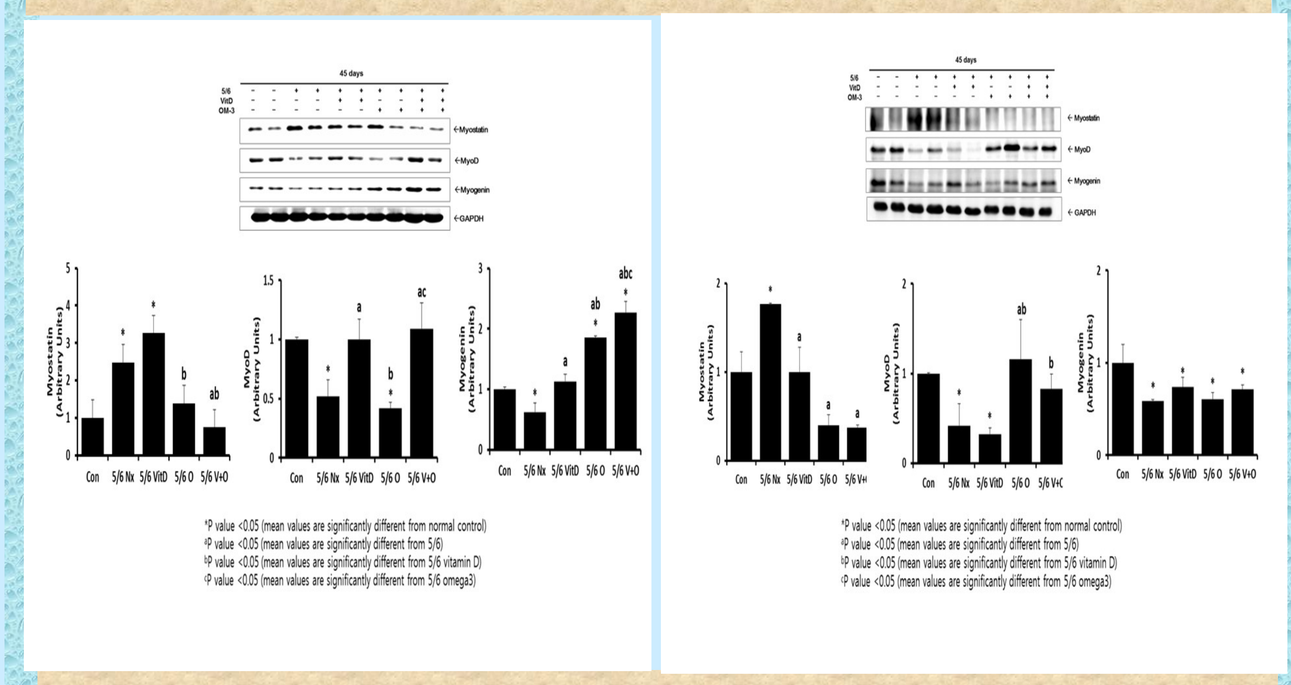


Figure 2 Expression of Akt-mTOR on skeletal and cardiac muscle in 5/6 Nx rats

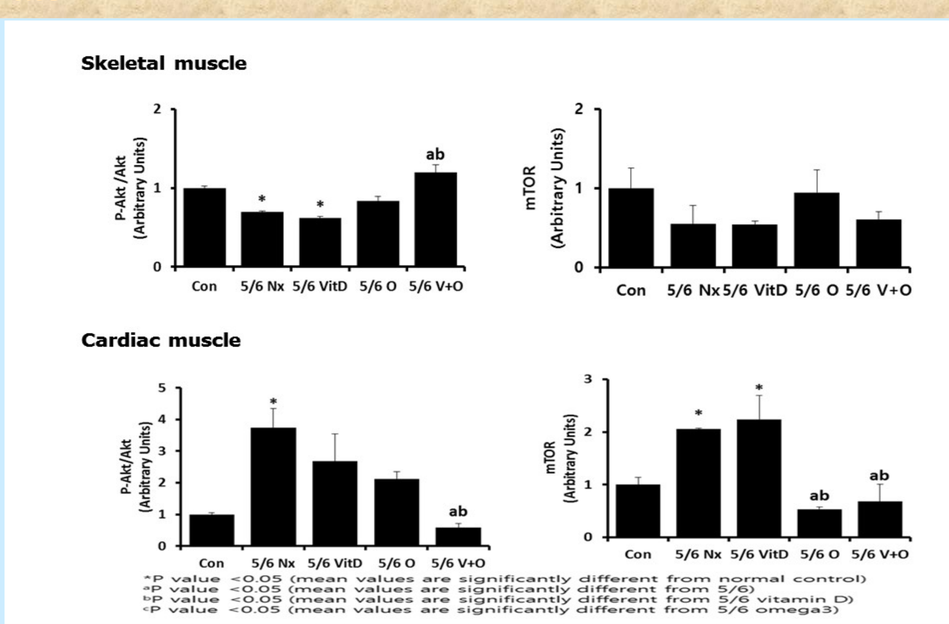
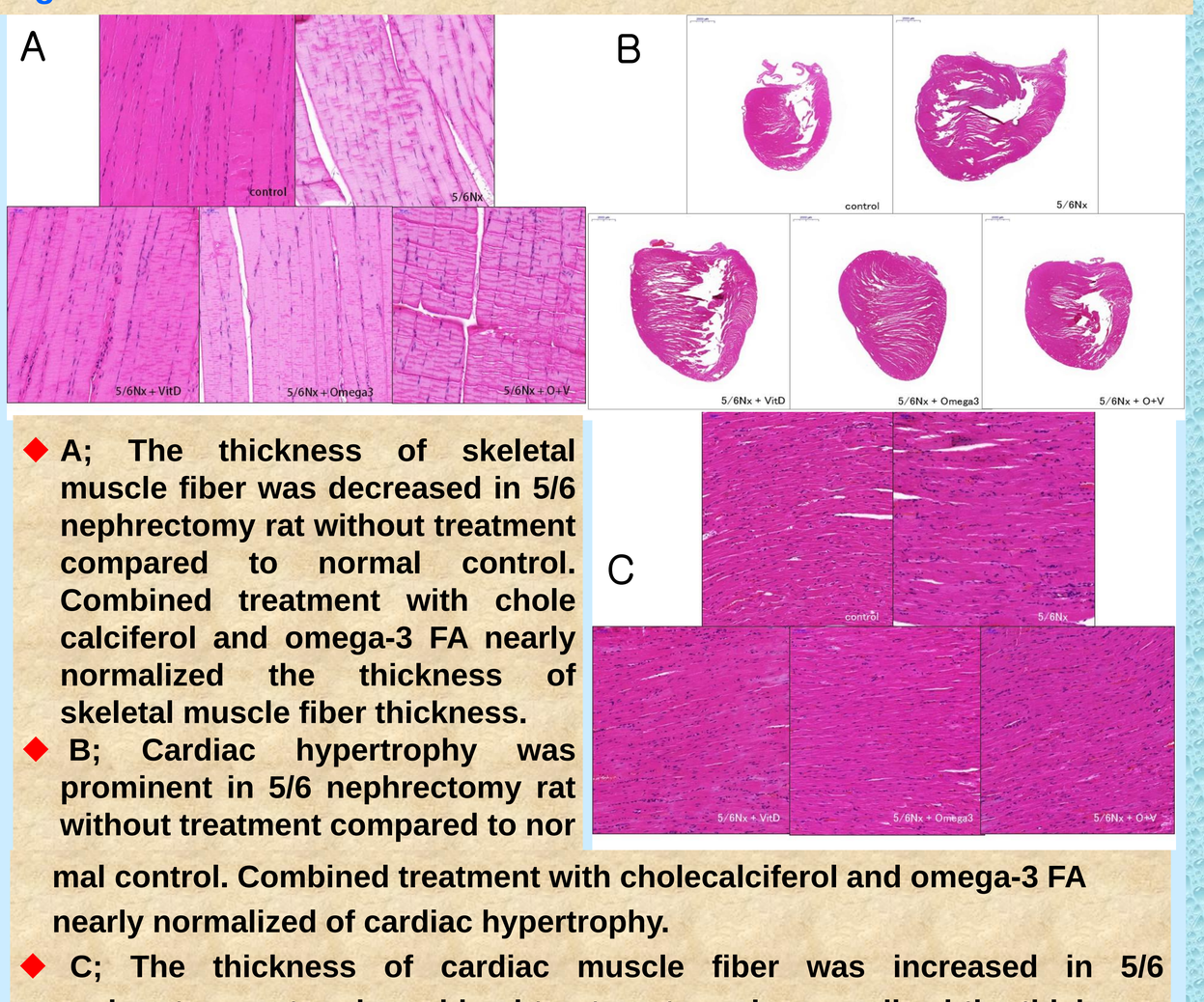


Figure 3. Thickness of muscle fiber in skeletal and cardiac muscle



◆ **A; The thickness of skeletal muscle fiber was decreased in 5/6 nephrectomy rat without treatment compared to normal control. Combined treatment with chole calciferol and omega-3 FA nearly normalized the thickness of skeletal muscle fiber thickness.**

◆ **B; Cardiac hypertrophy was prominent in 5/6 nephrectomy rat without treatment compared to normal control. Combined treatment with cholecalciferol and omega-3 FA nearly normalized of cardiac hypertrophy.**

◆ **C; The thickness of cardiac muscle fiber was increased in 5/6 nephrectomy rat and combined treatment nearly normalized the thickness of cardiac muscle fiber thickness.**

Discussion

◆ **Compared with control group, 5/6 Nx control group was consistently up-regulated myostatin and down-regulated myogenin and MyoD in both cardiac and skeletal muscle. Increased expression of myostatin in cardiac and skeletal muscle were definitely recovered by combined treatment with O-3 FA and cholecalciferol.**

Conclusions

◆ **Combined therapy of omega-3 FA and cholecalciferol may be helpful for decreasing cardiac hypertrophy and sarcopenia by increasing myogenin and MyoD, decreasing myostatin and modulating Akt-mTOR axis in both cardiac and skeletal muscle of 5/6 Nx rats.**

DOI: 10.3252/pso.eu.54ERA.2017