Effect of Short-Term Medroxyprogesterone Acetate on Left Ventricular Mass: Role of Insulin-Like Growth Factor-1

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Previous studies using 17β-estradiol and medroxyprogesterone acetate (MPA) have shown that hormone replacement therapy (HRT) increases left ventricular mass (LVM). To determine if insulin-like growth factor-1 (IGF-1) is associated with the increase in LVM, we measured IGF-1 and IGF-binding protein-3 (IGFBP-3) levels in 19 postmenopausal women before and after 8 weeks of oral treatment with MPA 5 mg/d. LVM was measured by two-dimensional echocardiography. Changes in IGF-1, IGFBP-3, and LVM from baseline were analyzed by paired *t* test. Regression analysis was used to determine if changes in the IGF-1 axis with MPA treatment affect the increase in LVM. LVM increased 4.4% during the study ($P = .006$ *v* baseline). IGF-1 increased 17% with MPA ($P = .008$), whereas IGFBP-3 did not change. The IGF-1/IGFBP-3 ratio increased 16.8% ($P = .0003$). Regression analysis of LVM with IGF-1, IGFBP-3, and the IGF-1/IGFBP-3 ratio suggested that IGF-1 during MPA therapy explains 2.4% and the IGF-1/IGFBP-3 ratio explains 3.2% of the variation in LVM. There was no effect of IGFBP-3 on LVM. Most of the variation in LVM with MPA (90.5%) was explained by baseline LVM. The IGF-1/IGFBP-3 ratio on MPA treatment was inversely related to the change in LVM: women with a lower LVM at baseline had the greatest increase in LVM with MPA. These findings suggest that MPA increases IGF-1 and LVM. Because the increase in IGF-1 with MPA treatment explains a fraction of the increase in LVM, other mechanisms must also be operative.

GROWTH HORMONE and insulin-like growth factor-1 (IGF-1) have long been associated with the growth of muscle and viscera. Patients with acromegaly who have elevated growth hormone and IGF-1 levels have hypertrophy of many organs, including the myocardium.

We have shown recently that sequential oral 17β-estradiol and medroxyprogesterone acetate ([MPA] hormone replacement therapy [HRT]) increase left ventricular mass (LVM) and contractile function in postmenopausal women within weeks of starting therapy, with some of the increase observed after MPA alone.[1] The mechanism for this increased mass is unknown, but the increase is not associated with an elevation in blood pressure or blood volume.[1]

IGF-1 is known to decline sharply after natural menopause in women,[2] surgical menopause in women,[3] and surgical menopause in rats.[4] There is evidence that oral estrogen decreases IGF-1[5-8] but transdermal estrogen does not.[2,9] Furthermore, combination estrogen plus progestin may increase IGF-1.[10,11] Because IGF-1 has been linked to myocardial growth[12] and some evidence suggests that estrogen plus progestin increases IGF-1, the aim of the present study was to determine if the increase in LVM with MPA therapy in postmenopausal women is associated with changes in IGF-1 or its principal tissue binding protein, IGF-binding protein-3 (IGFBP-3). Although MPA is the most commonly prescribed progestin for postmenopausal women in the United States on HRT, there is no information available on the effect of this hormone on IGF-1 and IGFBP-3 in humans. Furthermore, it is unknown whether increases in LVM with MPA treatment can be explained by changes in IGF-1 or IGFBP-3. The present study was performed to determine whether the increase in LVM on MPA therapy is related to changes in the IGF-1 axis.

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Submitted February 8, 1999; accepted April 27, 1999.

Supported by a grant from the American Heart Association (9606309S) and a grant to The University of Vermont Clinical Research Center (GCRC MO1 RR109).

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0026-0495/99/4810-0021$10.00/0

SUBJECTS AND METHODS

Subjects

Twenty-two healthy postmenopausal women with a mean age of 54.2 ± 6.2 years (median, 53.5) who were never on HRT or did not use HRT for at least the prior 2 months were recruited to participate. Since 19 of 22 individuals had a complete echocardiography data set at the conclusion of the study, LVM changes in 19 subjects were analyzed and reported. Twenty of 22 subjects had complete IGF-1 and IGFBP-3 data sets, so the effect of MPA on the IGF-1 axis is reported for 20 subjects. The inclusion criteria were a follicle-stimulating hormone level more than 40 mIU/mL and a normal mammogram within the past year. Exclusion criteria were known cardiac disease, hypertension, migraine, or stroke on oral contraceptive therapy, allergy to progestins, and untreated thyroid disease. The study was approved by the Institutional Review Board and the Clinical Research Center at The University of Vermont, and all women provided written informed consent.

Study Design

The subjects received HRT consisting of MPA (Provera; Pharmacia & Upjohn, Kalamazoo, MI) 5 mg/d for 8 weeks. Medication was administered in the evening, and study visits occurred during the afternoon. Subjects underwent a two-dimensional echocardiogram and measurement of IGF-1 and IGFBP-3 levels before initiating HRT (baseline) and on MPA therapy 8 weeks later.

Echocardiography

All studies were performed with the subjects supine in the left lateral decubitus position with a phased-array ultrasonoscope (Acuson HP-10; Acuson, Mountain View, CA) using a 2.5-MHz transducer as previously described.[1] Two-dimensional images were obtained sequentially from the parasternal long-axis, parasternal short-axis, apical four-chamber, and apical two-chamber views. All images were recorded in coded fashion by one sonographer and read by one cardiologist in batches to allow for blinding of subject name and medication status. There was no interobserver variation, since we used only one reader. Intraobserver

Table 1. Effect of MPA on LVM, IGF-1, and IGFBP-3 (mean ± SD)

Variable	No. of Subjects	Baseline	MPA Therapy	% Change	*P*
LVM (g)	19	135.7 ± 27.3	141.7 ± 25.5	+4.4	.006
IGF-1 (ng/mL)	20	123.5 ± 52.3	144.5 ± 53.4	+17.0	.0008
IGFBP-3 (ng/mL)	20	3,262.6 ± 722.4	3,290.9 ± 711.5	+0.87	.69
IGF-1/IGFBP-3 ratio	20	.0370 ± .0099	.0432 ± .0089	+16.8	.0003

variation, calculated for duplicate measurements as the measurement reliability, was excellent at 99%.[13]

IGF-1 and IGFBP-3 Assays

Samples were prepared for IGF-1 assay by acid ethanol cryoprecipitation according to the method of Breier et al[14] and analyzed using the Nichols Institute extraction radioimmunoassay kit, a double-antibody assay (40-2100; Nichols Institute Diagnostics, San Juan Capistrano, CA). The intraassay coefficient of variation was 4.51% and the interassay coefficient of variation 3.50%. IGFBP-3 analysis was performed using an immunoradiometric kit (Diagnostic Systems Laboratories, Webster, TX). This assay uses a two-site immunoradiometric principle to measure nonglycosylated IGFBP-3. The intraassay coefficient of variation was 0.95% and the interassay coefficient of variation 4.72%.

Statistical Analysis

Each individual's baseline value was used as a control value. We compared changes over time for LVM, IGF-1, IGFBP-3, and the IGF-1/IGFBP-3 ratio using a paired *t* test. Linear and multiple linear regression analyses were used to evaluate LVM at baseline versus the 8-week follow-up point on MPA therapy, and to determine if changes in IGF-1 and IGFBP-3 could explain LVM changes. Effects were considered statistically significant at a P level less than .05.

RESULTS

MPA significantly increased LVM by 4.4%. Furthermore, MPA increased IGF-1 and the IGF-1/IGFBP-3 ratio significantly by 17% and 16.8%, respectively, with no significant change in IGFBP-3. The IGF-1/IGFBP-3 ratio, used to assess IGF-1 action in target tissues, increased similarly to IGF-1 alone. This indicates that serum IGF-1 itself reflects tissue bioavailability (Table 1).

To determine if the changes in IGF-1 or IGFBP-3 were associated with an increase in LVM, we performed a regression analysis of LVM on MPA treatment versus IGF-1, IGFBP-3, and the IGF-1/IGFBP-3 ratio (Tables 2 and 3). The tables represent models with LVM at baseline, along with additional models including changes in IGF-1, IGFBP-3, or the IGF-1/IGFBP-3 ratio with MPA therapy. After 8 weeks of treatment, LVM on MPA was strongly related to LVM at baseline (multiple $R^2 = .905$; Table 1). This indicates that 90.5% of the variation in LVM on MPA is explained by the baseline LVM. The addition of IGF-1 at baseline did not significantly increase this strong relationship ($\Delta R^2 = .008$, $P = .23$). (ΔR^2 is the incremental change in R^2 due to adding another variable.) However, the addition of IGF-1 on MPA therapy did significantly change the regression equation for LVM ($\Delta R^2 = .024$, $P = .04$). This indicates that 2.4% of the total variation in LVM beyond that of the baseline LVM can be explained by the IGF-1 level on MPA therapy.

IGFBP-3 alone at baseline did not significantly explain any of the variation in the LVM relationship ($P = .43$). This lack of effect of IGFBP-3 on LVM is also found with progestin ($P = .32$) (Table 3).

The IGF-1/IGFBP-3 ratio on MPA therapy, believed to reflect IGF-1 availability to the tissues (ie, myocardium), appears to affect the LVM relationship ($\Delta R^2 = .032$, $P = .01$; Table 3). This indicates that 3.2% of the variation in the relationship of LVM on MPA therapy can be explained by the IGF-1/IGFBP-3 ratio in combination with the baseline mass.

The prior use of HRT 2 months or more before the study appears to influence the change in LVM (Fig 1). Although women with the smallest baseline LVM had the largest increase in LVM with MPA therapy, women with prior HRT exposure (estrogen plus progestin) appeared to have the greatest increase in LVM. The subjects' age, weight, or time since menopause did not affect this increase in LVM significantly. Furthermore, the IGF-1/IGFBP-3 ratio on MPA therapy was inversely and significantly correlated with the change in LVM regardless of prior hormone exposure.

DISCUSSION

This study shows that the increase in LVM with MPA therapy can be partly explained by the increase in circulating IGF-1. To our knowledge, the link between LVM and IGF-1 with MPA therapy has not been previously reported. This result might be expected, since we demonstrate that MPA increases IGF-1 and others have hypothesized that IGF-1 increases ventricular mass.[12]

In addition to circulating IGF-1, it is possible that IGF-1 produced locally in the myocardium stimulates ventricular growth.[12] However, animal studies have not confirmed this hypothesis. In the rat, Cittadini et al[15] showed that local

Table 2. Association (R^2) Between LVM on MPA Therapy, Baseline LVM, and IGF-1

Variable	LVM on MPA Therapy			
	Intercept 21.3	Intercept 30.1	Intercept 38.7	Intercept 25.5
LVM at baseline	.89 ($P < .01$)	.87 ($P < .01$)	.84 ($P < .01$)	.87 ($P < .01$)
IGF-1 at baseline		−.05 ($P = .23$)		
IGF-1 on MPA			−.08 ($P = .04$)	
ΔIGF-1				−.14 ($P = .08$)
Multiple R^2	.905 ($P < .001$)	.913 ($P < .001$)	.929 ($P < .001$)	.922 ($P < .001$)

Table 3. Association (R^2) Between LVM on MPA Therapy, Baseline LVM, IGFBP-3, and IGF-1/IGFBP-3 Ratio

Variable	LVM on MPA Therapy					
	Intercept 21.3	Intercept 29.4	Intercept 32.6	Intercept 30.3	Intercept 54.6	Intercept 23.8
LVM at baseline	.89 ($P < .01$)	.88 ($P < .01$)	.88 ($P < .01$)	.87 ($P < .01$)	.83 ($P < .01$)	.89 ($P < .01$)
IGFBP-3 at baseline		−.002 ($P = .43$)				
IGFBP-3 on MPA			−.003 ($P = .32$)			
IGF-1/IGFBP-3 ratio at baseline				−.171 ($P = .42$)		
IGF-1/IGFBP-3 ratio on MPA					−.575 ($P = .01$)	
ΔIGF-1/IGFBP-3 ratio						−.488 ($P = .09$)
Multiple R^2	.905 ($P < .001$)	.909 ($P < .001$)	.911 ($P < .001$)	.909 ($P < .001$)	.937 ($P < .001$)	.920 ($P < .001$)

expression of IGF-1 in the myocardium is not necessary for the increase in ventricular wall thickness observed after myocardial infarction. Furthermore, Donath et al[16] found that recombinant IGF-1 did not affect α- or β-myosin heavy-chain synthesis in rats. It is unknown whether IGF-1 increases locally with progestins in humans and what effect this has on ventricular growth, if any.

Only limited information is available on the effect of progestins on IGF-1 and IGFBP-3. To our knowledge, this is the first report of an effect of progestins alone on IGF-1 in humans. Our finding of increased IGF-1 with oral MPA therapy is similar to findings in dogs that received parenteral MPA.[17,18] We could not find any previous studies with progestins and IGFBP-3. Searching for an effect of HRT on IGFBP-3 as a separate entity is worthwhile, since IGFBPs may have their own independent actions.[19]

The effect of HRT on IGFBPs has received little attention. Shewmon et al[6] found that oral conjugated estrogens decreased IGF-1 by 30% with no change in IGFBP-3 after 3 months of treatment. Helle et al[7] compared oral estrogen plus an oral progestin against transdermal estrogen plus an oral progestin, finding that oral estrogen plus oral progestin decreased IGF-1 without significantly decreasing IGFBP-3. No significant effects on other IGFBPs measured by Western ligand blot analysis were found with either treatment. The fact that our study found an increase in IGF-1 with oral progestin rather than the decrease found by Helle et al might be explained by the condition that our subjects received a progestin but not estrogen. Our findings agree with those of Helle et al and Shewmon et al in that IGFBP-3 did not change.

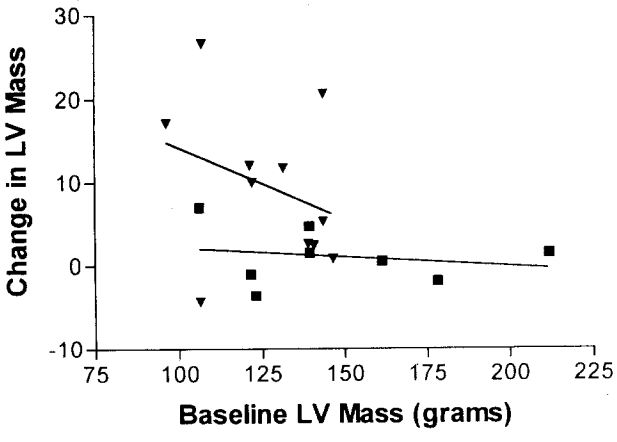

Fig 1. Change in LVM and prior HRT exposure. Women with prior HRT exposure (▼) had a larger increase in LVM with MPA therapy *v* women without prior HRT exposure (■).

Because the increase in IGF-1 with MPA therapy explains only 2.4% of the change in LVM beyond baseline LVM, one would expect other mechanisms to be operative. It is possible that MPA itself or a metabolite has a direct anabolic action on myocardial muscle, as progestins have a structure similar to both androgens and progesterone. The effect of various progestins of different androgenicity on the myocardium clearly deserves further study.

Our finding that women with the smallest baseline LVM had the largest increase in LVM on MPA therapy is interesting, and it was not affected by body weight, age, or time since menopause. Only exposure to HRT at least 2 months prior to the study affected the increase in LVM with MPA, suggesting that prior HRT exposure primed the myocardium to increase its mass with progestin.

Our study has several limitations, including the absence of age-matched controls. We expected no change in LVM in healthy women in such a short-term study, as confirmed by Snabes et al,[20] who measured ventricular mass in untreated healthy postmenopausal women over 12 weeks. Our sample size is relatively small, although we found statistical significance. The statistical power to detect incremental R^2 values had a range from 82% for the IGF-1/IGFBP-3 ratio on MPA therapy to 42% for the change in this ratio, while the power to detect the incremental effect of IGF-1 on MPA therapy was 66%. Furthermore, the amount of increase in LVM in this short-term study is small, and the clinical significance and long-term effects are unknown.

We conclude that MPA increases IGF-1 levels in women and partly explains the increase in LVM found with MPA therapy. Further studies are necessary to determine whether these effects are long-term and to explain the other possible mechanisms underlying this progestin-induced increase in LVM.

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