BESINS HEALTHCARE
Innovating for Well-being

BESINS HEALTHCARE SCIENTIFIC LITERATURE REVIEW – May 2021

Must Read Articles in Women's Health

Pregnancy (IVF)

Impact of low serum progesterone levels on the day of embryo transfer on pregnancy outcome: a prospective cohort study in artificial cycles with vaginal progesterone.

Human Reproduction. 2021 :36 :3 : 683-692

Labarta E *et al*

Pubmed Link: 10.1093/humrep/deaa322

Menopause Hormone Therapy (MHT)

Recommended Hormone Therapy in Menopause: Concepts, Controversies and Approach to Treatment

Endocrine Reviews April 2021

Flores V.A *et al*

Pubmed Link: 10.1210/endrev/bnab011

Other Articles of Interest - Women's Health

Menopausal Hormone Therapy and Cardiovascular Disease: The Role of	Shufelt C.A. *et al.* Journal Clinical Endocrinology &	This mini review discusses the risk of MHT and CVD, focusing on hormone dose, formulation and route of delivery. It

Formulation, Dose, and Route of Delivery	Metabolism. 2021: 106:6: 1245-1254	highlights the importance of not using HRT for the primary of secondary prevention of CVD.
A 10-year follow-up on the practice of luteal phase support using worldwide web- based surveys	Reproductive Biology and Endocrinology 2021	Over 10 years, 4 web-based surveys investigated the LPS practices among IVF clinics. Despite all the research on LPS over 10 years, there is still no 1 approved protocol and guidelines are based on low quality evidence. These surveys highlight the lack of consensus in treatment Protocols. Clinicians desire high quality guidelines and now recognise the importance of individualising LPS protocols for patients.

Must Read Articles in Men's Health

Testosterone Replacement Therapy (TRT)

Testosterone Replacement Therapy added to Intensive Lifestyle Intervention in Older Men with Obesity and Hypogonadism

Journal of Clinical Endocrinology and Metabolism 2021, 106:3:1096 -1110

Barnouin Y *et al*

Pubmed Link: 10.1210/clinem/dgaa917

Other Articles of Interest Men's Health

Compliance with Testosterone Replacement Therapy in Patients with Testosterone Deficiency Syndrome: A 10-Year Observational Study in Korea.	Kang B *et al* World J Mens Health 2021	A Korean single centre retrospective observational follow up study of men taking various formulations of TRT over a 10 year period. The second highest compliance rate was with Testosterone Gel, the reasons for dicontinuation of Testosterone Gel was mostly due to "inconvenience of medication" and the reason given for this was considered to be "the strangeness of applying medical treatment to the skin" in Korean Culture.

Title	Authors	Journal and Issue	Article Type
Impact of low serum progesterone levels on the day of embryo transfer on pregnancy outcome: a prospective cohort study in artificial cycles with vaginal progesterone.	Labarta E. *et al*	Human Reproduction 36:3:683-692	Prospective cohort study

What this study brings: **Highlights the need to prioritize research into individualized luteal phase supplementation (i.e. by increasing the daily dose of MVP) as not all patients may benefit from a one size fits all protocol. Raises a relevant research question for BH IIR strategy**

Background:

- Artificial endometrial preparation with Hormone Replacement Therapy (HRT) is frequently used for frozen embryo transfer (FET) and egg donation cycles.
- Protocol consensus for endometrial preparation is not available and HRT guidelines are not clear.
- Estrogen administration is tailored to patient need; however, all patients receive the same progesterone (P) dose irrespective of the differences in luteal phase support.
- Previous research by Labarta E *et al* (2017) in an oocyte donation setting examined the relationship between serum P levels on the day of embryo transfer and ongoing pregnancy rate. All patients in this study received (2 x 200mg) 400mg Micronized Vaginal Progesterone (MVP) twice daily (Utrogestan®).
- Patients with a serum P <9.2ng/ml had a 20% lower on going pregnancy rate than those with higher values ($p<0.05$).

Aim:

To define the critical threshold of serum progesterone on the day of embryo transfer in HRT cycles that significantly alters the ongoing pregnancy rate (OPR) and live birth rates (LBR) in patients undergoing oocyte donation cycles and own oocyte cycles.

Methods:

N = 1150 women ≤ 50 yrs old with a triple layer endometrium ≥6.5 mm (658 oocyte donation cycles, 492 own oocyte cycle) included in study.

Estrogen treatment in proliferative phase and MVP Oil Capsules LPS support (2 x 200mg BD = 800mg per day) for 5 days before ET of 1 to 2 blastocysts.

Primary endpoint: OPR beyond week 12 based on serum P levels before ET.

Secondary endpoints: Analysis of serum P levels on day of ET, determination of critical threshold P levels and subsequent impact on ongoing pregnancy rate.

Results:

- OPR – reported in 1148 pts/1150 patients.
    - Overall OPR was 49% (95% CI, 46.2-51.9)
- LBR – reported in 1125/1150 patients.
    - Overall LBR was 47% (95% CI, 44.1-49.9)

A critical cutoff of 8.8ng/ml serum P was observed

- Patients with serum P <8.8ng/ml had a significantly lower OPR
  - 36.6% vs 54.4% Crude Odds Ratio (OR) 95% CI: 0.49 (0.35-0.63) P< 0.001
- Patients with serum P <8.8ng/ml had a significantly lower LBR
  - 35.5% vs 52%; OR (95% CI): 0.51 (0.39-0.66) P<0.001
- Patients with serum P <8.8ng/ml had a higher clinical miscarriage rate
  - 13.5% vs 23%; OR (95% CI):1.9 (1.2 – 2.9); P=0.006).
- Patients with serum p below 8.8ng/ml had a significantly higher body weight than the rest. 65.9kg vs 63.4kg (P=0.001)
- 555 women remained pregnant after 20 weeks, 529 women had a live birth, 2 had stillbirths and 1 preterm death, no birth confirmed for the remaining 23.

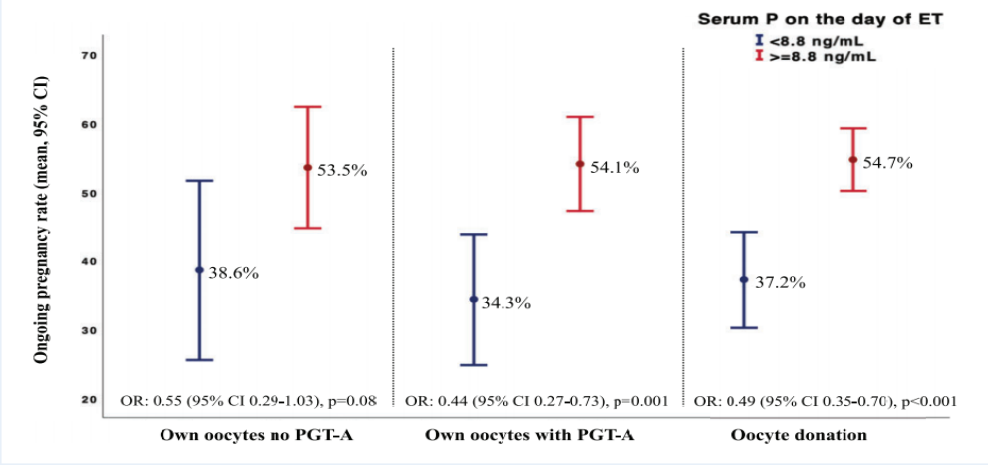

Figure 3. Mean ongoing pregnancy rate (95% CI) and crude odds ratios in the three treatment groups based on serum P level on the day of ET below or above 8.8 ng/ml. ET, embryo transfer.

Discussion:

- Low serum P levels on the day of ET lead to worse pregnancy outcomes even after adjusting for all possible confounding factors.
- All patients who receive MVP in HRT cycles need to reach a minimum of 8.8ng/ml circulating P levels to maintain pregnancy regardless of the origin of the oocyte.
- 30% of patients receiving MVP at a dose of 400mg (2 x 200mg) twice daily are below the optimal P threshold
- This study only focused on women using natural MVP's and other forms of administration need to be validated
- Serum P levels differ greatly when using MVP compared to subcutaneous or intramuscular P due to differences in PK and PD, therefore the results presented in this study cannot be applied to all progestogens.
- Important to note is that although serum P levels are associated with pregnancy outcomes, they do not show a high predictive value for ongoing pregnancy in this study, implying that P levels are not a single predictor for treatment success as other factors such as embryo quality determine the cycle fate.

Practice points:

- **Serum P levels <8.8 ng/ml on the day of ET lower ongoing pregnancy rate (OPR) in both own or donated oocyte cycles.**

- **It is worth to monitor P blood levels on the day of ET or the day prior in order to individualize the P daily dose regimen for Luteal Phase Support.**
- **Serum P levels differ greatly when using MVP compared to subcutaneous or intramuscular P due to differences in PK and PD characteristics**

Title	Authors	Journal and Issue	Article Type
Recommended Hormone Therapy in Menopause: Concepts, Controversies and Approach to Treatment	Flores *et al*	Endocrine Reviews April 2021	Review

What this review brings: **Very comprehensive overview paper with strong points to support BH transdermal Oestrogel and micronized Progesterone. Highlights the importance of individualizing treatment to each woman based on risks and benefit. Benefits of transdermal therapies in sexual function is a key learning to be reinforced: empowering educated and informed women to make important treatment decisions**.

- Hormone therapy (HT) is an effective treatment for menopausal symptoms, including vasomotor symptoms (VMS), genitourinary syndrome of menopause (GMS), as well as for prevention of bone loss, and treatment of premature hypoestrogenism.
- Key lessons from the WHI trials were that the risk: benefit ratio and safety profile of HT differed markedly by clinical characteristics of the participants e.g. age, time since menopause, comorbidity status and GMS.
- An improved understanding of the importance of the timing of HT initiation, type and route of administration, and of patient-specific considerations should be considered when prescribing HT.

WHI Trials Post intervention and follow up

- In the E-alone trial, the reduced risk of invasive breast cancer in hormone users achieved statistical significance during cumulative follow-up.
- Results for stroke, PE, DVT, and colorectal cancer remained neutral after 13 years of cumulative follow-up in both hormone trials.
- Results for all-cause mortality were neutral at all follow-up time points in both trials.
- The risk reduction in fractures was attenuated during the postintervention period for both trials, although the positive effects of HT persisted over the 13-year cumulative follow up for the E+P trial.

Meta-analyses of RCTs of hormone therapy in relation to cardiovascular disease (CVD), venous thromboembolism (VTE), breast cancer, fracture, and all-cause mortality

- VTE risk was increased in postmenopausal women using oral HT (ET or EPT), however there was no significant excess risk in women using non-oral HT.
- Importantly in the WHI E-alone trial, breast cancer risk was decreased with long-term follow-up.
- The E3N French Cohort Study also found different relative risks of breast cancer based on HT type and years of use.
- Many of the analysed studies were observational studies with the potential for differential surveillance (i.e. mammographic screening) for breast cancer in HT users and nonusers, and as such the potential for residual confounding by other factors.

- In a metanalysis of RCTs assessing fracture risk in women using oral CEE, transdermal or oral E2 (with or without the addition of a progestin) there was a 20-37% reduced risk of hip, vertebral, and total fracture.
- Use of HT and effect on mortality has also been assessed in a meta-analysis and systematic review of 43 RCTs, which demonstrated that HT does not affect risk of death from all-causes.

Do HT effects differ by formulation, dose, or route of administration?

ESTROGEN FORMULATIONS:

VMS:

- All forms of Estrogen are similarly effective in treating VMS.

Cardiovascular:

- In the WHI Observational Study, no differences were observed in CV outcomes for women taking CEE to compared to oral E2. In a separate 6 year study, CEE had a slightly higher risk of VTE then oral E2.

Fracture Risk:

- Meta-analysis of RCT's of estrogen formulations and fracture risk, all were effective in reducing fracture risk.

PROGESTOGEN FORMULATIONS:

CV risk:

- In the PEPI trial, women randomized to CEE or CEE/MP had an increase in HDL that was significantly higher and a better 2H Glucose Tolerance Test than in women randomized to CEE/MPA.
- The addition of progestogens to estrogen HT did not increase VTE risk for MP.

Breast Safety:

- Several observational studies have also demonstrated an increased risk of breast cancer with synthetic progestins, but not with MP.
- E2 plus natural progesterone blocked E2 mediated proliferative effects and increased the number of apoptotic cells.
- E2 plus MPA resulted in breast cell proliferation while treatment with E2 + natural progesterone did not.

Cognition Risk:

- CEE/MP significantly improved working memory.

Endometrial Safety:

- The PEPI trial and systematic review using MP doses of 200 mg per day demonstrated endometrial protection, emphasizing the importance of dosing in providing adequate endometrial protection.

By dose of estrogen or progestogen:

- In order to achieve a 75-80% reduction in hot flashes, standard doses of estrogens are needed. In several trials, lower doses of estrogens reduce hot flashes by 65% (twice as effective than placebo,) although the time needed to achieve this rate was 8-12 weeks, compared to 4 weeks for standard doses).
- VTE risk is dose dependent.
- The lowest effective dose is recommended, in those with inadequate relief of symptoms with lower doses, consideration should be given to increasing to standard dose regimens to alleviate clinical symptoms.
- Monitoring serum estradiol levels in postmenopausal women should not be used in the routine management or dose titration of HT.
- MP at 300 mg are also effective at treating VMS.

ORAL VS. TRANSDERMAL: ROUTE OF ADMINISTRATION

Estrogens:

Venous Thromboembolism:

- Transdermal estrogens avoid first-pass hepatic metabolism, and available studies have not found an increased risk of venous thrombosis. While an observational study noted no increased risk of cerebral vascular accidents with low dose transdermal E2, no large-scale RCTS have assessed transdermal E2 use and VTE risk.

Fracture:

- Both oral and transdermal formulations are effective for fracture prevention, without appreciable differences by regimen.

Cognition and mood:

- In a subset of women in KEEPS, those in the transdermal E2-arm with the apoliprotein e4 allele (associated with increased risk of Alzheimer's disease) had reduced beta amyloid deposition.

Sexual Function:

- Only transdermal E2 was associated with significant improved sexual function (i.e. libido and sexual satisfaction).
- The lack of effect of transdermal E2 on sex hormone binding globulin levels (as compared with increased levels with oral estrogens), results in increased free testosterone, likely explaining the improvement in sexual function.
- Both oral and transdermal formulations of estrogens are effective for treatment of VMS.

Progestogens:

- Transdermal cream application of Progestogens is not effective given the lack of systemic levels achieved.

Selective estrogen receptor modulators (SERMs):

- Raloxifene does have a VTE risk similar to that of oral estrogens, and unlike E, can lead to an increased incidence of hot flushes.

- Raloxifene does not reduce hip or wrist fractures.
- VTE risk is increased with ospemiphene, likely with a similar risk profile to oral ET and other SERMs

Clinical guide for treatment of menopausal symptoms:

- For those who are less than 10 years since menopause onset but with risk factors for CVD, if HT is considered for symptom control, transdermal rather than oral route of ET should be considered
- For women who are considered high risk for VTE, e.g. obese women, or smokers, transdermal route HT would be preferred given the higher risk of thrombosis with oral route of estrogen therapy.

Special Populations – early menopause

- HT dosing should be such that E2 levels reach 100 pg/mL which is the usual premenopausal serum level.
- Progestogen e.g. 200 mg natural micronized progesterone should be added for women with uterus.

Hysterectomy with bilateral oophorectomy

- Women who experience hypoactive sexual desire following surgical menopause may benefit from the addition of androgen (testosterone) to ET.

Women with a personal or family history of VTE or other cardiovascular disease

- Very low dose transdermal E regimen may be considered.

Duration of treatment and importance of shared decision making:

- The decision regarding duration of treatment and when to stop HT must be considered in the context of the individualized risk/benefit profile, as well as the personal preferences of the patient.
- Prescribers must remain vigilant about risk stratification and risk mitigation strategies such as switching from oral to transdermal E and lowering of dosing regimens.
- Choice of transdermal estrogen with or without micronized progesterone (depending on presence or absence of uterus) with periodic E dose reduction offers benefits of symptom control and long-term fracture risk reduction while minimizing some risks (such as VTE) thus may be a safer strategy for long-term HT.

Conclusions:

- Menopausal hormone therapy (MHT) is one of the most effective treatments available to relieve menopausal symptoms.
- For most symptomatic women, the benefits of HT outweigh the risks. It is imperative that the choice of treatment be individualized and that patients share in the decision making.

Practice points:

- **One regimen doesn't fit all.**
- **Both oral and transdermal formulations are similarly effective in treating VMS or for fracture prevention.**
- **There is no class effect for MHT in terms of benefits/risks ratio**
- **Transdermal estradiol (i.e. Oestrogel®) avoids first-pass hepatic metabolism with no increased risk of venous thrombosis or cerebral vascular incidents based on a body of evidence (several independent observational studies)**
- **Only transdermal E2 was associated with significant improved sexual function (i.e. libido and sexual satisfaction) due to the lack of effect on sex hormone binding globulin (SHBG) levels.**
- **The type of progestogen in MHT is crucial in terms of cardiovascular (i.e. on VTE risk and lipid profile) and breast safety.**
- **Several observational studies have demonstrated an increased risk of breast cancer with synthetic progestins, but not with MP**

Title	Authors	Journal and Issue	Article Type
Testosterone Replacement Therapy added to Intensive Lifestyle Intervention in Older Men with Obesity and Hypogonadism	Barnouin Y. *et al*	Journal of Clinical Endocrinology and Metabolism 2021, 106, 3 1096 -1110	Randomized, parallel, double blind trial

What this study brings: **These findings demonstrate that TRT (Androgel 1.62%) may not only attenuate the weight loss–induced reduction of muscle and BMD that occurs with lifestyle therapy but may improve sexual health and very importantly further improve aerobic capacity.**

Androgel 1.62% was shown to restore T blood levels in the optimal physiological range (low mid-range) of eugonadal men after 3 and 6 months of therapy.

Adding testosterone to lifestyle therapy in this population should be decided on an individual basis after carefully weighing the risks and benefits. These findings also support the short-term prostate safety of Androgel 1.62% in older men with obesity and hypogonadism and a clinically acceptable slight increase in hematocrit.

Background:

- Obesity exacerbates the age-related decline in physical function resulting in frailty and decreased quality of life (QOL).
- The authors had previously reported that weight loss and exercise improved physical function and decreased frailty in older obese subjects but there was still a concern that the weight loss could worsen the age-related decline in muscle and bone mineral density (BMD) which would worsen frailty.
- It has also been previously reported by the authors and in the literature that there is a high level of hypogonadism in older men with obesity.

Study Aim:

- The study aimed to show that testosterone replacement therapy plus lifestyle therapy would increase physical function, preserve muscle and bone mineral density (BMD) more than lifestyle therapy alone in older men with obesity and hypogonadism.

Methods:
All patients (N = 83) who met the inclusion criteria, were randomized to 2 groups for 26 weeks duration.
Group 1: Lifestyle Therapy and Testosterone Replacement Therapy (LT +Test) – 40.5mg TRT (Androgel 1.62%) x 1 daily.
Group 2: Lifestyle Therapy and Placebo (LT + Pbo) -40.5mg Pbo x 1 daily.

Primary Endpoint: Change in the Physical Performance Test (PPT) from baseline to 6 months.
Secondary Endpoint: Frailty measures, body composition, hip bone mineral density (BMD), physical functions, hematocrit, prostate specific antigen (PSA) and sex hormones.

Results:

- Similar PPT scores were seen in the LT + Test and the LT + Pbo group (17% vs. 16%; P=0.58)
- VO_{2peak} increased more in LT + Test than in LT + Pbo (23% vs 16%; P = 0.03)
- Similar weight loss of -9% was observed in both groups
- Lean body mass and thigh muscle mass decreased less in the LT +Test compared to LT + Pbo
- (-2% vs -3%; P=0.01 and -2% vs -4%; P=0.04).
- Hip BMD was preserved in LT + Test compared with LT + Pbo (0.5% vs -1.1%; P=0.003)
- Hematocrit levels but not PSA increased more in LT + Test than LT + Pbo (5% v's 1%; P < 0.001)

Discussion:

- TRT may further increase aerobic capacity and minimize or prevent muscle and BMD loss that occurs with lifestyle therapy in addition to improving sexual function.
- Concomitant correction of hypogonadism during lifestyle therapy in older men with obesity decreased the weight loss induced reduction of muscle mass and prevented the weight loss induced reduction of hip BMD.
- LT + Test improved aerobic capacity more than LT + Pbo.
- VO_{2peak} is the best indicator of aerobic fitness that has been shown to be a better predictor of mortality then conventional risk factors such as hypertension, hyperlipidemia and smoking.
- VO_{2peak} identifies a person's ability to perform work over prolonged periods that is highly dependent an oxygen delivery an important requirement for maintenance of independence.
- TRT has been associated with decreased mortality independent of CVD risk factors especially in older men with lower weight.
- LT + Test but not LT alone improved areas of sexual function (p 0.04), orgasmic function (p 0.03), sexual desire (p 0.02) and intercourse satisfaction (p 0.03) that translated into improvement in overall satisfaction (p 0.006).
- These findings in older men with obesity and hypogonadism expand observations of the positive effects of TRT on sexual function in younger men and in older nonobese and obese men.
- The increase in testosterone levels in response to LT + T was accompanied by an increase in estrogen levels due to aromatization of testosterone which likely contributed to the maintenance of BMD.
- As expected TRT increased hematocrit but did not lead to any discontinuation because of polycythemia.
- These findings support the short-term prostate safety of testosterone replacement in older men with obesity and hypogonadism.

Table 3. Effect of lifestyle therapy ± testosterone replacement therapy on tertiary outcomes

	LT+Pbo (n = 41)	LT+Test (n = 42)	Difference (95% CI)	*P* value[a]
Tertiary outcomes				
Sex Hormones				
Total testosterone (nmol/L)				
Baseline	7.6 ± 0.2	7.3 ± 0.3		
Change at 3 months	1.6 ± 0.7[b]	10.5 ± 0.8[b]		
Change at 6 months	2.1 ± 0.7[b]	10.6 ± 0.8[b]	−8.7 (−11.6 to −5.9)	<0.001
Free testosterone (nmol/L)				
Baseline	0.18 ± 0.01	0.19 ± 0.01		
Change at 3 months	0.06 ± 0.04[d]	0.39 ± 0.06[b]		
Change at 6 months	0.07 ± 0.04[d]	0.41 ± 0.04[b]	−0.35 (−0.50 to −0.19)	<0.001
Estradiol (pmol/L)				
Baseline	100.6 ± 8.1	102.4 ± 7.3		
Change at 3 months	−6.2 ± 9.6	85.5 ± 10.6[b]		
Change at 6 months	−11.0 ± 9.9[d]	81.1 ± 10.6[b]	−91.4 (−129.6 to −53.6)	<0.001

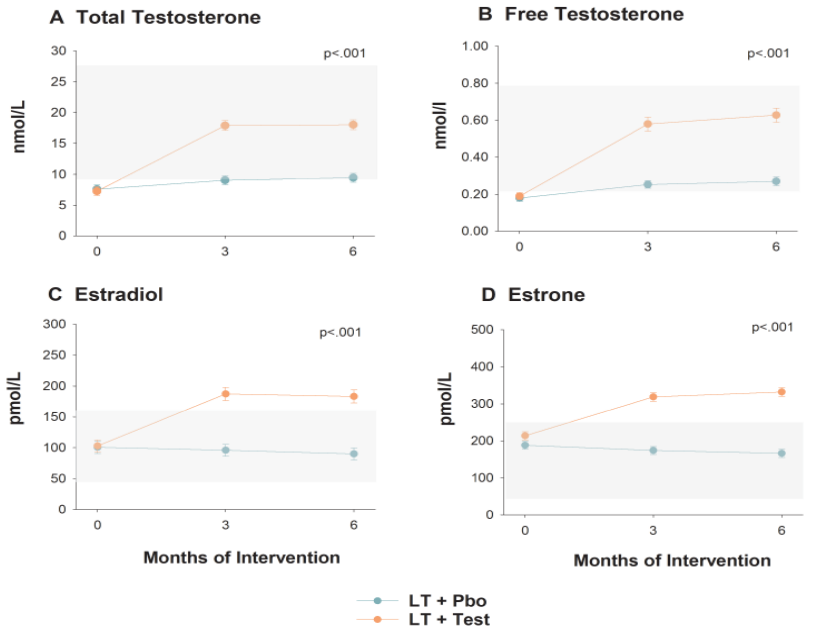

Figure 4. Testosterone, free testosterone, estradiol, and estrone levels during the interventions. Groups: lifestyle therapy (weight management and exercise training) plus placebo (LT+Pbo) and lifestyle therapy plus testosterone (LT+Test). I bars indicate standard errors. Shaded areas represent reference ranges.

Practice Points:

- **This is the first RCT to examine both lifestyle therapy plus TRT in obese hypogonadal frail men.**
- **Lifestyle therapy has been previously proven to benefit obese hypogonadal men's physical functioning.**
- **Results of this small study suggest that TRT does not further improve overall physical function or decrease frailty, however, these study findings suggest that testosterone replacement may attenuate the weight loss–induced reduction of muscle and BMD that occurs with lifestyle therapy in obese hypogonadal men, may improve sexual health and, more importantly, may also further improve aerobic capacity.**
- **Whether to add testosterone to lifestyle therapy in this population should be decided on an individual basis after carefully weighing the risks and benefits of testosterone therapy.**