

Referencias: enfoque integrativo para la gestión de la edad. Beatriz Olson MD, FACP (3/2019)

References: Integrative approach to age management. Beatriz Olson MD, FACP (3/2019)

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Metformin as a tool to target ageing: Nir Barzilai *Cell Metab* 2016 23(6):1060-1065

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Red meat and heart disease

Limit red meats, eggs and cheese to avoid increases of trimethyl amine oxide (TMA) made by gut microbiome from it and then converted by liver to TMA-N-oxide which increases platelet aggregation and thrombosis, accumulation of foam cells and macrophage specific cholesterol macrophages, and reduces net reverse cholesterol transfer.

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Characteristics of successful dieters

Lorraine G Ogden, et al. Dietary habits and weight maintenance success in high versus low exercisers in the National Weight Control Registry J physic Act Health . 2014 Nov; 11(8): 1540-8.

Karfopoulou E Dietary patterns in weight loss maintenance: results from the MedWeight study. Eur J Nutr. 2017 Apr; 56(3):991-1002. Rena Wing 2005

- NWCR: 3560 Participants f/u since 1993 lost on average 18 kg, maintained for ~28 months.
- Their average dietary intake was 2199 kcal/day, with 33 % of energy coming from fat.
- About 78 % engaged in moderate-plus-vigorous physical activity exceeding 150 min/week (51 % above 250 min/week), with men accumulating 82 more minutes than women ($p < 0.05$).
- The most frequently reported strategies for both weight loss and maintenance were keeping healthy foods at home, consuming vegetables regularly, and having daily breakfast. Greater weight loss maintenance was associated with higher levels of physical activity, walking, weight self-monitoring, establishing specific goals, and with reduced portion size use, reduced consumption of carbohydrates, and increased consumption of protein, ($p < 0.05$).
- Med weight 294/361: higher physical activity, healthy dietary pattern featuring mainly unprocessed cereal, fruit, vegetables, olive oil and low-fat dairy : involvement in meal preparation and eating at home for men, and a higher eating frequency and slower eating rate for women (karfopoulou 2017)
- members NWCR that have lost an average of 33 kg and maintained for more than 5 y. engaging in high levels of physical activity (- 1 h/d), eating a low-calorie, low-fat diet, eating breakfast regularly, self-monitoring weight, and maintaining a consistent eating pattern across weekdays and weekends. Moreover, weight loss maintenance may get easier over time; after individuals have successfully maintained their weight loss for 2-5 y, the chance of longer-term success greatly increases. Continued adherence to diet and exercise strategies, low levels of depression and disinhibition, and medical triggers for weight loss are also associated with long-term success. (wing 2005)

HRT see also my various HRT blogs 2016, beatrizolson.com

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Manson JE, Chlebowski RT, Stefanick ML et al. Menopausal hormone therapy and health outcomes during the intervention and extended poststopping phases of the Women's Health Initiative randomized trials. *JAMA* 310, 1353–1368 (2013).

Manson JE, Allison MA, Rossouw JE et al. Estrogen therapy and coronary-artery calcification. *N. Engl. J. Med.* 356, 2591–2602 (2007).

JoAnn E Manson The 'timing hypothesis' for estrogen therapy in menopausal symptom management. *Women's Health*. July 2015 ,Vol. 11, No. 4, Pages 437-440 , DOI 10.2217/whe.15.24 (doi:10.2217/whe.15.24)

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Shifren, Jan L. MD^{1,2}; Desindes, Sophie MD³ ; McIlwain, Marilyn BS⁴ ; Doros, Gheorghe PhD⁵; Mazer, Norman A. MD, PhD⁶ A randomized, open-label, crossover study comparing the effects of oral versus transdermal estrogen therapy on serum androgens, thyroid hormones, and adrenal hormones in naturally menopausal women *Menopause: November/December 2007 – Volume 14 – Issue 6 – pp 985-994*doi: 10.1097/gme.0b013e31803867a

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Sigl, V., Owusu-Boaitey, K., Penninger, J., et al. 2016. RANKL/RANK control Brca1 mutation-driven mammary tumors. *Cell Research*.

Beatriz Olson. See also my prior posts on Set 19, 2014, and October 26, 2014 on FDA- approved HRT, and Compounded non FDA approved HRT on my web site BeatrizOlson.com , or integrative endocrinology with Dr. Beatriz Olson .

Cognitive Function and HRT

- Prospective, 9651 white women 65 years and older enrolled in the Study of Osteoporotic Fractures, a modified Mini-Mental Status Exam (mMMSE), and digit symbol substitution and Trails B tests were administered twice, 4 to 6 years apart. Current oral ERT does not protect against age-related declines in cognitive function in older non-demented women, whereas formal education does protect, even though it had been completed many years earlier. The influence of education in late-life on cognitive function should be tested. **Estrogen Replacement Therapy and Cognitive Decline in Older Community Women** [Karen Matthews](#) et al. *J Am Geriatr Soc* 47:518–523, 1999. <https://doi.org/10.1111/j.1532-5415.1999.tb02563.x>
- In this randomized, double-blind, placebo-controlled trial, 567 healthy women were included in modified intention-to-treat analyses after a mean treatment duration of 57 months. Tx within 6 years of menopause or 10+ years after menopause were randomly assigned to oral 17 β -estradiol 1 mg/d or placebo. Results estradiol initiated within 6 years of menopause does not affect cognition at 2.5 years differently than estradiol initiated 10+ years after menopause.
Cognitive effects of estradiol after menopause: A randomized trial of the timing hypothesis. [Henderson VW](#) et al. *Neurology*. 2016 Aug 16;87(7):699-708.
- Women, 5-36 months past menopause in the Kronos Early Estrogen Prevention Study, a randomized, double blinded placebo-controlled clinical trial to estradiol, progesterone (if uterus). 68 Women were tested 7 years after randomization and 3 years after stopping therapy. Women (age=52-65) randomized to transdermal 17 β -estradiol (n=21) had lower PiB SUVR compared to placebo (n=30) after adjusting for age [odds ratio (95% CI)=0.31(0.11-0.83)]. In the APOE ϵ 4 carriers, transdermal 17 β -estradiol treated women (n=10) had lower PiB SUVR compared to either placebo (n=5) [odds ratio (95% CI)=0.04(0.004-0.44)], or the oral CEE treated group (n=3) [odds ratio (95% CI)=0.01(0.0006-0.23)] after adjusting for age. Hormone therapy was not associated with PiB SUVR in the APOE ϵ 4 non-carriers. **Early Postmenopausal Transdermal 17 β -Estradiol Therapy and Amyloid- β Deposition.** [Kantarci K](#) et al. *J Alzheimers Dis*. 2016 May 7;53(2):547-56.

Testosterone does not increase risk of breast cancer or risk of recurrence

Sex hormone levels and risks of estrogen receptor-negative and estrogen receptor-positive breast cancers. [Farhat GN](#) et al. *J Natl Cancer Inst*. 2011 Apr 6;103(7):562-70.

WHI study compares 317 menopausal women with ER(+) and ER(-) invasive breast cancer versus 594 with breast cancer. Testosterone decreases risk of ER(-) breast CA. Testosterone is not associated with breast cancer. Estradiol levels are higher in women with Er(+) breast cancers.

Reproductive steroid hormones and recurrence-free survival in women with a history of breast cancer. Rock CL et al Women's Healthy Eating and Living Study Group. *Cancer Epidemiol Biomarkers Prev.* 2008 Mar;17(3):614-20.

This is a 7 year follow up study of 153 case controlled pairs of women. Estradiol levels are higher in women with breast cancer recurrence than in women who do not. Testosterone and SHBG levels are not different in these women

Transdermal and vaginal testosterone administrations for women help libido and urogenital atrophy

Chiara Achilli et al Efficacy and safety of transdermal testosterone in postmenopausal women with hypoactive sexual desire disorder: a systematic review and meta-analysis. *Fertility and sterility* 107(2):475-482, 2017. Study is metanalysis of 7 studies 1350 women treated with T, and 1379 to placebo, which favors trans dermal patch of testosterone twice a week usual dose is 300mcg/d delivery. This shows significant improvement in postmenopausal women with hypoactive sexual desire with or without use of HRT. The domains improved are sexual activity, orgasm, sexual desire and SSE, It also shows decrease in personal distress without significant adverse effects or significant changes in lipid profiles, carbohydrate metabolism or weight in 24 week study.

Vaginal Testosterone Cream vs Estradiol Vaginal Ring for Vaginal Dryness or Decreased Libido in Women Receiving Aromatase Inhibitors for Early-Stage Breast Cancer: A Randomized Clinical Trial Clinical Trial. Michelle E. Melisko, MD¹; Mindy E. Goldman, MD¹; Jimmy Hwang, PhD¹; et al Amy De Luca, BA¹; Sally Fang, BA²; Laura J. Esserman, MD¹; Amy J. Chien, MD¹; John W. Park, MD¹; Hope S. Rugo, MD¹

JAMA Oncol. 2017;3(3):313-319. doi:10.1001/jamaoncol.2016.3904

Use large dose 5000mcg tiw versus estring (estradiol) 7.5 mcg

Topical testosterone for breast cancer patients with vaginal atrophy related to aromatase inhibitors: a phase I/II study. Witherby S et al. *Oncologist.* 2011;16(4):424-31. doi: 10.1634/theoncologist.2010-0435. Epub 2011 Mar 8. They look at 150 mcg or 300 mcg vaginal testosterone daily for 4 weeks. Estradiol levels remained suppressed after treatment to <8 pg/mL. Mean total symptom scores improved from 2.0 to 0.7 after treatment (p < .001) and remained improved 1 month thereafter (p = .003). Dyspareunia (p = .0014) and vaginal dryness (p < .001) improved. The median vaginal pH decreased from 5.5 to 5.0 (p = .028). The median maturation index rose from 20% to 40% (p < .001). Although improvement in total symptom score was similar for both doses (-1.3 for 300 µg, -0.8 for 150 µg; p = .37), only the 300-µg dose was associated with improved pH and maturation values.

Vaginal hormone applications

Efficacy of vaginally applied estrogen, testosterone, or polyacrylic acid on vaginal atrophy: a randomized controlled trial. Fernandes T, Costa-Paiva LH, and Pinto-Neto AM. **Efficacy of vaginally applied estrogen, testosterone, or polyacrylic acid on sexual function in postmenopausal women: A randomized controlled trial.** *J Sex Med* 2014;11:1262–1270. 12 week study, 80 postmenopausal women with symptoms of vaginal atrophy were randomized to either polyacrylic acid, testosterone, estrogen, placebo. polyacrylic acid, testosterone, estrogen all produced improvements in self-reported female sexual function when compared with a placebo lubricant. They used the Female

Sexual Function Index (FSFI) to assess changes in sexual response. The intragroup analysis over the time of the treatment showed improvements in the fields of desire, lubrication, and reduced pain for polyacrylic acid, testosterone, and estrogen. Furthermore, women who used testosterone showed improvements over time in the fields of arousal, orgasm, and satisfaction.

Efficacy of vaginally applied estrogen, testosterone, or polyacrylic acid on vaginal atrophy: a randomized controlled trial. [Fernandes T1](#), [Costa-Paiva LH](#), [Pedro AO](#), [Baccaro LF](#), [Pinto-Neto AM](#). *Menopause*. 2016 Jul;23(7):792-8. doi: 10.1097/GME.0000000000000613. The same group of women above but this report looks at vagina atrophy. After a 12-week treatment with topical estrogen and testosterone compared with the lubricant, an increased percentage of participants had vaginal pH less than 5, increased vaginal score, and an increase in the number of lactobacilli. Treatment with topical estrogen improved the vaginal maturation index and showed increased levels of estradiol in three women. No changes were observed in the endometrial evaluation of all treatment groups.

Breast cancer risks with varied HRT protocol: use natural progesterone in women receiving estradiol

Risk of breast cancer by type of menopausal hormone therapy: a case-control study among postmenopausal women in France. Cordina –Duverger et al [PLoS One](#). 2013 Nov 1;8(11):e78016. doi: 10.1371/journal.pone.0078016. eCollection 2013.

We found that breast cancer risk differed by type of progestagen among current users of EP therapies. No increased risk was apparent among EP therapy users treated with natural micronized progesterone. Among users of EP therapy containing a synthetic progestin, the odds ratio was 1.57 (0.99-2.49) for progesterone-derived and 3.35 (1.07-10.4) for testosterone-derived progestagen. Women with continuous regimen were at greater risk than women treated sequentially, but regimen and type of progestagen could not be investigated independently, as almost all EP combinations containing a testosterone-derivative were administered continuously and vice-versa. Tibolone was also associated with an increased risk of breast cancer. Early users of MHT after onset of menopause were at greater risk than users who delayed treatment. This study confirms differential effects on breast cancer risk of progestagens and regimens specifically used in France. Formulation of EP therapies containing natural progesterone, frequently prescribed in France, was not associated with increased risk of breast cancer but may poorly protect against endometrial cancer.

Unequal risks for breast cancer associated with different hormone replacement therapies: results from the E3N cohort study. Agnès Fournier, Franco Berrino, and Françoise Clavel-Chapelon **Breast Cancer Res Treat. 2008 Jan; 107(1): 103–111.**

80,377 postmenopausal women for analysis. They were followed for an average of 8.1 postmenopausal years (standard deviation [SD] 3.9). The last follow-up questionnaire (July 2002) was completed by 88.7% of the 80,377 women; of the 9,095 non-respondents, 892 had been diagnosed with a cancer, 866 had died, and 7,337 were lost to follow-up (of them, 3,979 had replied to the previous questionnaire).

The average age at start of follow-up was 53.1 years (SD 4.5; range 40.0–66.1 years). A total of 652,972 person-years were accumulated and 2,354 cases of invasive breast cancer were identified, 2,243 (95.3%) of which were confirmed by pathology reports.

Compared with HRT never-use, use of estrogen alone was associated with a significant 1.29-fold increased risk (95% confidence interval 1.02–1.65). The association of estrogen-progestagen

combinations with breast cancer risk varied significantly according to the type of progestagen: the relative risk was 1.00 (0.83–1.22) for estrogen–progesterone, 1.16 (0.94–1.43) for estrogen–dydrogesterone, and 1.69 (1.50–1.91) for estrogen combined with other progestagens. This latter category involves progestins with different physiologic activities (androgenic, nonandrogenic, antiandrogenic), but their associations with breast cancer risk did not differ significantly from one another. This study found no evidence of an association with risk according to the route of estrogen administration (oral or transdermal/percutaneous). These findings suggest that the choice of the progestagen component in combined HRT is of importance regarding breast cancer risk; it could be preferable to use progesterone or dydrogesterone.

Progesterone

Oral micronized progesterone for vasomotor symptoms—a placebo-controlled randomized trial in healthy postmenopausal women. Hitchcock, Christine L. PhD; Prior, Jerilynn C. BA, MD. *Menopause: The Journal of The North American Menopause Society*: August 2012 - Volume 19 - Issue 8 - p 886–893. randomized double-blind placebo-controlled trial of progesterone (300 mg daily at bedtime in 44–62 yo) VMS score of 17.0 (10.4) at run-in (VMS frequency 6.8 [3.2] episodes/d). Women were randomized to progesterone (n = 75) or placebo (n = 58); analysis included all with VMS data at run-in and on therapy (n = 68 and 46, respectively). The VMS scores of women taking progesterone were better than placebo (mean adjusted difference, –4.3 (95% CI, –6.6 to –1.9), with mean reductions of 10.0 (95% CI, –12.0 to –8.1) and 4.4 (95% CI, –6.6 to –2.2) in the progesterone and placebo arms, respectively. Discontinuation with adverse events was 9% (progesterone, 8; placebo, 4), with no serious cases.

Oral micronized progesterone is effective for treatment of hot flushes and night sweats in healthy women early in postmenopause.

Micronized progesterone and its impact on the endometrium and breast vs. progestogens. Gompel A. Climacteric. 2012 Apr;15 Suppl 1:18-25.

“ The protective effect of progestogens seen in the endometrium is not replicated in the breast. Progestogens combined with estrogens are generally associated with a small increase in the risk of invasive breast cancer, which is believed to be due to a promoter effect. However, all progestogens are not equivalent in their effects on the breast and breast cancer risk. Micronized progesterone does not increase cell proliferation in breast tissue in postmenopausal women compared with synthetic medroxyprogesterone acetate (MPA). Experimental evidence suggests that the opposing effects of MPA and micronized progesterone on breast tissue are related to the non-specific effects of MPA, including glucocorticoid activity and differences in the regulation of gene expression. Therefore, for women with an intact uterus, micronized progesterone may be the optimal choice as part of combined HRT.”

Transdermal progesterone cream as an alternative progestin in hormone therapy. Leonetti HB; Landes J; Steinberg D; Anasti JN *Altern Ther Health Med. 2005; 11(6):36-8 (ISSN: 1078-6791*

OBJECTIVE: To evaluate the endometrial effects and determine patients' acceptance of transdermal progesterone cream compared to standard hormone therapy.

METHODS: Healthy menopausal women were recruited and received a pretreatment endometrial biopsy (EMB). They were randomized to 0.625 mg conjugated equine estrogen (CEE) daily and 2.5 mg medroxyprogesterone acetate (MPA) (Prempro, Wyeth USA) or daily 0.625 mg CEE and twice daily 20 mg transdermal PC (Pro-gest, Transitions for Health USA). At the end of 6 months, a repeat EMB was obtained, and the women were crossed over to other treatment. A final EMB was performed after the final 6 months.

RESULTS: Twenty-six women completed both arms of the study. Seventy-seven percent of women

preferred the CEE/PC to the CEE/MPA ($P < .001$). Of the 52 post-treatment endometrial biopsies: 40 revealed atrophic endometrium and 12 proliferative endometrium (7 in the oral progestin group and 5 in the PC group). There was no evidence of endometrial hyperplasia in any of the specimens. The incidence of vaginal spotting was similar in both groups.

CONCLUSION: Patients preferred transdermal PC over oral MPA. This preliminary data indicate that CEE/PC has a similar effect on the endometrium as standard oral HT over a 6-month period.

Progestins and progesterone in hormone replacement therapy and the risk of breast cancer. Carlo Campagnoli et al. J Steroid Biochem Mol Biol. 2005 July; 96(2): 95–108. Data supports protective effect of natural progesterone on breast, and other metabolic markers, insulin, IGF-I, SHBG in contrast to progestins

Postmenopausal hormone replacement therapy and cardiovascular disease: the value of transdermal estradiol and micronized progesterone. Mueck AO¹. Climacteric. 2012 Apr;15 Suppl 1:11-7.

Most available postmenopausal hormone replacement therapies (HRT) offer similar efficacy, but differ with respect to the cardiovascular risks associated with their use. There is a wealth of evidence to suggest that, unlike oral estrogens, transdermal estradiol does not increase the risk of venous thromboembolism, probably due to its lack of effect on the coagulation cascade, including thrombin generation and resistance to activated protein C, and does not increase the risk of stroke. It is cardioprotective, significantly reducing the incidence of myocardial infarction compared with non-users; it significantly reduces the incidence of new-onset diabetes, a risk factor for myocardial infarction. Micronized progesterone has also been shown not to increase the risk of venous thromboembolism and further reduced the incidence of new-onset diabetes when combined with transdermal estrogen. Micronized progesterone has a neutral effect on the vasculature, including a neutral or beneficial effect on blood pressure. Therefore, experimental and clinical data indicate that transdermal estradiol and micronized progesterone could represent the optimal HRT, particularly in women at risk of adverse events.

Wirth MM. Beyond the HPA Axis: Progesterone-Derived Neuroactive Steroids in Human Stress and Emotion. *Front Endocrinol (Lausanne)*. 2011;2:19. Published 2011 Aug 11. doi:10.3389/fendo.2011.00019. Progesterone through metabolite allopregesterone has gabaergic effects in the brain, may have anxiolytic effect during stress in humans. Effects may differ with hormonal menstrual status.

Selective Use of Coronary Artery Calcium score testing for Shared decision making: Guidelines endorsed and ready for Prime time. Cardoso R et al. *Annals of Internal Medicine* 170 (4):262-263. 2018 AHA/ACC now endorse CAC testing in patients with 10 year risk for ASCVD 5-20%. If score is 0 then no need for statin, scores 1-99 consider statin, score >100 give statin and heart healthy lifestyle intervention. APO-B presence of sdLDL . consider bergamot 500 mg bid or RED rice yeast. Radiation from this is 0.9 mSV, compared to yearly background radiation exposure of 3 mCV in the US. There is a 5% chance that other findings like lung nodules are detected which lead to further evaluation with a pulmonologist and likely a follow up CT in 3-6 months.

Vitamin D

Kärkkäinen MK , Tuppurainen M , Salovaara K , Sandini L , Rikkinen T , Sirola J , Honkanen R , Arokoski J , Alhava E , Kröger H . Does daily vitamin D 800 IU and calcium 1000 mg supplementation decrease the risk of falling in ambulatory women aged 65–71 years? A 3-year randomized population-based trial (OSTPRE-FPS). *Maturitas* . 2010;65(4):359–365.

Avenell A , Gillespie WJ , Gillespie LD , O’Connell D . Vitamin D and vitamin D analogues for preventing fractures associated with involutional and post-menopausal osteoporosis. *Cochrane Database Syst Rev* . 2009; (2):CD000227.

Meditation and mindfulness

What Are the Benefits of Mindfulness? A Practice Review of Psychotherapy-Related Research. Daphne M. Davis and Jeffrey A. Hayes Pennsylvania State University Psychotherapy 2011, Vol. 48, No. 2, 198–208. This is an academic literature review.

Jon Kabat Zinn: Wherever you go there you are: Full Catastrophe Living

Effect of bariatric surgery on oncologic outcomes: a systematic review and meta-analysis. Tee MC¹, Cao Y, Warnock GL, Hu FB, Chavarro JE. *Surg Endosc.* 2013 Dec;27(12):4449-56. Meta-analysis of Six observational studies (n = 51,740) comparing relative risk (RR) of cancer in obese patients undergoing bariatric surgery versus obese control subjects were analyzed. Overall, the RR of cancer in obese patients after undergoing bariatric surgery was 0.55 [95% confidence interval (CI) 0.41-0.73, p < 0.0001, I(2) = 83%]. The effect of bariatric surgery on cancer risk was modified by gender (p = 0.021). The pooled RR in women was 0.68 (95% CI 0.60-0.77, p < 0.0001, I(2) < 0.1%) and in men was 0.99 (95% CI 0.74-1.32, p = 0.937, I(2) < 0.1%). CONCLUSIONS: Bariatric surgery reduces cancer risk and mortality in formerly obese patients. When stratifying the meta-analysis by gender, the effect of bariatric surgery on oncologic outcomes is protective in women but not in men.

VO₂ max and cardiorespiratory index

Long-term Change in Cardiorespiratory Fitness and All-Cause Mortality Jari a Laukkanen et al. *Mayo Clinic proceedings, Long-term Change in Cardiorespiratory Fitness and All-Cause Mortality.* 2016 Volume 91, Issue 9, Pages 1183–1188

A population-based sample of 579 men aged 42 to 60 years with no missing data at baseline examination (V1) and at reexamination at 11 years (V2) were included. Maximal oxygen uptake (VO_{2max}) was measured at both visits using respiratory gas exchange during maximal exercise testing, and the difference (ΔVO_{2max}) was calculated as VO_{2max} (V2) – VO_{2max} (V1). Deaths were ascertained annually using national death certificates during 15 years of follow-up after V2. The mean ΔVO_{2max} was –5.2 mL/min*kg. During median follow-up of 13.3 years (interquartile range, 12.5-14.0 years), 123 deaths (21.2%) were recorded.

Finding: A 1 mL/min*kg higher ΔVO_{2max} was associated with a 9% relative risk reduction of all-cause mortality (hazard ratio, 0.91; 95% CI, 0.87-0.95). This study suggested that in this population, long-term CRF reduction was associated with an increased risk of mortality, emphasizing the importance of maintaining good CRF over the decades.

Midlife Cardiorespiratory Fitness and the Long-Term Risk of Mortality. 46 Years of Follow-Up
Johan S.R. Clausen, MD et al. *J Am Coll Cardiol* 72(9), 2018:987-95.

Cardiorespiratory Fitness and Mortality in Healthy Men and Women. Imboden MT et al
J Am Coll Cardiol. 2018 Nov 6;72(19):2283-2292. doi: 10.1016/j.jacc.2018.08.2166.

HIIT best time for diabetics is later in the day

Practice Pearls:

- The data highlights the importance of optimizing the timing of exercise when prescribing HIIT as a treatment for type 2 diabetes.
- Morning HIIT had an acute deleterious effect on glucose values in men with type 2 diabetes
- High-intensity interval training (HIIT) has a beneficial effect on glucose concentration in individuals with type 2 diabetes.
- Most importantly, afternoon exercise is more efficacious than morning exercise at improving glucose levels in individuals with type 2 diabetes.

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Pregnenolone

Pregnenolone. Edward Henderson, m.d. et al. *The Journal of Clinical Endocrinology*, Volume 10, Issue 4, 1 April 1950, Pages 455–474.

Pregnenolone as a novel therapeutic candidate in schizophrenia: emerging preclinical and clinical evidence. Marx CE et al. , *Neuroscience*. 2011 Sep 15;191:78-90. Review of pregnenolone action as a neurosteroid based on studies with mice, and clinical trial of pregnenolone in schizophrenia showing positive effects. “Pregnenolone is a neurosteroid with pleiotropic actions in rodents that include the enhancement of learning and memory, neuritic outgrowth, and myelination. Further, pregnenolone administration results in elevations in downstream neurosteroids such as allopregnanolone, a molecule with neuroprotective effects that also increases neurogenesis, decreases apoptosis and inflammation, modulates the hypothalamic-pituitary-adrenal axis, and markedly increases GABA(A) receptor responses. In addition, pregnenolone administration elevates pregnenolone sulfate, a neurosteroid that positively modulates NMDA receptors. There are thus multiple mechanistic possibilities for pregnenolone as a potential therapeutic agent in schizophrenia, including the amelioration of NMDA receptor hypofunction (via metabolism to pregnenolone sulfate) and the mitigation of GABA dysregulation (via metabolism to allopregnanolone).”

A Randomized, Double-Blind, Placebo-Controlled Trial of Pregnenolone for Bipolar Depression E

Sherwood Brown et al. *Neuropsychopharmacology*. 2014 Nov; 39(12): 2867–2873. PCRT of 80 patients randomized to 500 mg pregnenolone versus placebo. Significant earlier improvement in depression was found at 12 weeks using Hamilton rating scale for depression. Dosing 50 mg bid, then 150 mg BID week 2, 250 mg BID wk 4. Levels of pregnenolone and allopregnenolone increased 5 fold, androsterone levels did not change very much. Side effects were similar in both groups.

Re-assessing the Notion of “Pregnenolone Steal” (poitinstitute.org) Sept 21, 2015

“there is no known adrenal pool of pregnenolone for one cell to steal away from another, and no known mechanism has been described that could facilitate the transfer of pregnenolone between the

mitochondria of different cells (in this case, from the mitochondria of cells within the zona reticularis to those within the zona fasciculata). “

What about the role of oral pregnenolone therapy for supporting adrenal DHEA production? Well, it's a bit complicated. While HPA axis stress and subsequent cortisol synthesis and secretion may be related to the acceleration of reduced DHEA production (i.e., a stress-induced down-regulation of DHEA), this relationship is facilitated by regulatory processes (e.g., feedback inhibitions, receptor signaling, genomic regulation of enzymes, etc.), not an intra-adrenal depletion of pregnenolone as a precursor to downstream hormones. For instance, experimentally-induced hyperglycemia and hyperinsulinemia has been shown to affect DHEA and androstenedione production in human subjects.^{[1],[2]} In one study of poorly-controlled type 2 diabetic subjects with elevated cortisol and low DHEA levels, the enzyme necessary for DHEA formation in the zona reticularis (17,20 lyase) was shown to limit the production of DHEA. The enzyme activity was corrected (along with near normalization of cortisol, DHEA and DHEA-S levels) after six months of diet or pharmacotherapy to improve blood glucose control.^[3] Additionally, cell-culture studies suggest that under inflammatory stress (IL-4 and other cytokines), the zona reticularis will down-regulate DHEA production when ACTH is present.^{[4],[5]} These and many other factors (e.g., aging) are likely the driving influences affecting the dynamic relationship between cortisol (activated by the HPA axis) and measured DHEA and/or DHEA-S levels.

Sex- and age-related changes in epitestosterone in relation to pregnenolone sulfate and testosterone in normal subjects. Havlíková H et al. J Clin Endocrinol Metab. 2002

May;87(5):2225-31. “Epitestosterone and its major circulating precursor pregnenolone sulfate and T were measured in serum from 211 healthy women and 386 men to find out whether serum concentrations of epitestosterone are sufficient to exert its antiandrogenic actions. Pregnenolone sulfate levels in women reached their maximum at about age 32 yr and then declined continuously, and in males the maximum was reached about 5 yr earlier and then remained nearly constant.”

I think this may be why there may be better response in depressed women given pregnenolone.

Life Extension suggests that serum pregnenolone levels of 180 nanograms per deciliter (ng/dL) for men and 200 ng/dL for women may be optimal.

DHEA replacement

Oral Dehydroepiandrosterone for Adrenal Androgen Replacement: Pharmacokinetics and Peripheral Conversion to Androgens and Estrogens in Young Healthy Females after Dexamethasone Suppression Wiebke Arlt. et al. *The Journal of Clinical Endocrinology & Metabolism*, Volume 83, Issue 6, 1 June 1998, Pages 1928–1934. **Normal women** (Nine healthy female volunteers (age 19–30 yr, mean age 23.3 ± 4.1 yr; eight nonsmoking, one smoking) were included in the study. All subjects were nonobese with a body mass index of 19.5 to 25.1 kg/m² (mean 22.5 ± 1.8 kg/m²) and were regularly menstruating). Dexamethasone (0.5 X4) which suppresses ACTH and all androgenic hormones. DHEA 50 mg restores normal levels of DHEA, peak levels are reached 3-5 hours after administration this dose replaces normal levels, higher doses are needed to normalize testosterone. This dose does not affect menstrual cycling. DHEA is a precursor of estrone so monitor this.

The effects of oral very high dehydroepiandrosterone doses on endocrine-metabolic parameters in postmenopausal women.

Mortola JF and Yen SSC. *J Clin Endocrinol Metab* 7:696-704, 1990. They give very high dose to post menopausal women for 28 days 1600 mg/day. All hormones increase and peak at 2 weeks. This high dose decreases SHBG, and does cause some insulin resistance but glucose levels remain the same.

Serum steroid concentrations remain within normal postmenopausal values in women receiving daily 6.5mg intravaginal prasterone for 12 weeks. Martel C¹ other participating members of the Prasterone Clinical Research Group. et al. *J Steroid Biochem Mol Biol*. 2016 May;159:142-53. doi: 10.1016/j.jsbmb.2016.03.016. Epub 2016 Mar 10.

Effect of Intravaginal Prasterone on Sexual Dysfunction in Postmenopausal Women with Vulvovaginal Atrophy. Labrie F¹, Derogatis L et al. *J Sex Med*. 2015 Dec;12(12):2401-12. doi: 10.1111/jsm.13045. Epub 2015 Nov 23.

Comparison of intravaginal 6.5mg (0.50%) prasterone, 0.3mg conjugated estrogens and 10µg estradiol on symptoms of vulvovaginal atrophy. Archer DF¹, Labrie F², Montesino M³, Martel C³. *J Steroid Biochem Mol Biol*. 2017 Nov;174:1-8. Prasterone 21 days on 7 off, versus CEE 0.3 mg or vagifem. Daily 0.5 % or 6.25 mg is as effected as vagifem in addressing vulvovaginal symptoms.

Effect of dehydroepiandrosterone supplementation on bone mineral density, bone markers, and body composition in older adults: the DAWN trial.von Mühlen D¹et al.

Osteoporos Int. 2008 May;19(5):699-707. Epub 2007 Dec 15. We present results of a randomized, placebo-controlled trial to examine the effect of 50 mg daily oral DHEA supplementation for one year on bone mineral density (BMD), bone metabolism and body composition in 225 healthy adults aged 55 to 85 years. CONCLUSION: Among older healthy adults, daily administration of 50 mg of DHEA has a modest and selective beneficial effect on BMD and bone resorption in women, but provides no bone benefit for men.

SLEEP and drainage of toxicities from the brain during sleep

Conclusions: These scientists suggest that part of the restorative function of sleep may be in allowing increase in glymphatic flow so that toxic or waste products accumulated in awake time can be flushed out or removed from the brain.

Source reference: Xie L, et al "Sleep drives metabolite clearance from the adult brain" *Science* 2013; 342:373-377.

Melatonin

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Sleep

Meditation

Cancer prevention

