Smart Life Forum

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Thursday, March 18th 2010, at 7pm

Ron Rothenberg, MD

On

Hormone Myths versus Medical Evidence

Meet Ron Rothenberg, MD

Dr. Ron Rothenberg received his medical degree in 1970 from Columbia University in New York. He completed his residency in Emergency Medicine in 1975 from the University of Southern California in Los Angeles. In 1998 he founded the California HeathSpan Institute in Encinitas, California. He completed his Fellowship in Anti-Aging and Regenerative Medicine in 2007. He is

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Notices

1.Starting in March we will be back in Room H1 permanently

2.FMBR Meeting Notice: March 26, 2010: Dr. Stuart Sovatsky of California Institute of Integral Studies will speak on "Male-Female Relationship as the Creative Center of the Human Universe."

In This Issue

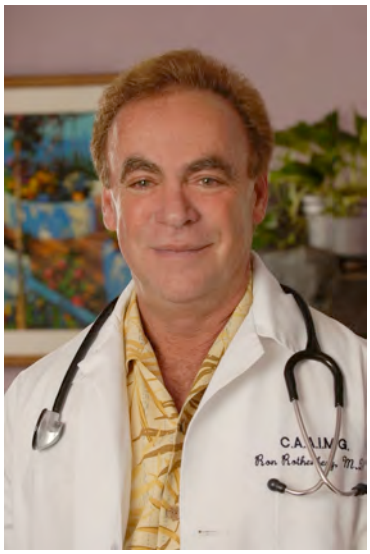
Presentation Location:

Cubberley Community Ctr.

Room H1

4000 Middlefield Rd..

Palo Alto, CA



Ron Rothenberg, certified by the American Board of Anti-Aging and Regenerative Medicine, as well as the American Board of Emergency Medicine. Formerly a Clinical Professor in Family and Preventive Medicine at UCSD School of Medicine. he has authored numerous publications in Emergency Medicine and Preventive Regenerative Medicine. He is actively involved as an educator, and over 50,000 physicians have attended his seminars from 1975-2009. He has continued as an Attending Physician at Scripps Memorial Hospital in Encinitas, California from 1980 to the present.

Future Speakers:

May 20,2010
(in Room H1)
Gary Taubes, on
Good Calories, Bad
Calories

Main Presentation:

HORMONE MYTHS VERSUS MEDICAL EVIDENCE

There are many myths surrounding hormone replacement therapies. These range from the notion that thyroid hormone is dangerous for the heart to the widespread belief that growth hormone replacement therapy (GHRT) increases the risk of cancer. The aim of this presentation is to review the current medical literature surrounding these myths and to demonstrate the safety and efficacy of hormone replacement therapies. We will explore these myths by reviewing several cases.

MYTH 1: THYROID IS DANGEROUS FOR THE HEART

Our first patient is a 60-year-old physician with acute myocardial infarction (MI), congestive heart failure (CHF), and tachycardia. [Myocardial infarction, or "heart attack", is the interruption of blood supply to part of the heart, causing some heart cells to die. Heart failure (HF) is a condition in which a problem with the structure or function of the heart impairs its ability to supply sufficient blood flow to meet the body's needs. Tachycardia typically refers to a heart rate that exceeds the normal range for a resting heart rate.]

Laboratory results show that his TSH (thyroid stimulating hormone) is 3.5 (reference range 0.2-5.5 μIU/mL): free T4, Thyroxine, is 1.3 (reference range 0.70-1.53 ng/dL); free T3, Triiodothyronine is

About Smart Life Forum

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2.1 (reference range 2.3-4.2 pg/mL); and his reverse T3 is 380 (reference range 90-350 pg/mL). Would you treat this patient with thyroid? Would it be best to steer clear? Or, would optimizing his thyroid hormone improve the situation?

Is thyroid hormone bad for the heart? No. It is true that hyperthyroidism is associated with atrial fibrillation (abnormal heart rhythm). However, optimizing thyroid hormone is associated with numerous benefits (Asvold et al[1], Rasvi et al[2],) including:

- Improved lipid profile
- Improved CHF
- A positive inotropic effect upon the heart
- Vasodilation
- Prevention of maladaptive cardiac remodeling after acute MI
- Normalization of the QT interval, thus reducing the odds of lethal arrhythmias
- Improvement of C-Reactive protein (CRP) and homocysteine levels
- Improvement of arterial stiffness and endothelial dysfunction.

What if a patient with cardiovascular disease has low T3? It is important to remember that T3 is the active hormone (metabolically active triiodothyronine) and T4 is the prohormone. The heart needs T3 as it is unable to convert T4 into T3. Signs of low T3 in cardiovascular disease include (Fernandez-Real et al[3]):

- Bradycardia, narrowed pulse pressure, and diastolic hypertension
- Dyslipidemia
- Endothelial dysfunction
- Elevated CRP and homocysteine

Lervasi et al[4] found that low T3 is a strong predictor of death in cardiovascular patients. In this study, low T3 was defined as <3.1 pg/m. The free T3 value is of interest because while it is within the confines of the reference range (2.3 to 4.2 pg/mL), it falls in the less desirable half of the reference range. **Remember, as anti-aging physicians we want optimal levels, not reference range levels.** Results showed that low T3 was the strongest independent predictor of death – more than

dyslipidemia and more than a poor ejection fraction. Furthermore, the authors concluded that low T3 might be directly implicated in the poor prognosis of cardiac patients.

So, low T3 is associated with a poor prognosis, but what factors are associated with survival after an acute MI? A study of acute MI patients by Satar *et al* found that patients who survived had higher free T3 levels than those who died, and that non-survivors had higher TSH and higher reverse T3 than controls.[2] High reverse T3 levels are seen in many critical clinical situations such as MI and unstable angina because a survival mechanism is triggered by such circumstances. Unfortunately, it is a maladaptive survival mechanism, and it causes a condition called euthyroid sick syndrome (ESS). Patients with ESS have low T3 levels and increased reverse T3 levels (TSH and T4 may be in the reference range), so it is vital to order the right tests in order to detect ESS. Pavlou *et al* found that the degree of T3 decrease in patients with acute MI was proportional to the severity of cardiac damage sustained.[3]

New research suggests that we may soon be treating patients with low T3 syndrome and ischemic or non-ischemic dilated cardiomyopathy with intravenous (IV) T3. At first thought, this sounds crazy. However, Pingitore *et al* showed that this treatment was both safe and effective.[4] Patients were given an infusion of T3 in order to restore circulating T3 levels to within the normal range. No adverse side effects were observed. Heart rate and B-type natriuretic peptide levels decreased significantly after infusion, and ventricular performance improved. Perhaps the notion of IV T3 is not so crazy after all. If further studies are successful, we may well be giving patients IV T3 to treat CHF and acute MI.

After MI, the body attempts to remodel the ischemic area. However, once again, a maladaptive mechanism comes into play, and the body employs fetal-type myosin to remodel the damaged tissue. Thus, the body thinks a new heart is being born resulting in an inappropriate remodeling of the heart. Research suggests that thyroid hormone prevents this maladaptive remodeling.[8,9,10]

So, we can see that thyroid hormone is clearly not dangerous for the heart. It is very important to measure free T3 and reverse T3 in cardiac patients. It is equally important not to be afraid of optimizing T3 – it should be in the upper third of the reference range (3.5-4.2 pg/mL). A patient's life may well depend on it. **Treat mild hypothyroidism by optimizing free T3 to reduce all components of metabolic syndrome.** Do not rely on the TSH. Look at the patient's clinical picture and look at free T3, and remember that it is important to consider symptoms, not just numbers.

MYTH 2: TESTOSTERONE CAUSES PROSTATE CANCER TO GROW

Our second patient is a 60-year-old physician with a history of prostate cancer. He was treated with a radical prostatectomy (surgical removal of the prostate gland) two years ago. The clinical picture (irritable, low libido, erectile dysfunction) and laboratory results – testosterone 350 ng/dL (reference range 300-1000 ng/dL), free testosterone 6 pg/mL (reference range 8-24 pg/mL), sex hormone binding globulin (SHBG) 40 nmol/L (reference range 30-65 nmol/l), estradiol (E2) 25 ng/dL (reference range 15-50 ng/dL) –suggest hypogonadism. He is interested in testosterone replacement therapy (TRT); however his wife is worried that TRT will increase his risk of cancer recurrence. Would you treat the patient with testosterone?

The bottom line is that **testosterone does not cause prostate cancer to grow**. The notion that

testosterone causes prostate cancer to grow was based on one case report from 1941 – one patient![11] There is no relationship between testosterone, dihydrotestosterone (DHT), estradiol, and prostate cancer, and there are no reports of prostate cancer in men treated with testosterone after radical prostatectomy.

Results of a perspective study of 11,606 men by Khaw *et al* led the authors to conclude: "In men, endogenous testosterone concentrations are inversely related to mortality due to cardiovascular disease and all causes."[12] The authors also write: "Prospective studies or supplementation studies, reviewed elsewhere, have not reported significant relationships of endogenous testosterone concentrations or of testosterone supplementation with prostate cancer. Although in the present analysis, there was insufficient power to examine the relationships with prostate or other specific cancers, we observed an inverse relationship of endogenous testosterone concentrations with cancer mortality."

Another study, this time a review of 18 prospective studies that included 3886 men with incident prostate cancer and 6438 control subjects, examined the association between endogenous sex hormones and prostate cancer risk.[13] No associations were found between the risk of prostate cancer and serum concentrations of testosterone, calculated free testosterone, dihydrotestosterone, dehydroepiandrosterone (DHEA) sulfate, androstenedione, androstanediol glucuronide, estradiol, or calculated free estradiol.

So, there is plenty of evidence to show that testosterone does not increase the risk of prostate cancer. There is also evidence showing that endogenous testosterone concentrations are inversely related to mortality due to cardiovascular disease and all causes, but is there any evidence to show that treating men with testosterone after radical prostatectomy is safe? Yes, there is. Agarwal and Oefelein studied 10 hypogonadal patients treated with radical prostatectomy for organ-confined prostate cancer to determine if TRT could be administered safely without causing recurrent prostate tumor.[14] Results showed that after receiving TRT for approximately 19 months total testosterone levels and hypogonadal symptoms had improved significantly, and there were no prostate cancer recurrences or increases in PSA. These results led the authors to conclude: "In highly select patients after radical prostatectomy TRT can be administered carefully and with benefit to hypogonadal patients with prostate cancer."

Not everyone will be comfortable with prescribing TRT to men who have undergone radical prostatectomy; however it is clear that the medical literature does support the carefully monitored use of TRT in men with a history of prostate cancer. (15,16,17,18)

MYTH 3: TESTOSTERONE CAUSES ANGRY AND AGGRESSIVE BEHAVIOR

So, after careful consideration, we have decided to put patient #2 on TRT. However, Patient #2 is known to have a short temper, and now that his wife's fears concerning prostate cancer recurrence have been put to rest, she is concerned about so-called "roid rage". In short, she is worried that TRT will make him angry and aggressive. Is this true?

No, it is not. This is just another hormone replacement myth. In fact, TRT has quite the opposite effect on behavior. Much of the bad press about TRT stems from media stories about anabolic steroid abuse – we are not concerned with abusing anabolic steroids, we are concerned with restoring testosterone to physiologic levels. Studies have shown that men who have their testosterone levels

restored with TRT are less likely to suffer from depression, are less moody, more sociable and gregarious, and have more energy.19 O'Connor *et al* investigated the effects of TRT on self- and partner-reported aggression and mood.[20] Eight hypogonadal men received 200 mg intramuscular testosterone biweekly for 8 weeks. Results showed that TRT led to significant reductions in negative mood (tension, anger, and fatigue). Furthermore, there was no increase in self- and partner-reported aggression or mood disturbances. Thus, we can conclude that TRT does not cause or worsen angry or aggressive behavior.

MYTH 4: GROWTH HORMONE CAUSES CANCER

Patient #3 is a 60-year-old woman with a clinical and laboratory picture of adult growth hormone deficiency (AGHD). However, she also has a strong family history of breast cancer. Is it safe to treat her for AGHD? Does GH cause cancer?

A paper by Jenkins *et al* entitled "*Does growth hormone cause cancer?*" concluded: "Extensive studies of the outcome of GH replacement in childhood cancer survivors show no evidence of an excess of *de novo* cancers, and more recent surveillance of children and adults treated with GH has revealed no increase in observed cancer risk.[21]

As GH increases levels of insulin-like growth factor-1 (IGF-1), could it be possible that the increase in IGF-1 levels associated with GH replacement therapy (GHRT) increases the risk of cancer? Results of a case-control study by Schernhammer *et al* led the authors to conclude: "Circulating IGF-I, IGFBP-1, IGFBP-3, and GH levels appear to have no important association with breast cancer risk in a large cohort of premenopausal women.[22]

If you look at the package insert for GH it says that it should not be used in patients with an active malignancy. However, the Growth Hormone Research Society published a paper in the *Journal of Clinical Endocrinology and Metabolism,* saying that there is no data to support this labeling, and that current knowledge does not warrant additional warning about cancer risk.[23] The authors of this paper say that this line should be removed from the package insert because there is no evidence to show that GH increases cancer recurrence or *de novo* cancer or leukemia. In conclusion, the notion that GH causes cancer is another myth. (24)

MYTH 5: ADULT GROWTH HORMONE DEFICIENCY IS ONLY SEEN IN PATIENTS WITH SEVERE MULTIPLE PITUITARY DEFICIENCIES SINCE CHILDHOOD

After taking a detailed medical history of Patient #3, we learn that she was thrown from her horse a year ago. In fact, she had a head injury and was comatose for four hours. Results of a CT scan taken at that time showed cerebral contusion (a bruise, caused by bleeding into the extracellular space). Does AGHD only occur in patients who have had severe multiple pituitary deficiencies since childhood? Or, is that simply a myth? Is there a relationship between traumatic brain injury (TBI) and AGHD?

Yes, it is a myth, and yes there is a relationship between TBI and AGHD. GH deficiency is common in survivors of moderate-to-severe, and even mild, TBI. The onset of TBI-induced GH deficiency can present up to a year after the injury, and therefore assessment of the GH/IGF-1 axis is important in

anyone with a history of TBI.

A review by Popovic *et al* showed that some degree of hypopituitarism is found in 35-40% of TBI patients, and suggested that untreated TBI-induced hypopituitarism contributes to the chronic neurobehavioral problems seen in many head-injured patients.[25] Preliminary data suggests that people suffering from TBI-induced hypopituitarism experience significant improvements in concentration, memory, depression, anxiety, and fatigue when treated with GH. The authors of this review concluded that pituitary failure is poorly recognized and can occur even with minor head injuries. (26,27)

Thus, all TBI, cerebrovascular accident, and subarachnoid hemorrhage patients should be evaluated for AGHD within a year of the event, and they should be treated if a deficiency exists. In the future, it may be possible to treat all TBI patients with GH if they have symptoms of GH deficiency, however at present patients need to have been given a diagnosis of AGHD before they can be treated.

MYTH 6: PROGESTERONE TREATMENT IS ONLY FOR MENOPAUSAL WOMEN WHO HAVE A UTERUS

Is there another hormone therapy that could have helped Patient #3 when she fell off her horse? Could progesterone have helped her, or is progesterone treatment only for menopausal women who have a uterus?

Progesterone is neuroprotective. There is basic science to support this and now there are human trials. Pettus *et al* found that when progesterone is given after TBI it reduces the initial cytotoxic surge of inflammatory factors, decreases levels of nuclear factor kappa beta (NFKβ), and decreases levels of inflammatory eicosanoids.[28] So, how does progesterone exert this neuroprotective effect?

The neuroprotective properties of progesterone are probably derived from the action of allopregnanolone (APα), a neuroactive metabolite of progesterone, which turns on neuronal stem cells. Wang *et al* found that APα promotes the proliferation of rodent neuroprogenitor cells (NPCs) derived from the hippocampus, and increases human neural stem cells (hNSCs) derived from the cerebral cortex. Results also showed that APα regulates cell-cycle gene and protein expression.[29]

Could we have treated Patient #3 with progesterone? Research published in the last few years suggests that progesterone may well play an important role in the treatment of TBI. First there was the ProTECT study, a randomized, placebo-controlled, clinical trial of 100 patients evaluating the safety and potential efficacy of progesterone in patients with TBI, which was the first human study to prove the benefits of progesterone as a neuroprotective agent.[30] The study used the both the Glasgow Coma Scale (GCS) and the Glasgow Outcome Scale (GOS) score. The GCS was used to record the condition of the patient upon admission to hospital and the GOS was used to record their condition after treatment. The GOS ranges from 1 to 5: 1 – dead, 2 – permanent vegetative state, 3 – severe disability, 4 – moderate disability, 5 – good recovery.

The patients in the study had a GCS of between 4 (signifying a severe TBI) and 12 (signifying a moderate TBI) when they were admitted to hospital. Patients were randomized on a 4:1 basis to receive either intravenous progesterone or placebo. Those selected for progesterone treatment were given progesterone via intravenous drip for three days. Each patient received 37 mg progesterone per kilogram of body weight.. Results showed that the 30-day mortality rate was cut in half in those treated with progesterone. Severe brain injury (GCS 4-8) survivors in both progesterone and control groups

scored poorly on the GOS. However, moderate brain injury (GCS 9-12) survivors in the progesterone group were significantly more likely to receive a moderate or good GOS – that is a GOS of 4 or 5. In the placebo group none of the seven patients with a moderate brain injury were given a moderate or good GOS; however in the progesterone group ten out of eighteen patients were given a moderate or good GOS.

Another study of great interest is a prospective, randomized, placebo-controlled trial by Xiao *et al*.[31] This study involved 230 TBI patients who had a GCS score of 8 or less on admission. Therefore all the patients in this study had a severe TBI. Patients were randomly assigned to receive either progesterone or placebo. The primary endpoint was the GOS score three months and six months after injury. Results showed that GOS scores were more favorable and modified Functional Independence Measure scores were higher in patients treated with progesterone than in those given placebo. Furthermore, at six month follow-up the mortality rate of the progesterone group was significantly lower than that of the placebo group.

The results of these studies are extremely promising. However, using progesterone to treat TBI is still classed as an experimental treatment. Despite this, I know that if I sustained a brain injury I would certainly want to be treated with it.

MYTH 7: PROGESTERONE EQUALS PROGESTIN

Patient #3 is pleased that treating her with progesterone when she fell off her horse would, most likely, improve her chances of making a full recovery; however having read reports about the Women's Health Initiative Study, she is concerned that being treated with progesterone will increase her risk of cancer and ischemic heart disease. Is that the case? Is progesterone the same as progestin?

Fournier *et al* compared the association between different forms of hormone replacement therapy (HRT) and breast cancer risk, using data from the French E3N cohort study – a large, ongoing study of more than 80,000 women.[32] **Results showed that women treated with bioidentical estradiol and progesterone were no more likely to develop breast cancer than women who had never used any form of HRT. However, women treated with estradiol and progestin (Provera) had a 69% increased risk of developing breast cancer.**

Other research has shown that the more progesterone a woman is exposed to over the course of her life, the lower her risk of breast cancer. (33) So, let's make it clear once and for all – progesterone and progestin are not the same.

MYTH 8: THE MANY VITAMIN D MYTHS

Patient #4 is a 60-year-old physician with a family history of colon cancer and autoimmune disease. She takes a daily multivitamin that contains 1000 IU of vitamin D3 and her 25-(OH) vitamin D3 level is 33 ng/mL (reference range 33-105 ng/mL). Should Patient #4 increase her dose of vitamin D3?

There are so many myths surrounding vitamin D. First and foremost, is the myth that vitamin D is a vitamin. Vitamin D is not a vitamin, it is actually a steroid hormone. Vitamin D is produced in one part of the body (the skin), and then travels to a remote site, where it exerts an endocrine effect. Thus, it fulfills the definition of a hormone. Another vitamin D myth is that its only function is calcium

regulation. That idea has been well and truly debunked in recent years. Then there is the idea that 1000 IUs a day is more than enough, which is simply not true. Other myths of interest include:

- Most people living in the US get adequate amounts of vitamin D – not true (see below).
- Extreme care must be taken to avoid toxicity – not true! There have been numerous studies on vitamin D toxicity and no toxicity has been seen in doses lower than 30,000 IU/day (200 ng/mL). An excess of vitamin D causes hypercalcemia, however all known cases of vitamin D toxicity with hypercalcemia have involved intakes of 40,000 IU or more per day.
- Spending 15 minutes in the sun each day enables the body to produce ample amounts of vitamin D – that may be true if you are sitting on a beach in Hawaii at noon wearing nothing but a bikini, but for the vast majority of us that is a myth. If you live above 35 degrees latitude, the body is unable to produce adequate amounts of vitamin D from the winter sun.
- Eating a balanced diet will provide adequate amounts of vitamin D – not true! Vitamin D is present, in small amounts, in only a handful of foods – oily fish, eggs, and fortified foods. Thus it is very unlikely that adequate amounts could be obtained from the diet.
- Vitamin D does not prevent cancer – it does (see below).
- Vitamin D does not prevent autoimmune disease – it does (see below).
- Vitamin D does not prevent acute MI and heart disease – it does (see below).

As mentioned above, the notion that most people living in the US get adequate amounts of vitamin D is far from true. Research has shown that Vitamin D deficiency is present among all age groups of US citizens from children to the elderly, and especially in African-Americans.[34] Studies have shown that the prevalence of low 25-(OH) D3 levels (<20 ng/mL) is approximately 36% in young adults aged 18-29,[35] 42% of African-American women aged 15-49,[36] 41% of outpatients aged 49-83,[37] and 57% of inpatients.[41] In Europe, it is believed that between 28 and 100% of healthy adults and 70-100% of hospitalized adults have low 25-(OH) D3 levels (<20 ng/mL).[37-40]

Research has shown that the incidence of many diseases could be dramatically reduced by increasing serum 25-(OH) D3 levels, and by looking at the list below, it is easy to see why vitamin D has become a very hot topic in recent years:

- Increasing serum 25-(OH) D3 levels to 35 ng/mL could prevent 30% of MI in men[42] and reduce the risk of fracture in elderly people by 50%.[43]
- Increasing serum 25-(OH) D3 levels to approximately 40 ng/mL could reduce the risk of cancer in postmenopausal women by 35%[44] and reduce the risk of falls in elderly people by 50%.[45]
- Increasing serum 25-(OH) D3 levels to 50 ng/mL could reduce the incidence of breast cancer by as much as 80%,[46] multiple sclerosis by as much as 60%,[47] and type 1 diabetes by up to 50%.[48]

Why is vitamin D so beneficial? There is no clear answer at present. However, anything that has such wide-ranging benefits has to possess the ability to modulate inflammation. Indeed, studies have shown that vitamin D inhibits nuclear factor-κβ (NF-κβ)[49] – a protein that plays a key role in the

inflammatory response and in the proliferation of cancer cells. It has also been shown to lower levels of the inflammatory marker CRP.[50] Thus, it is vital that we ensure our patients are getting plenty of vitamin D.

What about Patient #4, does she need to increase her daily dose of vitamin D3? Yes. The reference range for 25-(OH) D is 33-105 ng/mL. **Given the evidence published in the medical literature over the last few years, it is advisable to try and keep patients at the top end of the reference range – so, we should be aiming for 75-100 ng/mL. The optimal dose is 5000-15,000 IU/day.** However this should be lowered for people who get a lot of sun exposure. **It is also advisable to regularly check serum calcium in patients who take supplementary vitamin D, just to ensure there is no risk of hypercalcemia.**

CONCLUSIONS

There are many myths surrounding hormone replacement therapies. However, from the evidence presented above, we can see that not one of the above myths is true. Hormone optimization provides us with an extremely powerful anti-aging tool to maximize quality of life. It is important to note that there is increasing evidence to suggest that hormones may also play an important role in the treatment of acute coronary syndrome and Traumatic Brain Injury.

NOTE: As the list of References for Dr. Rothenberg's article is rather long (50 references), we are providing the References as a separate document, so subscribers can choose whether or not to download and/or print them out. For those who want them, the References are available via the following link:

http://www.smartlifeforum.org/Rothenberg-References.pdf