Clinical Briefs in Primary Care™

The essential monthly primary care update

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Testosterone in Older Men: Is Low Normal Too Low?

Source: Emmelot-Vonk, et al. *JAMA.* 2008;299(1):39-52.

After attaining peak adult testosterone levels, men experience a continuous decline in testosterone (TST) of about 1% per year. Concomitant changes with aging such as sarcopenia, cognitive decline, reduced strength, and increased abdominal fat mass have been associated with this loss of TST. The definition of "normal" testosterone includes a wide range, and since most late-life males who have TST levels checked do not have an available early-life TST level for comparison, it is difficult to know whether or not low-normal levels represent a significant pathologic contrast from levels in youth.

Emmelot-Vonk et al studied the effects of TST supplementation among Dutch men with low-normal TST levels. Outcomes measured included functional mobility, handgrip strength, leg strength, cognitive function, BMD, lipids, glucose and quality of life (scored by SF-36). In this randomized double-blind trial, men (n=237) received either 80 mg testosterone undecenoate P.O. b.i.d. or placebo for 6 months.

Although TST did produce meaningful increases in lean body mass, and a corresponding decrease in fat mass, there was no concomitant functional mobility or strength change. Of concern, TST was associated with a 20% decline in HDL, without any measurable benefits in QOL or cognitive function.

This study does not support benefit from supplementing TST in men with low-normal TST levels. ■

CT Pulmonary Angiography is at Least as Good as Ventilation-perfusion Scanning for Suspected Pulmonary Embolus

Source: Anderson DR, et al. *JAMA.* 2007;298(23):2743-2753.

Pulmonary embolism (PEM) is responsible for over ¼ million deaths in the US each year, but accurate and timely diagnosis can sometimes prove elusive. The "gold standard" noninvasive test for at least 3 decades has been the ventilation-perfusion scan (VQS), which has an extraordinarily high specificity: a negative VQS essentially excludes PEM. Unfortunately, the majority of VQS results are reported as low-intermediate PEM probability, leaving a great deal of diagnostic uncertainty.

CT pulmonary angiography (CTPA), because it can be read simply as either positive or negative, is not hampered by this same uncertainty. Additionally, it can detect other chest pathology, although historically it has been considered less sensitive than VQS.

In this study, patients suspected of having PEM (n=1417) were randomized to PEM or CTPA. It is critical that PEM diagnostic tests not falsely exclude individuals who actually have the disorder (false negatives). Hence, the primary endpoint of the study was the number of individuals developing symptomatic proximal deep vein thrombosis (DVT) or PEM in the 3 months following an initial negative investigation.

There was no statistically significant difference in the accuracy of PEM vs CTPA. Using standard protocols which employ d-Dimer and leg venous ultrasound, CTPA and VQS have similar predictive value. ■

Vertebral Fracture Begets Vertebral Fracture

Source: Cauley JA, et al. *JAMA.* 2007;298(23)2761-2767.

Vertebral fracture may be defined as a decrease of at least 20% in vertebral height, amounting to a height decrement of at least 4 mm. The Study of Osteoporotic Fractures offers a long-term observation of risk of osteoporotic vertebral fracture (VFX) in women with and without VFX at baseline. This study population was comprised of 9,704 midlife Caucasian women (mean age = 68.8, range 65-99 years) recruited within the United States from 1986-1988 and followed for an average of 14.9 years.

At the 15-year follow-up clinic visit, overall 18.2% of women had a new VFX, but the disproportion of incident VFX was markedly skewed towards those had had a prevalent VFX at baseline: 41.4% of the 394 women with baseline VFX at study enrollment had experienced one or more incident VFX, as compared with 14.2% of the 2,286 women without baseline VFX.

Currently recognized risk factors were associated with VFX including low body weight, BMD, smoking history, and age.

Pre-existing VFX was the most potent

predictor of future VFX, and was also associated with increased risk for nonvertebral fracture. The predictive capacity of preexisting VFX was independent of BMD, corroborating the current philosophy that BMD is a major contributor to, but not the only factor involved in, bone fragility. ■

I've Heard of TIA, but what the heck is a TNA?

Source: Bos MJ, et al. JAMA. 2007;298(24):2877-2885.

The formal classification of cerebrovascular disorders as we know it today is only a few decades old. One of the categories named in the original 1975 classification system was "transient attacks of neurological dysfunction," comprised of transient ischemic attacks (TIA) and transient non-localizing or mixed neurologic syndromes, generally considered to be more benign. The authors have suggested that transient neurologic attacks (TNA) be subdivided into focal TNA (=TIA, usually of ischemic vascular origin) and non-focal or mixed TNA (nf/m-TNA), of diverse etiology (including, but not limited to, vascular origin). It has been observed that in clinical practice nf/m-TNA and TIA are often grouped together by primary care clinicians and neurologists alike, attesting to the sometimes "fuzzy borders" distinguishing these entities. At the same time, nf/m-TNA has generally been regarded as more "benign," and less likely to be associated with subsequent increased stroke risk.

To better study TNA, adults aged 55 years or older (n = 6,062) were followed for 60,535 person years (about 10 years each, on average). During that time a TNA occurred on 548 individuals; the incidence of nf/m-TNA (4.4/1000 person-years) and TIA (4.7/1000 person-years) were very similar. Prognostically, the hazard ratio for subsequent stroke was increased both for victims of TIA (HR = 2.4) and nf/m-TNA (HR = 1.56-2.48). TNA that are non-focal or mixed have a less benign future than has been widely appreciated. ■

Advancing Insulin Therapy in Type 2 Diabetes Previously Treated with Glargine Plus Oral Agents

Source: Rosenstock J, et al. *Diabetes Care.* 2008;31:20-25.

When oral agents alone fail to attain glycemic goals, clinicians have numerous therapeutic options for advancing glucose control, the most common of which (currently) is addition of basal insulin (eg, insulin glargine, NPH, insulin detemir), followed by targeted prandial insulin for specific excessive postmeal glucose excursions (basal/prandial treatment). Rather than adding prandial insulin to glargine (in addition to oral agents), substituting multi-dose premix for basal/prandial insulin has some advocates, and has not yet been studied in a comparative trial.

Type 2 diabetics (n=374) unable to attain satisfactory control with oral agents plus basal insulin alone were randomly assigned to thrice daily premix insulin (Humalog Mix 50/50 or Humalog Mix 75/25) or glargine/lispro. At 24 weeks, the A1C attained was superior in the basal/prandial group to the premix group (6.78% vs 6.95%, $p = 0.021$). Since the trial was designed to test the non-inferiority of premix compared to basal/prandial with a prespecified margin of 0.3%, premix was NOT confirmed as non-inferior to basal/prandial. Similarly, the percent of patients achieving goal A1C < 7.0 was greater for basal/prandial than premix (69% vs 54%, $p = 0.009$); if the A1C target was the more strict <6.5%, basal/prandial still maintained advantage (50% achieved vs 35% on premix). ■

A Relationship Between Linolenic Acid and Neuropathy in Diabetics

Source: Tao M, et al. Diabetes Care. 2008;31(1):93-95.

Over 25% of mid-life diabetics have peripheral neuropathy (DPN), which is categorized as one of the microvascular consequences of diabetes based upon its putative origin in dysfunction of the vasonervorum. Good glycemic control has been found to forestall and prevent progression of neuropathy, but not reverse it. The search for etiologic factors in development of DPN has come to consider linolenic acid because of an identified relationship between high dietary linolenic acid intake and lesser macrovascular disease.

The NHANES (National Health and Nutrition Examination Survey) has periodically provided diverse US population data since 1971. In their most recent data set (1999-2004), an analysis of dietary linolenic acid in relation to DPN was examined.

Mean daily intake of linolenic acid (based upon 24-hour dietary recall report) was remarkably lower in persons with DPN (1.25 g/d) than diabetics without DPN (16.82 g/d).

This is the first investigation to characterize the inverse association between linolenic acid and DPN, and as such requires replication and further elucidation of mechanisms by which linolenic acid might be protective. ■

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