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Benefits of Calcium and Vitamin D: A Meta-analysis

Tang BMP, et al. *Lancet.* 2007;370:657-666.

In an era of multiple randomized controlled trials that have documented the efficacy of antiresorption agents (eg, alendronate, risedronate, ibandronate, raloxifene) both to enhance bone mineral density (BMD) and reduce osteoporotic fractures, there remains some uncertainty about the efficacy of calcium supplementation, vitamin D supplementation, or the combination. Even meta-analysis on the topic have been inconsistent.

The impact of supplementation is especially important to clarify since in developing nations, which are beginning to share the same "graying" demographics as America, the cost of preventive treatments is critical.

Tang, et al, performed a meta-analysis on all recorded randomized clinical trials of persons over 50 (n=29), comprised of 52,625 participants. The trial selection process can provide greater assurance than earlier meta-analysis, as they didn't include any observational trials. Their conclusions will help provide some closure and guidance about dosing regimens.

Overall, calcium or calcium plus vitamin D were associated with a 12% relative risk reduction in fracture risk (p=0.0004) in a time span of approximately 3.5 years. Beneficial effects are greatest in the highest risk, elderly, slender population who have low calcium intake at baseline, but is still beneficial in the over-50 population as a whole. Comparing various doses of calcium, more benefit was seen with doses over 1200 mg/day of calcium. Although in the large category of "any" supplementation with vitamin D, no measurable benefit was seen over calcium supplementation alone; when higher doses of vitamin D (at least 800 IU) were used, there was additional benefit. Outcomes were similar regardless of gender. The authors suggest that calcium and vitamin D, when given at doses of at least 1200 mg/d and 800 IU/d respectively, improves BMD and reduces fractures in persons over age 50. ■

ARBs Favorably Affect Inflammatory Markers in Diabetics

Touyz RM, et al. *J Am Society of Hypertens.* 2007;1(3):189-199.

Discussions about the role of inflammation in generating endothelial dysfunction, atherosclerosis, and cardiovascular (CV) endpoints continue to generate interest. Antibiotic therapy has not improved CV outcomes, nor has modulation of Homocysteine or antioxidants. NSAIDs remain under a cloud. But perhaps the method by which inflammation is reduced is pertinent. To address this, a study of diabetic hypertensives was performed comparing one year of atenolol (ATN) therapy with valsartan (VAL).

At baseline, inflammatory markers (cytokines, chemokines, and adhesion molecules) were measured in both groups; additionally, a group of nonhypertensive subjects was included for comparison.

Compared with non-hypertensive controls, inflammatory markers were 2-4 fold higher in diabetic hypertensives at baseline. During treatment, glucose and lipid levels did not change, hence any variation in inflammatory markers would not be attributable to enhanced management of diabetes or dyslipidemia.

ATN and VAL lowered blood pressure to a similar degree, but there was marked disparity in effects upon inflammation: VAL reduced all three categories of inflammatory markers, but only cytokine IL-18 was reduced by ATN.

Treating diabetic hypertension with VAL provides broad reductions of inflammatory markers compared to atenolol. Whether modulation of inflammation will ultimately impact the CV outcomes of hypertension remains to be seen. ■

When Oral Therapy Fails in Type 2 Diabetes

Riedel AA, et al. *Am J Manag Care.* 2007;13:457-463.

One might assume that the proliferation of tools to manage type 2 diabetes (2DM) would augur well for levels of diabetic control. Unfortunately, that appears to not be the case. The progressive nature of the disease, hesitance of clinicians to advance therapy, reluctance to employ parenteral agents, and growing burden of obesity and sedentary lifestyle all contribute. Thiazolidinediones (TZDs, ie, pioglitazone, rosiglitazone) have shown promise as potent agents to reduce glucose. In the recently published ADOPT trial, durability of glucose control with rosiglitazone monotherapy was found to be superior to other comparators; at 5 years, the failure rate was lowest with rosiglitazone (15%), next lowest with metformin (21%), and greatest with sulfonylurea (34%).

Riedel assessed retrospectively the time to loss of control after adding a TZD to a regimen of either metformin or metformin plus sulfonylurea in a managed care popu-

lation of diabetics (n=579).

Several interesting insights are provided by this examination of a "real world" (as opposed to data from a randomized clinical trial) patient population. First, the addition of a TZD did enable the majority to achieve a goal of < 7.0%. Second, the mean time to failure was 1.3 years. Finally, the addition of TZD to metformin provided more durable glucose control than adding sulfonylurea to metformin. Clinicians must remain vigilant for early treatment failure of oral hypoglycemic agents. It happens very quickly in some patients. ■

A1c as a Screening Tool for Diabetes

Buell C, et al. *Diabetes Care.* 2007;30(9):2233-2235.

The most recent 2007 position paper from the ADA suggest that all adults over age 45 receive screening for diabetes by a fasting blood glucose (FBG). Measurement of FBG is not always convenient for patients. The National Health and Nutrition Examination Survey (NHANES) population provides a window of observation into the potential utility of A1c, as opposed to FBG for screening purposes.

Based upon the NHANES subset of 6,012 individuals who had both FBG and A1c measured, an A1c of 5.8% had a sensitivity of 86% and a specificity of 92% for the confirmed diagnosis of diabetes.

The ADA has to date not supported use of A1c for screening because: 1. Although there is a nationally standardized method for measuring A1c, not all laboratories use the same method, hence A1c can vary from lab to lab; 2. At the earliest stages of diabetes, the A1c may be less sensitive than either the FBG or postprandial glucose.

Since 50% of persons with newly diagnosed diabetes already possess one or more of the complications of diabetes at the time of diagnosis, it is obvious we are not diagnosing early enough. Since A1c can be obtained at any time of day, patients do not have to arrive at any particular time and may or may not be fasting. The authors suggest that (using the A1c method of the DCCT) an A1c < 6.0 is normal, 6.0-6.9% is prediabetic, and > 7.0% is diabetic. Finally, they offer they opinion that an A1c >5.8% could stimulate further investigation or closer observation. ■

Effects of Cinnamon on Glucose and Lipids

Blevins SM, et al. *Diabetes Care.* 2007;30(9):2236-2237.

The concept that cinnamon could affect glucose control was first addressed in 1990, which was subsequently supported by animal studies demonstrating improved insulin signal transduction, lowered glucose, and favorable effects upon lipids when cinnamon was administered. In 2003, a clinical trial in Pakistan gave further credence to the cinnamon-glucose relationship by showing that 40 days of cinnamon ingestion reduced fasting glucose, triglycerides, and LDL. Blevins, et al, performed the first study of cinnamon treatment in diabetics in the United States.

Sixty diabetic subjects were randomized to receive either 500 mg/d cinnamon or placebo, both administered in identical capsules each night with the evening meal. Study subjects were followed for 3 months. Fasting glucose, total cholesterol, LDL, HDL, triglycerides, insulin levels, and A1c were measured at baseline and monthly thereafter.

At study end, there were no discernible effects of cinnamon upon any of the variables.

There were large differences between this study population and that of the Pakistan trial. In addition to ethnicity, for instance, the fasting glucose and triglyceride levels in the American population were much lower than the Pakistani study subjects. However, the dose of cinnamon used in the Pakistan trial was much higher: 1-6g daily. A beneficial metabolic impact of cinnamon in type 2 diabetic Americans has not been confirmed. ■

Do Residents Have a Strong Enough Grasp of Statistics?

Windish DM, et al. *JAMA.* 2007;298(9):1010-1012.

Best utilization of current available literature requires skillful interpretation of the statistical methods used to design and implement a study, as well as critical appraisal skills for outcomes of the trial. Most currently practicing clinicians received little training in biostatistics, and while evidence-based medicine curricula in medical schools in the country are growing in number, they aren't yet universal. So, it's not surprising that resident physicians may not be as well equipped to address the statistical aspects of the literature as we would like.

To assess knowledge of residents in reference to statistics, a 20-question test was completed by 277 residents from 11 different residency programs in the United States. The questions addressed commonly encountered issues in clinical trials: p values, standard deviation, confidence intervals, statistical significance, odds ratios, specificity, sensitivity, etc.

Overall, the resident knowledge score was approximately 41% (out of 100%). Residents with previous epidemiology training performed somewhat better, as did residents who most recently entered training.

It is tempting to just look at "bottom lines" in clinical trials. Unfortunately, subtleties of interpretation can turn out to be critical. Several recent clinical trials have failed to achieve statistical significance for their primary endpoint, thus rendering the secondary endpoints uncertain, yet clinicians who are unaware of this statistical "boundary" may give credence to those secondary endpoints, which in essence, remain unproven. More attention to instruction in pertinent biostatistics during clinical years may be required to remediate some of these deficits. ■

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