

# Clinical Briefs in Primary Care<sup>™</sup>

The essential monthly primary care update

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## Toenail Chromium in Men With Diabetes and Cardiovascular Disease

**Source:** Rajpathak M, et al. *Diabetes Care.* 2004;27(9):2211-2216.

AT ONE TIME IN THE NUTRITION LITERATURE, chromium (CRM) was known as glucose tolerance factor. The role of CRM in glucose homeostasis was further corroborated by studies of Asians with diets high in polished rice (and hence, low in chromium) whose abnormal glucose metabolism was restored by CRM repletion. Because CRM intake is difficult to quantify, alternative metrics for CRM nutriture status include toenail chromium levels (T-CRM). Previous case-control data indicates that a low T-CRM is associated with increased risk of cardiovascular disease in the general population.

A group of participants in the Health Professionals Follow-up Study (n = 37,737) provided toenail clippings which were stored for analysis of trace elements. A cross-sectional analysis divided subjects into men with diabetes, diabetes and established cardiovascular disease, and healthy controls at baseline. Subjects were followed over approximately ten years to assess incident cardiovascular disease.

At baseline, healthy men had the highest T-CRM, followed by diabetics, and then diabetics with evident cardiovascular disease. Additionally, incident cardiovascular disease was greater in men with the lowest levels of T-CRM.

In persons with frank CRM insufficiency (which is generally not seen in the United States except for recipients of total parenteral

nutrition inadequately balanced with chromium) CRM supplementation is clearly beneficial. Whether CRM intake should be increased in any other group remains unknown. ■

## Combination of Fenofibrate and Rosiglitazone and HDL Cholesterol

**Source:** Normen L, et al. *Diabetes Care.* 2004;27(9):2241-2242.

THE PRIMARY FOCUS OF LIPID CONTROL, even amongst diabetics, remains the LDL level, since most accumulated data provides good support for improvement in cardiovascular outcomes subsequent and proportional to LDL reduction. HDL levels may be an even more potent predictor of cardiovascular outcomes, but have generally remained a secondary target, perhaps to some degree since pharmacotherapy specifically designed to and indicated for enhancement of HDL are lacking.

Thiazolidinediones (TZD), like rosiglitazone and pioglitazone are usually associated with favorable changes in HDL. Fibrates (eg, fenofibrate, gemfibrozil) are also often associated with favorable HDL changes, especially in the face of high triglycerides. It was anticipated then, that the combination would be equally, if not more, favorable for HDL levels.

Patients on combination TZD + fibrate were compared with controls on fenofibrate alone. Whereas fibrate alone produced a mean change of 19% increase in HDL, combination

therapy produced a 20-33% decrease in HDL!

The finding of unfavorable effects upon HDL when fibrate is combined with TZD is both unexpected and inexplicable. This small study (n = 33) will require further confirmation in a larger population, but suggests a perspicacious eye by clinicians in monitoring HDL levels in persons on combination therapy with TZD and fibrate. ■

## Outcomes for Patients with Diet-Controlled Diabetes

**Source:** Hippisley-Cox J, Pringle M. *Lancet.* 2004;363:423-428.

THE UNITED KINGDOM PROSPECTIVE diabetes Study (UKPDS) is the landmark clinical trial which forms the foundation for treatment of persons with type 2 diabetes (DM2). UKPDS showed that treatment with metformin, a sulfonylurea, or insulin reduced microvascular complications of DM2. According to this communication by Hippisley-Cox and Pringle, some clinicians in the United Kingdom identify a group of DM2 patients with mild diabetes who are felt to require only a minimum of interventions, such as diet alone.

To study this phenomenon, a cross-sectional study of 253,000 UK patients was performed which included 8,626 diabetics. Amongst this population of diabetics, 31.3% (2,700) had DM2 treated with no pharmacologic agents, hence identified as 'diet only.' Only a minority of all DM2 patients had had microalbuminuria testing (14.5%), retinal screening (9%), or screening for neuropathy (4.9%). For DM2 patients registered as 'diet

only,' diabetic monitoring procedures were performed even less frequently than for those on pharmacotherapy. For instance, likelihood of A1c monitoring was 71% less amongst 'diet only' DM2.

This UK population survey revealed that almost one-third of DM2 is managed by diet alone, accompanied by much less frequent monitoring of nephropathy, neuropathy, and retinopathy than is optimal. ■

## Erythromycin and the Risk of Sudden Death

**Source:** Ray W, et al. *N Engl J Med.* 2004;351:1089-1096.

**A**GENTS WHICH ALTER CARDIAC repolarization have been associated with torsades de pointes. Although erythromycin (ERY) is a generally safe and efficacious medication, it does have the potential to prolong cardiac repolarization, especially when drug levels are elevated. Because ERY is metabolized through the CYP-450 3A system, substances which block CYP3A (such as antifungal agents, diltiazem, and verapamil) can have a potent effect upon raising ERY levels, resulting in at least a doubling of ERY plasma levels when coadministered.

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To evaluate whether coadministration of ERY with CYP3A blockers is associated with any meaningful risk of cardiac adversities, data from a Tennessee Medicaid cohort (n = 1,249,943 person-years of follow-up) was examined to identify persons who had received ERY, CYP3A inhibitors, or both. As a control, persons who had not received antibiotics, as well as a comparator control of persons who had received amoxicillin (which has no measurable effect upon cardiac repolarization), was included.

Persons who had used ERY had twice as high a death rate from cardiac causes than persons who had not used antibiotics. Amoxicillin was not associated with an increase in cardiac deaths. Although ERY in the absence of a CYP450 3A inhibitor was not associated with an increase in sudden death, concomitant administration was associated with a greater than 5-fold increase.

Coadministration of ERY with CYP3A inhibitors is associated with a meaningful increase in risk of adverse cardiac events, and should be avoided. CYP3A inhibitors which fall into this risk category include (but are not limited to) ketoconazole, itraconazole, fluconazole, diltiazem, verapamil, troleandomycin, nefazodone, and protease inhibitors. ■

## Acute Hyperglycemia, Mood, and Cognitive Performance in Type 2 Diabetics

**Source:** Sommerfield AJ, et al. *Diabetes Care.* 2004;27(10):2335-2340.

**H**YPERGLYCEMIA IN DIABETES IS ASSOCIATED with increased incidence of neuropathy, nephropathy, and retinopathy. Data about the effects of hyperglycemia upon cognitive function have been conflicting, however. To test whether hyperglycemia impacts cognitive function in type 2 diabetics, a study was performed by maintaining glucose levels using the glucose clamp method over brief, monitored time intervals.

Study subjects underwent cognitive testing after a sustained period of blood glucose levels maintained at either 81 mg/dL or 297 mg/dL. Testing modalities included complex visual scanning, motor performance, speed of coding, reaction time, auditory verbal learning (intermediate and delayed), visual

memory, attention, digit span, and letter/number sequencing. The University of Wales Institute of Science and Technology mood checklist was also administered.

Although not all metrics registered significant impairment during hyperglycemia, complex visual scanning, coding performance, and reaction time were significantly decremented. Digit Span and Letter/number sequencing were also impaired. For mood, decreased happiness and alertness were found, as well as an increased sense of agitation during periods of sustained hyperglycemia.

Because this study evaluated persons during a very brief window of observation (80 minute intervals), it is impossible to ascertain the long-term effect of hyperglycemia upon cognitive and mood function. Nonetheless, these data support energetically seeking euglycemia in an effort to maintain best cognitive function and mood. ■

## Psychosocial Risk Factors and Risk of Acute MI

**Source:** Rosengren A, et al. *Lancet.* 2004;364:953-962.

**S**TUDIES IN NORTH AMERICA, Europe, and Japan have provided some support for the concept that emotional stress is a risk factor for coronary heart disease (CHD), but there is scanty information about other populations. In addition to limited information, defining what actually constitutes stress, and how to measure it, has been elusive.

This study of 12,461 cases of acute MI in 52 countries included an assessment of psychological stress by means of questions about stress at home and at work. Stress was defined as "feeling irritable, filled with anxiety, or having sleeping difficulties as a result of conditions at work or at home." Patients were also asked to quantify their stress by indicating whether it was present never, some periods, several periods, or permanently.

All measurements of stress were more prevalent in persons who had suffered an acute MI. Confounders to the association included the fact that those who reported more stress also had a higher BMI and a greater incidence of smoking. According to this analysis, stress accounts for as much as 33% of the population attributable risk for MI, and hence may have been somewhat neglected as an important modifiable risk factor. ■