chain synthesis [Cabral WA et al. *Nat Genet* 2007]; FKBP65, which codes for a protein involved in formation of a triple helix from the alpha chains; and BMP1, which codes for an enzyme responsible for cleavage of the alpha chain [Marini JC, Blissett AR. *J Clin Endocrinol Metab* 2013].

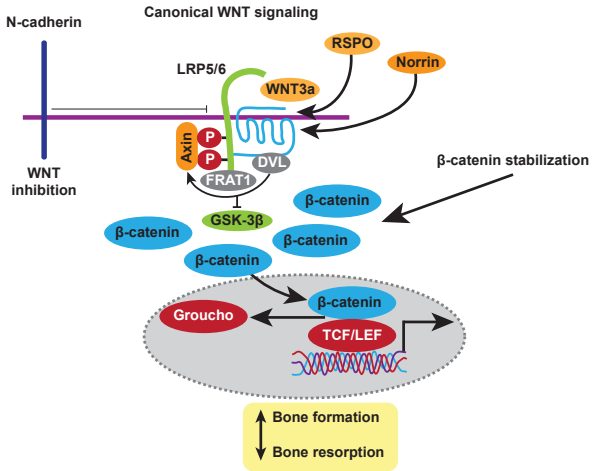
In contrast to these types with autosomal recessive inheritance, OI type V is caused by a dominant defect in IFITM5, the gene that encodes BRIL protein [Marini JC, Blissett AR. *J Clin Endocrinol Metab* 2013]. Phenotypically, this condition is associated with striking development of hyperplastic callus [Glorieux FH et al. *J Bone Miner Res* 2000], but although all patients have the same point mutation in the 5'-UTR of the gene, how this leads to this OI phenotype and bone fragility remains unknown [Rauch F et al. *J Med Genet* 2013; Cho TJ et al. *Am J Hum Genet* 2012; Semler Oet al. *Am J Hum Genet* 2012].

In addition to these forms of OI that are linked to collagen processing in some way, other gene defects have been described, although their exact association with collagen is unknown.

The gene SERPINF-1 codes for a protein known as pigment-epithelium derived factor (PEDF), and mutations in this gene produce a disease phenotype that was originally characterized as OI type VI. Clinically, children with this type are born without bone deformities, and do not experience their first fracture until they are 6 to 12 months old, but then develop progressively more fractures, leading to bone deformity [Homan EP et al. *J Bone Miner Res* 2011].

WNT proteins and their signaling cascades are key regulators of osteoblast activity, and mutations in the gene WNT1 have also been shown to cause OI, due to loss of WNT signaling (Figure 2) [Fahiminiya S et al. *J Med Genet* 2013].

Figure 2. The WNT Signaling Pathway



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Despite the paradigm shift for OI as a collagen-associated disorder, Prof. Rauch concluded by raising some unsolved philosophical questions relating to the more recent genetic findings, specifically as to whether OI should be defined by its clinical picture or in relation to its affected genes.

Responses to Estrogenic Hormonal Treatment in Menopausal Women

Written by **Nicola Parry**

Virginia Miller, MBA, PhD, Mayo Clinic, Rochester, Minnesota, USA, presented data from a multicenter study to compare outcomes of different formulations of estrogenic hormonal treatments in menopausal women. Results of the trial demonstrated a null effect on cardiovascular disease (CVD) progression in association with hormone treatment, as well as a reduction in menopausal symptoms, and maintenance of bone mineral density.

Genetic variations in estrogen metabolism and estrogen receptors account, in part, for the variability in clinical symptoms of menopause such as vasomotor instability and depression, in addition to the variability in response to exogenous hormones.

The modality of hormone delivery impacts the efficacy of the treatments because oral formulations absorbed directly into the hepatic-portal circulation have a different pharmacokinetic and pharmacodynamic profile than transdermal products, which directly enter the systemic circulation for example, oral products have a greater effect on some factors produced by the liver including low- and high-density lipoprotein cholesterol (LDL-C and HDL-C, respectively), inflammatory cytokines and proteins of the coagulation cascade [De Lignieres B et al. *J Clin Endocrinol Metab* 1986; Scarabin PY et al. *Lancet.* 2003; Bush TL et al. *Circulation* 1987].

Data from observational studies suggested that hormone therapy administered at menopause decreased risk factors for CVD and its adverse events [Grodstein F et al. *N Engl J Med* 1996; Psaty BM et al. *Arch Intern Med* 1994; Falkeborn M et al. *Br J Obstet Gynaecol* 1992; Hunt K et al. *Br J Obstet Gynaecol* 1990; Criqui MH et al. *Am J Epidemiol* 1988; Bush L et al. *Circulation* 1987].

The Kronos Early Estrogen Prevention Study [KEEPS; Harman SM et al. *Climacteric* 2005] was a multicenter, randomized, placebo-controlled, 4-year trial to compare the effectiveness of oral and transdermal estrogenic hormonal formulations (both accompanied by an oral progesterone), and placebo, in preventing progression of atherosclerosis as measured by carotid intimal medial thickness in women aged 42 to 58 years who were within 36 months of their final menstrual period. Secondary outcomes included coronary

arterial calcification, blood lipids and inflammatory markers, and changes in menopausal symptoms and sexual function. Seven hundred and twenty-eight women were enrolled in the trial, and 584 completed it.

In the oral formulation group (conjugated equine estrogen 0.45 mg/day), levels of HDL-C were increased, and LDL-C were decreased, compared with those in the transdermal formulation (50 µg/day 17β-estradiol) and placebo groups. However, there was no significant effect on CVD progression. This null effect on progression of carotid intimal medial thickening, however, at least indicates that CVD was not accelerated by hormonal treatment over 4 years. Additional treatment effects in women taking estrogen/progesterone included a reduction of menopausal symptoms (Figure 1) and prevention of bone loss (Figure 2) [Farr JN et al. *J Clin Endocrinol Metab* 2013].

Figure 1. Changes in Menopausal Symptoms Throughout the KEEPS Trial

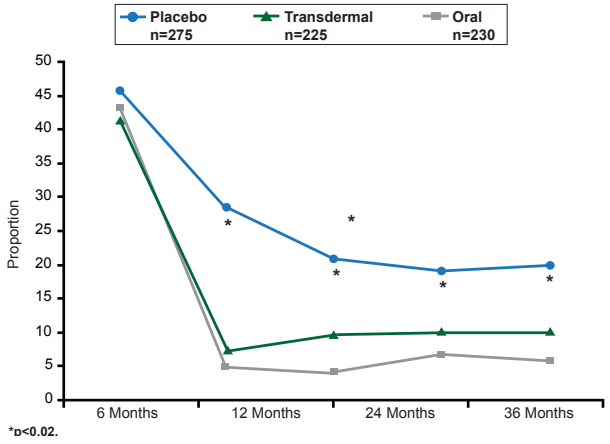

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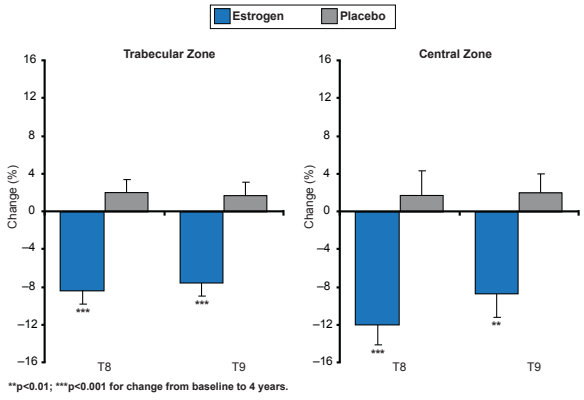
Figure 2. Changes in Bone Mineral Density Throughout the KEEPS Trial



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Dr. Miller concluded by emphasizing the need for further exploration of emerging data to determine whether hormonal treatment does have a preventive effect on CVD progression over a longer time period. She also stressed the importance of avoiding generalizations about the effects of hormone treatments in this era of personalized treatments. In particular, the different types, doses, and delivery modes of hormone treatments must be carefully considered in order to maximally impact the individual health of patients.

Individualized Diabetic Care Is Key for Athletic Success

Written by **Nicola Parry**

Anne Peters, MD, University of Southern California, Los Angeles, California, USA, discussed the challenge of caring for athletes with type 1 diabetes (T1D). Since athletic training and competition can markedly disturb blood glucose control, it can be difficult to manage diabetes in individuals who exercise excessively. Dr. Peters highlighted the importance of personalized care to optimize glycemic control for maximal health benefits and athletic success.

The Nutrition and Athletic Performance Joint Position Statement of the American College of Sports Medicine, American Dietetic Association, and Dietitians of Canada, most recently revised in 2009, suggests that athletes should eat 6 to 10 g/kg body weight of carbohydrates per day [*Med Sci Sports Exerc* 2009]. For many patients with T1D, this can represent a challenge in insulin dosing. Higher amounts of carbohydrates require larger doses of insulin but increased workouts may improve insulin sensitivity and lower insulin requirements. This balance between carbohydrate ingestion, exercise and insulin dosing can create a difficult balance for athletes to maintain.

Dr. Peters emphasized the need to understand the basics of exercise physiology. Muscles obtain glucose from their glycogen stores as a primary energy source, and once these sources are depleted, there is a balance between glucose production and uptake by exercising muscle. Immediately following exercise, in nondiabetic individuals, catecholamine levels rapidly decline and insulin increases, with restoration of muscle glycogen. Consequently, in individuals with T1D, glucose uptake may occur to such an extent that they become very sensitive to insulin and potentially hypoglycemic.

For individuals with T1D, the fear of hypoglycemia is the strongest barrier to regular physical activity, and is certainly a concept that athletes often struggle with [Brazeau AS et al. *Diabetes Care* 2008]. Although many athletes report reduced performance when their blood glucose levels are high, they conversely run into other problems if blood sugar