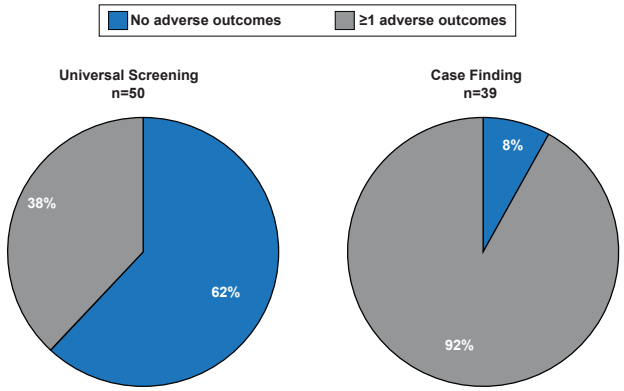
disease during pregnancy, with continued debate between the American College of Obstetrics and Gynecology (ACOG), The Endocrine Society (TES), and the American Thyroid Association (ATA).

For example, ACOG does not recommend treatment of SCH, while TES recommends treatment with levothyroxine in women who are positive or negative for thyroid antibodies. The ATA recommends treating SCH in antibody positive women, but considers the data insufficient to recommend for or against treating SCH during pregnancy in women with a thyroid-stimulating hormone between 2.5 and 10.0 who are antibody negative.

Figure 2. Outcomes Associated With Treating Hypothyroid Pregnant Women



Souce: Negro R et al. *J Clin Endocinol Metab* 2010.

Additionally, both the ATA and TES recommend screening for thyroid disease in all groups who have an increased risk for thyroid disease. In fact, a subgroup of the members who created guidelines for TES recommended screening all pregnant women for thyroid disease. On the other hand, ACOG recommends screening only a small subgroup of pregnant women.

Although universal guidelines for management of thyroid disease during pregnancy would provide clarity for patients and clinicians, according to Dr. Stagnaro-Green, there are numerous barriers to their establishment. Perceptions vary between the different organizations regarding the importance of the topic, and each has a different philosophy on granularity according to its focus. Additionally, organizations interpret data variably, and differ in their ideas on how much data are needed to produce a guideline. He remarked that although a consensus opinion is unlikely due to the difference in granularity of guidelines and interpretation of data between ACOG and the other two societies, the outcome of future studies might provide some impetus for these organizations to work together to produce consensus guidelines for clinicians and patients.

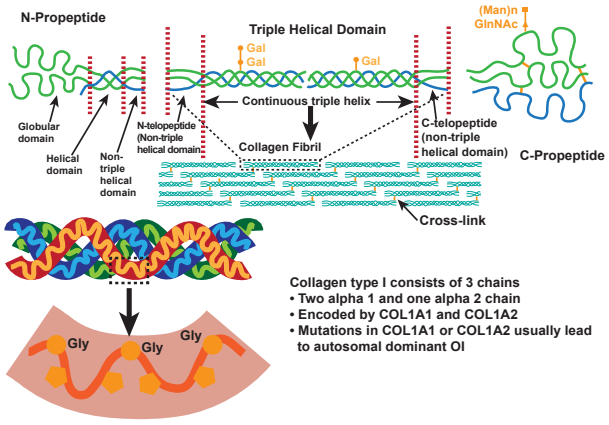
What's New in Osteogenesis Imperfecta?

Written by **Nicola Parry**

Frank Rauch, MD, Shriners Hospital for Children, Montreal, Quebec, Canada, discussed the pathophysiology of osteogenesis imperfecta (OI), in particular in relation to some rare, recessive forms of the condition. Although historically considered a collagen-related condition, predominantly due to mutations in genes that encode the alpha chains of collagen type I, mutations in various noncollagenous genes have also more recently been discovered to cause some forms of OI.

This inherited bone disorder is typically characterized by reduced bone mass, bone fragility, and often short stature. Most cases are due to dominant mutations in one of the two genes that encode alpha chains of collagen type I (COL1A1 or COL1A2; Figure 1), and disease severity varies across a range of four classical phenotypes: type I is the mildest form, characterized by patients with straight legs and spine; type II is the perinatal lethal form; type III is the most severe form seen in survivors; and type IV is intermediate in severity between types I and III. Some extraskeletal manifestations are also variably associated, including blue sclera, dentinogenesis imperfecta, and joint hyperlaxity [Sillence DO et al. *J Med Genet* 1979].

Figure 1. The Structure of Type I Collagen



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However, recessive types of OI have now also been described, caused by mutations in noncollagenous genes involved in various aspects of bone formation. OI due to mutations in genes associated with proteins involved in collagen type I processing are rare, but 8 forms are currently known. These include mutations in prolyl 3-hydroxylase 1, a gene that codes for an enzyme involved in collagen alpha 1

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].

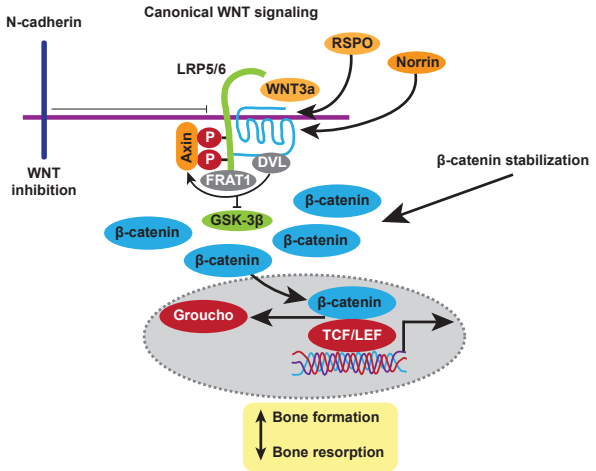
In contrast to these types with autosomal recessive inheritance, OI type V is caused by a dominant defect in IFITM5, the gene that encodes BRIL protein [Marini JC, Blissett AR. *J Clin Endocrinol Metab* 2013]. Phenotypically, this condition is associated with striking development of hyperplastic callus [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