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EDITORIAL

Editorial pediatric endocrinology series european journal of pediatrics "New developments and therapies in pediatric endocrinology"

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The landscape of paediatric endocrinology has changed considerably over the last decade. The advances in genetics have resulted in a wave of molecular research in paediatric Endocrinology, which has resulted in a better understanding of genetic causes and the molecular basis of endocrine conditions, which in turn has led to the identification of molecular targets for treatment. Together with a focus on rare diseases, this has resulted in developing new therapies for specific endocrine conditions. The series will update the readers on these advances in Paediatric Endocrinology.

The first example of translation into therapeutic advancement due to advances in knowledge is the development of drugs to increase bone mass as a result of increased knowledge of the key genes involved in the regulation of bone mass [1, 2]. Genetic analysis of patients with osteoporosis or high bone mass conditions has paved the way for these advances. The molecular pathways that regulate bone formation, resorption, and remodelling have been uncovered over the last two decades. The Wnt- beta-catenin signalling pathway plays a crucial role in the regulation of bone mass, and mutations in key pathway regulators, such as *LRP5* and *SOST* result in phenotypes of extremely low bone mass or high bone mass [3]. Loss-of-function of *LRP5* results in osteoporosis-pseudoglioma syndrome, whereas gain-of-function results in osteosclerosis. Likewise, mutations in *SOST*, encoding sclerostin, an inhibitor of Wnt signalling, result in the high bone mass condition sclerosteosis. Antibodies against sclerostin are now used as new therapeutic for osteoporosis [4]. Another pathway involved in bone metabolism regulation is the the RANK (Receptor Activator and Nuclear Factor Kappa-B)-RANKL (RANK Ligand)-OPG (osteoprotegerin) system, activation of the latter leading to bone resorption. Denosumab is an antibody directed against RANKL that reduces the binding of RANKL to RANK and, therefore, reduces bone resorption. Denosumab is approved for osteoporosis in adults [5], and trials are ongoing for its use in rare bone diseases in adults [6]. Denosumab is used in exceptional circumstances in children [7, 8], and there are ongoing trials, although rebound hypercalcaemia on cessation of treatment is a challenging side effect [9]. Therefore, currently bisphosphonates remain the mainstay for treatment in children with bone fragility.

The generation of normal ranges for bone mineral apparent density, which corrects for the size of the bones and thus the child's height, for the most common DXA scanners, has been a major achievement [10], and is now used in daily practice. The use of BMAD is essential, as BMD is not a reliable parameter for bone density in children.

Identifying the crucial pathways in the regulation of bone development and bone mass, has also led to the identification of new genetic causes of osteogenesis imperfecta, for which now more than 20 subtypes have been identified, each with its genetic cause [11].

Other significant breakthroughs relating to bone and cartilage are in the treatment of achondroplasia and X-linked hypophosphataemic rickets.

Achondroplasia is due to an activating mutation in *FGFR3*, resulting in over-activation of FGFR3 signalling and subsequently MAPK signalling leading to premature chondrocyte differentiation. Elegant mouse studies showed that inhibition

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of the MAPK pathway improves the effects of overactivated FGFR3 pathway and improves the premature chondrocyte differentiation. CNP (cartilage natriuretic peptide) inhibits the MAPK pathway by binding to its receptor NPR2 [12]. Vosoritide, a long-acting CNP analogue, has been developed as a new therapeutic for achondroplasia [13, 14]. Treatment improves height velocity in children with achondroplasia, and has recently been licenced for the treatment of patients > 2 yrs of age [15–17]. Additionally, other new therapeutics for the treatment of achondroplasia are in the pipeline.

Furthermore, small trials are being conducted to assess whether vosoritide can improve growth in children with other conditions with restricted growth.

X-linked hypophosphataemic rickets is the most common form of genetic rickets and is due to mutations in the *PHEX* gene, located on the X chromosome [18]. Patients have hypophosphataemia and rickets, with variable severity, as well as many other sequelae such as short stature, dental abscesses and craniosynostosis. Studies in the last decade identified that *PHEX* mutations resulted in increased concentrations of FGF23, a circulating peptide hormone produced in osteocytes, that stimulates renal phosphate excretion. An antibody against FGF23, Burosumab, is now available for the treatment of XLH and improves phosphate concentrations, bone pain, rickets and bowing [19, 20]. Correct and timely identification of these patients is therefore crucial.

Hypoparathyroidism in children and adults is conventionally treated with alphacalcidol with or without calcium supplementation. Recombinant PTH is available, but is licenced only for short term treatment of osteoporosis in adults. However, conventional treatment is insufficient in some children, especially those with autosomal dominant hypocalcaemia, due to mutations in the *CaSR* gene, and those with APECED (autoimmune polyendocrinopathy-candidiasis-ectodermal dysplasia syndrome). Recently, PTH injections and pump treatment have been used in these groups of children [21, 22]. Long-acting PTH molecules and negative modulators of the calcium sensing receptor have been developed recently and may become available for treatment in hypoparathyroidism in children [23, 24].

Diagnostics of short stature have improved with genetic advances too. GH deficiency may be overdiagnosed, and there is a move to re-testing of GH deficiency in puberty [25]. Genetic variants or deletions in the GH signalling pathway such as those in *GHR* (growth hormone receptor) [26], *STAT5B* (signalling transducer and activator of transcription 5B) [27], *IGF1* (insulin-like growth factor 1) [28] and *IGF1R* (IGF1 receptor) [29] may be more common than initially thought, but seem to be still far rarer than variants in genes involved in bone or cartilage development as a cause for short stature. Examples of such relatively frequent causes for short stature are mutations/deletions of *SHOX* (short stature gene on the X chromosome), *ACAN* (aggrecan), *NPR2* (natriuretic peptide receptor 2) and *CUL7/OBSL* (leading to 3M syndrome) [30]. Another common cause for short stature is Noonan syndrome, one of the 'rasopathies' due to abnormal RAS signaling [31]. GH treatment is now licensed for *SHOX* deficiency and Noonan syndrome, but no other remedy for short stature is available [32, 33]. Drugs developed for treatment of achondroplasia that modulate the FGFR3 and MAPK pathways may prove useful for the treatment of related milder growth conditions.

The next group of conditions that are starting to see a change in landscape, are obesity, type 2 diabetes and Prader-Willi Syndrome. The ongoing epidemic of obesity in children [34] is leading to an increased incidence of paediatric type 2 diabetes (T2D). Outcome of paediatric onset type 2 diabetes is poor and worse compared to Type 1 diabetes (T1D) or compared to adults with T2D [35]. No drugs have been available for treating T2D in children besides Metformin and insulin for many years, but recently GLP1 agonists (eg Liraglutide, Dulaglutide, Semaglutide) have been added as a therapeutic option for T2D and obesity [36–38]. They have been shown to reduce HbA1c and weight, and are likely going to be helpful in both T2D and obesity, although it is too early to tell how well they are tolerated by paediatric patients in the real world. Over the last two decades genetic causes of early-onset obesity have been unravelled, and this has been translated into gene panels for assessment of monogenic obesity in patients with early-onset obesity, increasing our ability to pinpoint causes of severe early-onset obesity [39]. The melanocortin 4 receptor (MC4R) pathway plays a crucial role in the regulation of hunger and satiety. Sufficient levels of melanocyte-stimulating hormone (MSH) neuropeptides are required to activate MC4R, resulting in a reduction in hunger and a concomitant increase in energy expenditure through actions in the hypothalamus [40]. Indeed, MC4R mutations are the most common monogenic cause of obesity [41]. In a new therapeutic development, an MC4R agonist (Setmelanotide) has been developed that activates the MC4R pathway. Mutations in the pathway upstream of MC4R are sensitive to treatment with Setmelanotide [42]. This upstream pathway consists of leptin binding to leptin receptors (LEPR) on hypothalamic pro-opiomelanocortin (POMC) neurons, which in response will produce POMC. POMC is then cleaved into melanocortin ligands (by PCSK-1) which bind to and activate the melanocortin-4 receptor pathway. Mutations in the key genes in this upstream pathway (*POMC*, *PCSK1*, *LEPR*) cause severe early-onset obesity and Setmelanotide is now available for treatment for these patients [43].

Bariatric surgery is also a therapeutic option to induce weight loss in adolescents with severe obesity, and has been used with increasing frequency over the last 5–10 years.

Treatment for PWS has seen progression too. The advantage of early GH treatment, starting before the age of 1 year, has become more clear [44]. Early diagnosis therefore is

paramount and the feasibility of screening is being assessed [45]. There have been multiple clinical trials to improve hyperphagia in PWS, e.g. with oxytocin [46, 47], carbetocin [48], unacylated ghrelin [49] and diazoxide choline controlled-release (DCCR) [50] with DCCR trials being in the most advanced stage.

In thyroid disease, there have been advances in our knowledge and treatment of the rare X-linked condition of MCT8 deficiency (also known as Allan-Herndon-Dudney Syndrome) [51, 52], and in the genetics of congenital primary and central hypothyroidism [53–55]. New guidelines for the treatment of paediatric Graves' disease have been developed by the European Thyroid Association [56]. New therapies for Graves' disease may be on the horizon [57].

Last but not least, is the progression in polycystic ovary syndrome (PCOS). PCOS is a challenging condition to diagnose and treat in adolescents. Several guidelines for PCOS have been published [58], although the majority are focused on adults rather than adolescents. The use of anti-androgens as a therapeutic option is still being assessed [59] and may hold some hope for the future.

We are confident that you will enjoy reading and learning from this Series "New Developments and Therapies in Paediatric Endocrinology".

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