Institution: Queen Mary University of London

Unit of Assessment: A1 (Clinical Medicine)

Title of case study: Treatment of adult growth hormone deficiency

1. Summary of the impact

Research at Queen Mary established the beneficial effects of adult growth hormone (GH) replacement. Prof Korbonits' team pioneered careful GH dose titration and adjustment of other concomitant pituitary hormone replacements, both crucial for effective and safe treatment. Collaborative research between adult and paediatric endocrinologists established a new model of GH deficiency treatment between completion of linear growth and full maturity at age 25. Findings led to [a] revised guidelines and policy in UK, Europe and USA; [b] new service models (especially at the paediatric-adult transition); [c] significant changes in clinical practice, [d] improved patient outcomes, notably dramatically improved quality of life, reduced cardiovascular risk and improved survival, [e] reduced costs.

2. Underpinning research

Background: Hypopituitarism affects at least 1 in 10,000 people. The commonest cause is pituitary tumours. The observation in 1990 of increased mortality in adult hypopituitary patients on conventional hormone replacement regimens (standardised mortality ratio, SMR, approximately 2:1 and 3:1 in males and females respectively) prompted detailed examination of the metabolic consequences of hormonal deficiencies, especially the impact of GH deficiency and replacement.

Aim: To evaluate the impact of GH replacement in adult and adolescence hypopituitary patients, optimise dose regimens, document changes in cardiovascular and bone risk factors and quality of life, and explore how best to adjust other pituitary hormone replacement.

Key studies and findings: The Department of Endocrinology at Queen Mary, led by Professor John Monson and including Profs Drake & Gelding, Drs Carroll, Swords, Agha, Brooke and Weaver, was at the forefront of this endeavour in collaboration with paediatric endocrinologist Prof Martin Savage and team. From 1993, using prospective placebo-controlled and observational studies, the team has been made pivotal contributions to the knowledge base on GH deficiency. Highlights include:

- The team demonstrated that GH deficient patients have a highly adverse cardiovascular risk profile and that this risk could be significantly reduced with GH replacement. In particular, we have shown systematically that GH replacement improves cardiovascular risk factors e.g. it reduces LDL-cholesterol by a mean of 0.4mmol/l [1].
- This department was the largest contributor to the major multinational database (KIMS) examining the impact of GH replacement on various indices of well-being and health and these data led to the introduction of the 2003 NICE guidelines on adult GH deficiency. This database has been crucial in documenting the impact of GH replacement on morbidity and mortality in a large cohort of GH deficient patients (see 'Impact' below).
- The research showed that GH replacement significantly improves overall well-being and energy levels, as demonstrated by reduction of the disease-sensitive QoL-AGHDA (Quality of Life – Assessment of GH Deficiency in Adults) score from median 15 to 7 [2,3].
- The team tested a number of approaches to establish the appropriate method of careful dose-optimisation for GH replacement in adults and adolescents [4].
- The team established optimal management of GH deficiency in the critical period between adolescence and adulthood, when linear growth is complete, which had previously been the subject of much clinical debate [4,5,6,7]. A structured programme of collaborative clinical care led the way in establishing a model for optimal paediatric to adult transitional care of endocrine disorders. The model, sited in the adult endocrine clinic, staffed by paediatric and adult endocrinologists and specialist nurses, was the first of its kind in the UK. Subsequent close paediatric-adult research collaboration led to original data that was pivotal in the 2003 NICE Guidance on GH therapy in GH deficient patients during transition from paediatric to adult care.
- In addition to the observed bone density improvement in adults [5], in adolescents the team showed, in a multicentre controlled trial co-ordinated from Queen Mary, that GH treatment after

completion of linear growth until acquisition of peak bone mass improves bone mineral density by 4% and lean body mass by 4% over 1 year, compared to non-treated controls [6,7].

- In prospective interventional studies they have demonstrated the important interactions between GH replacement and other hormonal systems, particularly the thyroid axis, and the effect of GH on increasing metabolic clearance of cortisol and the potential adverse effect of this phenomenon in patients with partial ACTH deficiency [8,9].
- They have shown a reduction on societal and healthcare costs for GH deficient patients [3].
- The adverse impact of GH deficiency on psychological well-being and energy levels, and the benefits of GH replacement on these aspects were clearly demonstrated. This provided the major evidence base for NICE guidance on the treatment of GH deficiency (see 'Impact').

3. References to the research

1. Weaver JU, Monson JP, Noonan K, John WG, Edwards A, Evans KA, &Cunningham J. The effect of low dose recombinant human growth hormone replacement on regional fat distribution, insulin sensitivity, and cardiovascular risk factors in hypopituitary adults. Journal of Clinical Endocrinology and Metabolism 1995; 80: 153-159.
2. Koltowska-Haggstrom M, Mattsson AF, Monson JP, Kind P, Badia X, Casanueva FF, Busschbach J, Koppeschaar H P & Johannsson G. Does long-term GH replacement therapy in hypopituitary adults with GH deficiency normalise quality of life? *European Journal of Endocrinology* 2006; 155: 109-119.
3. Hernberg-Stahl E, Luger A, Abs R, Bengtsson BA, Feldt-Rasmussen U, Wilton P, Westberg B, Monson JP. Healthcare consumption decreases in parallel with improvements in quality of life during GH replacement in hypopituitary adults with GH deficiency. *Journal of Clinical Endocrinology and Metabolism* 2001; 86: 5277-5281.
4. Drake WM, Coyte D, Camacho-Hübner C, Jivanji NM, Kaltsas G, Wood DF, Trainer PJ, Grossman AB, Besser GM, Monson JP. Optimising growth hormone replacement therapy by dose titration in hypopituitary adults. *Journal of Clinical Endocrinology and Metabolism* 1998; 83: 3913-3919. *and* Drake WM, Howell SJ, Monson JP, Shalet SM. Optimizing GH therapy in adults and children. *Endocrine Reviews* 2001; 22: 425-450.
5. Drake WM, Rodriguez-Arnao J, Weaver JU, James I, Coyte D, Spector T, Besser GM, Monson JP. The influence of gender on the short and long term effects of growth hormone replacement on bone metabolism and bone mineral density in hypopituitary adults – a five year study. *Clinical Endocrinology* 2001; 54: 525-532.
6. Carroll PV, Drake WM, Maher KT, Metcalfe K, Shaw NJ, Dunger DB, Cheetham TD, Camacho-Hubner C, Savage MO, Monson JP. Comparison of continuation or cessation of growth hormone (GH) therapy on body composition and metabolic status in adolescents with severe GH deficiency at completion of linear growth. *Journal of Clinical Endocrinology and Metabolism* 2004; 89: 3890-3895.
7. Drake WM, Carroll PV, Maher KT, Metcalfe KA, Camacho-Hubner C, Shaw NJ, Dunger DB, Cheetham TD, Savage MO, Monson JP. The effect of cessation of growth hormone (GH) therapy on bone mineral accretion in GH-deficient adolescents at the completion of linear growth Journal of Clinical Endocrinology and Metabolism 2003; 88: 1658-1663
8. Agha A, Walker D, Perry L, Drake WM, Chew SL, Jenkins PJ, Grossman AB, Monson JP. Unmasking of central hypothyroidism following growth hormone replacement in adult hypopituitary patients. *Clinical Endocrinology* 2007; 66: 72-77.
9. Gelding SV, Taylor NF, Wood PJ, Noonan K, Weaver JU, Wood DF, Monson JP. The effect of growth hormone replacement therapy on cortisol-cortisone interconversion in hypopituitary adults: evidence for growth hormone modulation of extrarenal 11 beta-hydroxysteroid dehydrogenase activity. *Clinical Endocrinology* 1998; 48: 153-162.

The research was supported by the Wellcome Trust, Queen Mary, NHS and visiting Fellowship from Beaumont Hospital and by unrestricted educational pharmaceutical industry grants.

4. Details of the impact

4a: Paradigm shift in how GH deficiency is conceptualised

Prior to mid-1990s, GH deficiency was primarily a paediatric disease focusing on achieving adequate stature. This research, together with other groups and collaborators, demonstrated symptoms and complications of adult GH deficiency, particularly its effect on lipid metabolism and (hence) cardiovascular risk, bone and quality-of-life and shown the importance of replacement after the cessation of linear growth. Professors Monson and Savage have given over 30 plenary lectures and talks on this topic at scientific, clinical and patient care fora 1993-2013, including lectures to GPs, trainees, meetings organised by the Royal College of Physicians and CPD.

4b: Change in national policy and clinical management guidelines

The team's work in adult and transitional-age GH-deficient patients was critical in informing the NICE guidance on the management of GHD in adults and the optimum treatment of this condition in the transition from childhood to adulthood. The NICE guidance was based on detailed cost effectiveness modelling [10]. The work has informed other national and international clinical guidelines. In particular, our recommendations feature in the 2002 Society for Endocrinology guideline on management of growth hormone deficiency in adults [11].

The Growth Hormone Research Society published a critical evaluation of the safety of recombinant HGH administration, which drew on the work of this group [12]. The team's research into thyroxine and glucocorticoid replacement established that patients must be reassessed after initiation of GH treatment. This recommendation is now also incorporated in drug prescribing information both in UK and internationally (see for example this from USA [13]). The new clinical care model, informed by this research, of replacing GH in adolescents so as to optimise peak bone mass and lean body mass, has now become the standard of care for this patient group nationally and internationally as accepted by the European Society of Paediatric Endocrinology [14].

4c: Establishing a new 'gold standard' service model

The formal paediatric-adult endocrine service at Barts led the way in establishing the model for transitional care of complex endocrine disorders, which is consistent with the 2006 Department of Health Guidance publication [15]. This model requires considerably greater collaboration between paediatric and adult endocrinology clinics than was previously the case.

4d: Change in clinical practice

Following the team's research publications (mostly between 1995 and 2001), and the incorporation of their recommendations into NICE guidelines in 2003, prescription rates for GH in the UK increased, as confirmed by Department of Health data (Figure 1) [16].

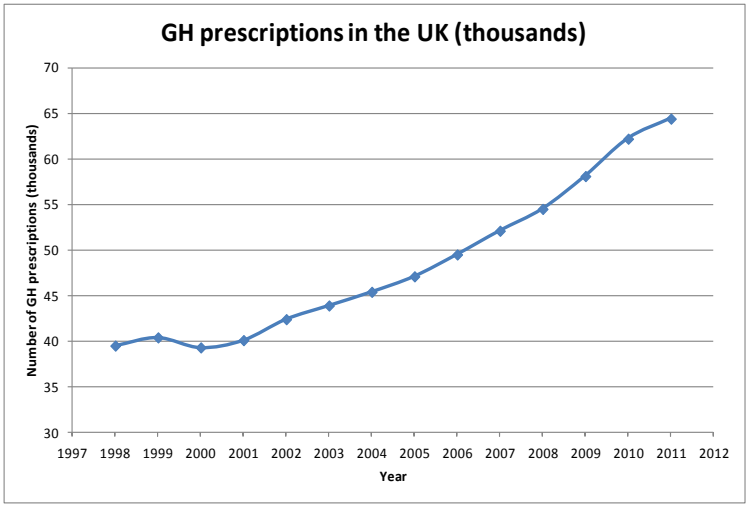

Figure 1; Number of GH prescriptions in the UK by year. The inflection in the curve starting in 2002 reflects the impact of clinical research in hypopituitary adults.

4e: Improved clinical outcomes (reduced morbidity)

GH replacement improves health, psychological well-being and quality of life (reference 3 above). Cardiovascular risk is reduced (reference 1 above) and real-time data from the KIMS database

have confirmed that standardised mortality ratios in hypopituitary adults receiving GH replacement are lower than the high rates documented in 1990 (2.0 in men and 3.0 in women) to a mean of 1.2 (0.94 in men and 1.56 in women). KIMS data also demonstrate that these improvements translate into a reduction in socio-economic costs (reference 3 above).

4f: Establishing a methodological approach to endocrine research in UK

This team's initiation and leadership of a combined adult-paediatric endocrinology UK multicentre study focused on the continuation of GH replacement in adolescents in optimising peak bone mass and lean body mass development was the first multi-centre controlled trial of its kind in this condition. Since that trial, other high-quality multi-centre trials of similar design have been initiated and supported by the clinical endocrinology community – see for example [17].

4g: Supporting informed choice by patients and informing the public

A summary of these research findings is distributed by the Pituitary Foundation in a patient booklet available to download free from their website: 'The Pituitary Gland' in 2012 [18]. Direct patient comments support the positive effects documented in clinical trials [19].

5. Sources to corroborate the impact

10. NICE Guideline. Growth Hormone Deficiency (Adults) – Human Growth Hormone. TA64 (2003). http://guidance.nice.org.uk/TA64. Professor Monson is referenced in Appendix B.
11. Society for Endocrinology Guideline on Management of Growth Hormone Deficiency in Adults 2002. See pages 28 – 33 for references to 10 papers co-authored by Prof Monson. http://jcem.endojournals.org/content/86/5/1868.full
12. Christiansen JS, Bengtsson BA, Thorner M et al. Critical evaluation of the safety of recombinant human growth hormone administration: statement from the Growth Hormone Research Society. Journal of Clinical Endocrinology and Metabolism 2001; 86: 1868-70. http://jcem.endojournals.org/content/86/5/1868.full
13. US Food and Drug Administration safety information: Somatropin [rDNA origin] for injection 2012. http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm203732.htm
14. European Society for Paediatric Endocrinology recommendation of transitional care: http://www.eurospe.org/clinical/Docs/ManagementGH-treatedAdolescentTransitionAdultCare.pdf
15. Department of Health guidance on transitional care in complex endocrine disorders 2006 (still current).
16. Department of Health Prescription Cost Analysis publications 2012: http://webarchive.nationalarchives.gov.uk/20120104142136/http://www.dh.gov.uk/en/Publicationsandstatistics/Statistics/StatisticalWorkAreas/Statisticalhealthcare/DH_4086488
17. Conway GS, Szarras-Czapnik M, Racz K et al. Treatment for 24 months with recombinant human GH has a beneficial effect on bone mineral density in young adults with childhood-onset GH deficiency. European Journal of Endocrinology 2009; 160: 899-907.
18. Pituitary Foundation information leaflet 'The Pituitary Gland' 2012. http://www.pituitary.org.uk/information/publications/essential-free-publications/hydrocortisone-advice-pituitary-patient-leaflet/ This leaflet has been downloaded or distributed as hard copies 6,297 times in the last three years.
19. Levy,M. Interview with Peter Sonksen. Endocrinologist 2013: Spring; page 6-9. http://www.endocrinology.org/endocrinologist/107/107.pdf#page=6