ESE INSIGHT

Supplement | 2017 | Number 1 | ISSN 2057-4312 (print) ISSN 2057-3286 (online)

Conference report on the 7th Annual European Meeting on the Management of Acromegaly, Berlin, Germany, 13-15 October 2016

Featuring summaries of presentations from:

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This supplement has been independently written on behalf of ESE and presents highlights of the meeting. Its publication and distribution have been made possible by an unrestricted grant from Pfizer Ltd.

Welcome to the 7th Annual European Meeting on the Management of Acromegaly

Berlin, Germany, 13 -15 October 2016

On behalf of the scientific planning committee of the seventh annual European meeting on the Management of Acromegaly, we are pleased to provide *European Society of Endocrinology* members and the wider international community with conference highlights of this event.

The German anatomist Arnold Berthold performed a world's first endocrine experiment in 1849 by demonstrating how cockerel testis produces hormones that reach other tissues via the bloodstream. With such a strong endocrine history, it was fitting to welcome more than 200 delegates from 22 countries to Berlin and 30 further virtual delegates who joined us from centres of excellence in Europe.

We are thankful to many individuals who helped make this event a success again. We especially thank Dr Josef Köhrle, as director of the Institute for Experimental Endocrinology in Berlin for his welcome on behalf of the host country, and the German Endocrine Society (DGE) for endorsing the meeting.

Our thanks to ESE for publishing and distributing this independent supplement and to Dr Rachel Arthur specifically, for her help in writing it. We also thank Pfizer for their support of this educational event and the supplement's distribution.

Our final thanks go to all the contributors and our delegates who actively participated and engaged with the speakers' exciting scientific programme. We hope you find the supplement educational and thought-provoking to help advance your management of acromegaly.

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This supplement has been commissioned and published independently by the European Society of Endocrinology for the continuing education of ESE members, affiliate Society member and other health care professionals. The views expressed by the contributors are not necessarily those of ESE. This content focus around Pituitary and Neuroendocrinology reflects an evolving strategic approach to provide Society activity and services organised around eight specialised areas. To learn more about the benefits of ESE membership from just €10 per year, please visit **www.ese-hormones.org.** Project delivery on behalf of ESE: **Editorial review:** Wouter de Herder, AJ van der Lely and Helen Gregson. **Supplement Independent Medical Writer:** Dr Rachel Arthur MB BS. **Membership & Fulfillment:** Andrea Davis & Mail Handling International. **Project Management:** Versatility Consultants. **Design and production:** Qube Design Associates.

Pfizer Ltd. has initiated and funded the 7th Annual European Meeting on the Management of Acromegaly. The Scientific Planning Committee for this event (SPC) is comprised of specialists who provide scientific and planning oversight for the overall program and content. Its members are recognised authorities in the field of endocrinology, and they receive an honorarium from Pfizer Ltd. for this work. The highlights of this symposium reflect the scientific opinions of the individual presenters and may not necessarily reflect the opinions of Pfizer Ltd., or any of its subsidiaries, partners or employees. The publication and distribution of the ESE INISIGHT Conference Report on the 7th Annual European Meeting on the Management of Acromegaly have been made possible by an unrestricted grant from Pfizer Ltd. A member of the SPC has reviewed ESE INSIGHT Supplement, 2017/1 to ensure its content accurately reflects the presentations and discussions of the meeting. Pfizer have reviewed the content for medical accuracy and regulatory compliance of medical literature purposes only and otherwise has had no input into its content or publication nor of ESE News 32 it is distributed with.

Tissue-specific effects of growth hormone

Dr Darlene Berryman

The third plenary lecture was given by Professor Darlene Berryman from Ohio University, US. Looking at GH signalling, she said, we have GH binding to the receptor and obviously the tissue-specific effects are related to the amount of receptor on a specific tissue. There are a number of other signalling pathways inside the cell. In addition you have IGF-I and its signalling pathways, so with all of these factors you can get a very different response from one tissue to another.

Mice can be very valuable in terms of the study of GH action. Bovine GH (bGH) transgenic animals are available in our lab, she said. These animals produce excessive amounts of GH, very comparable to an acromegalic state, and are in an insulin-resistant state in early life. Next is the growth hormone receptor antagonist mouse. They have lower than normal levels of IGF-I and lower than normal levels of GHR signalling. In the GH receptor knockout mouse, GHR is removed in all tissues. These animals have high levels of GH and very low levels of IGF-I, with very low insulin. And in the liver-specific receptor knockout mouse, GH and IGF-I action are fairly normal in all other tissues except liver and fat tissues.

These mice are very interesting from the ageing perspective because the bGH animals live about half the lifespan of a normal mouse. Mice usually live about two and a half years and these live maybe 14 or 15 months. GHR knockout mice are very long-lived, they live just shy of 5 years.

In the liver-specific knockout mice (LiGHRKO), GH receptors specific to the liver have been removed. Essentially they have an extrahepatic acromegalic situation. So all the other tissues are being exposed to high GH but low IGF-I, with the exception of the liver. They will be interesting to follow. In the fat-specific GH receptor knockout mouse (FaGHRKO), males have increased IGF-I, the trend is more subtle in females. There is no change in glucose metabolism.

There are many misconceptions about fat tissue. When we think of fat we usually think of its classical function, which is essentially an energy warehouse, storing nutrients and releasing nutrients. We think of fat as a very simple tissue, but it has a much more complex function, she said.

But it is very plastic, very malleable: it can actually be modified and remoulded based on stimuli. Immune cells can infiltrate the tissue based on certain stimuli; macrophages are probably the best studied but in fact most of the immune cells can influence the tissue. White adipocytes can also become brown-like adipocytes: they can take on the phenotype of a brown adipocyte, in other words they can have a more thermogenic capacity, they can increase their mitochondria, and instead of storing they use the energy to produce heat. Pre-adipocytes can also senesce. And then of course you have the endocrine function not just of the adipocyte but also the stromovascular or immune cell population. So fat is quite complex, not as simple as we once thought.

In addition to that there are depot-specific differences so subcutaneous fat has more of that capacity to brown and also more of that capacity to senesce. Intra-abdominal fat depots tend to have more immune cells, the adipocytes tend to be larger. So depot to depot the effects of GH may be very different because depot to depot the cell types and the composition of the different depots are very different.

What is the fat profile, the body composition of the different mouse types? So bGH animals are relatively lean compared to their littermate controls. The GHA mice are significantly more obese, and so are the GHR knockout mice.The fat-specific knockout has a fat pattern very similar to the global knockout, and liver-specific knockout is sort of a moderate acromegalic situation in terms of its fat mass. The body weights for bGH transgenic animals are relatively increased throughout life for both males and females, but when it comes to fat mass there are very significant differences based on sex and age. This is an interesting disconnect. It is rare that obesity is associated with a long lifespan.

Adipose tissue responds to the GH signal very differently depending on the depot. Historically, the epididymal depot was the main depot that everyone looked at in mice—it is the easiest to dissect and it is the largest, so usually people focus on that if they want to study adipose tissue. Inguinal or subcutaneous is just under the skin, mesenteric is around the intestine and is the hardest to dissect, retroperitoneal is behind the kidney. So these three fat pads (epididymal, mesenteric and retroperitoneal) are essentially intra-abdominal, but the mesenteric is the only one that is truly visceral.

There are many examples in the lab of depots behaving differently. Over and over again the depots behave differently, with epididymal the least affected.

So to summarise, GH action is tissue-dependent. White adipose tissue is an excellent example of this because different depots behave differently depending on their location and cell composition. Even though overall GH levels are negatively correlated with white adipose tissue mass, the depots do respond differently. Historically epididymal fat pad has been the one that everyone has looked at because it is the easiest to collect, but it is actually the least impacted so it does not really tell the full story. You need to look at various different depots if you want to know the tissue-specific effects of GH.

Berryman Key Learning Points

- **Mouse models allow researchers to pick apart the GH/IGF-I axis and to knock out GH receptors even in a tissue-specific manner**
- **Adipose tissue can be modified and remoulded based on stimuli**
- **There are depot-specific differences, between subcutaneous and intra-abdominal fat, for example**

The role of GH, IGF-I and insulin in cancer

Dr Derek LeRoith, New York, US

The first plenary lecture was given by Dr Derek LeRoith, New York, US. Melmed and colleagues (PNAS 2016)[1] recently suggested that GH might be permissive for neoplastic colon growth. What they were looking at in this particular case was intestinal and colon tumours in the APC heterozygous +/- mouse. If these mice are crossed with a mouse that is not producing GH there is a large reduction in cancer development. Also, in both mammary tumours and other tumours, GH may be produced locally and may have a paracrine effect in addition to circulating GH. Finally, higher GH receptor expression is associated with a worse prognosis in certain cancers, including breast and gastric cancer.

Plasma IGF-I levels may be increased in individuals with prostate cancer, breast cancer and other cancers. Those in the upper quartile for IGF-I have a worse prognosis than those in the lower quartile. Again, epidemiological studies do not show causality, but they strongly suggested that there may be an effect or a role for IGF-I or the IGF-I receptor in cancer growth.

So this work led to the question, can you interfere with various epithelial cancers by pharmacologically inhibiting the IGF-I system. One of the first studies to look at a tyrosine kinase inhibitor of the IGF-I receptor showed that the normal growth of tumours in mice was inhibited when you gave these mice a tyrosine kinase inhibitor. Clinical trials were started but most of these trials have been stopped because they were inadequate. Some of the patients did very well, some did not respond at all, and some of the patients responded partially but had side effects. Diabetes also developed in many of these trials.

Dr LeRoith went on to discuss the insulin system. Why does the Laron type dwarf not develop cancer and diabetes? One reason may be that GH has a direct effect on cancer but of course cannot do that in the absence of growth hormone receptor. Furthermore if IGF-I stimulates cancer, the IGF-I levels are low because GH is not stimulating IGF-I. There seems to be a relationship between GH, IGF-I and insulin: all of these may be related or they may be separate entities.

Cancer deaths are increased in obese individuals. Even in non-diabetics, if you just measure the insulin level in women with breast cancer those that have endogenous hyperinsulinaemia (in other words, their insulin levels are in the upper quartile) have the worst prognosis for breast cancer. This again suggests that insulin may be playing a role.

Gallagher (2010)[2] showed an association between type 2 diabetes and risk of cancer at specific sites. Although insulin works with many other factors, the epidemiology strongly suggests insulin as a big player in this field.

We created a mouse model of diabetes where we induced muscle insulin resistance genetically, said Dr LeRoith; this eventually leads to type 2 diabetes. A mouse model that produces breast cancer (polyoma virus middle T antigen, PyVmT) was crossed with this so-called MKR mouse. The tumours were more aggressive in the mice that had hyperinsulinaemia, and many more metastases were present. Again, insulin is not oncogenic and the insulin receptor is not oncogenic: once you have the tumour, the hyperinsulinaemia can drive the growth of the tumour and further metastases.

How does the insulin receptor do this? If you express IR-B, the insulin receptor B isoform, you will get the metabolic effects of insulin. But there is a second receptor, IR-A, a subtype of the insulin receptor where exon 11 is excluded by splicing. This particular receptor is found on cancer and it is found in the fetus so it is for fetal growth but also can stimulate growth of cancer. So this subtype IR-A could be driving the cancer. If the IR-A to IR-B ratio is increased patients have a worse prognosis. Also a recent publication showed that some of the IGF-I receptor antibody-resistant patients were resistant because they had high levels of IR-A expression.

Cancer is a multistage process. You need oncogenes to start the cancer process, but the promotion and progression may be through these three hormones. Dr LeRoith concluded that there seems to be a role for GH, IGF-I and insulin, separately or together, in cancer growth and metastases. We should consider this in many different syndromes and disease states, and the take-home message is to be aware of it so that we screen our patients and treat them appropriately.

LeRoith Key Learning Points

- **Circulating GH may have an effect on cancer development and growth, and there may also be a paracrine effect**
- **There may be causality between IGF-I and cancer growth, though inhibitors of the receptor have not shown definitive clinical benefit**
- **Insulin by itself may be a driving force for cancer**

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1. Chesnokova V, Melmed S. *PNAS* 2016;113 (23): E3250-9.
2. Gallagher EJ. *Endocrine Pract* 2010;**16**: 864-73.

Is it possible to measure cumulative GH response in acromegaly — if so, is it relevant?

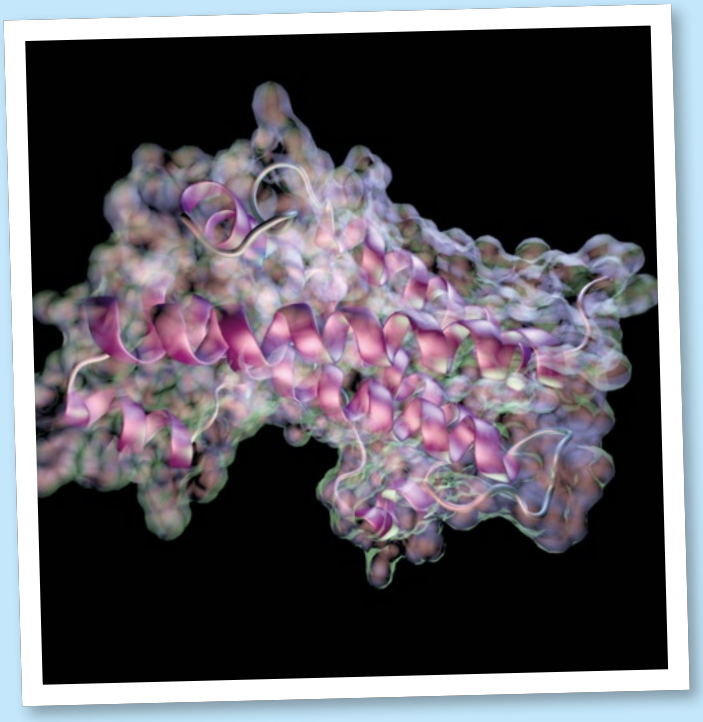
Dr John Wass

The second plenary lecture was given by Dr John Wass, from the University of Oxford, UK. A 2008 meta-analysis showed an increased standardised mortality ratio in acromegaly ($p<0.00001$) for all 18 studies considered: the mortality ratios were significantly higher in those patients who had uncontrolled GH and IGF-I. These figures are now quite out of date in terms of the GH criteria that were used to define active disease with a cut-off of 2.5µg/L.

So what about cumulative GH? This is a measure of GH over time and it is obviously a better reflection of GH exposure. The question is whether it reflects more accurately what is happening in terms of mortality and morbidity.

Dr Wass referred to a study from Dr Richard Clayton's group (Varadhan, Pituitary 2016).[3] They looked at 167 patients and calculated their cumulative GH and its role in determining mortality and morbidity. In the pre-1992 era, they showed a highly significant increase in SMR of 2.5 whereas post-1992 it was 1.0. The cumulative GH was higher in the dead than alive patients ($p<0.01$); cardiovascular complication rates were higher in the older, pre-1992 cohort ($p<0.001$); and radiotherapy was more commonly used in those who died ($p<0.001$). This study shows changes in practice: there is more surgery in the new cohort (81% vs. 28%) and less radiotherapy.

Looking at the comparison in this paper between those who died and the survivors, cumulative GH was greater and radiotherapy frequency was higher (69% vs. 38%) in those who died; and the control achieved was higher in those who survived than those who died (81 vs. 52). The rate of microadenomas before 1992 was 1.3%, and after 1992 was 18.2%. This is obviously a significant change, and it suggests that acromegaly patients are being diagnosed earlier.



Colleagues at the Hammersmith Hospital have looked at the effects of long-term GH and IGF-I exposure in developing co-morbidities over many years in a cohort of 116 patients. They calculated the cumulative GH and IGF-I over this period of time and showed that there were significantly higher GH levels in those with abnormal glucose tolerance and ischaemic heart disease.

Sherlock (JCEM 2014)[4] compared the effect of analysing the last available GH sample versus GH over a period of time. The last available GH measurement may overestimate risk. Cumulative GH may be really important and add more data than single last GH measurement.

There are now 3,000 patients on the acromegaly register database in the UK. Dr Wass said that it worried him that GH was controlled in only 57% and IGF-I in 55% of those patients whereas IGF-I at least can be controlled in the vast majority of patients. We need to be much more assiduous in how we manage our acromegaly patients, he said, and be much more aggressive in how we look after them and pugnaciously try to decrease their GH and IGF-I levels. In a specialised department like Oxford we are not getting above 80%, he said. It would be really nice to analyse why we are not getting control. Some of them are elderly patients, some people have only mildly abnormal levels, and sometimes we cannot get hold of drugs such as pegvisomant.

We need more data on mortality in pegvisomant-treated patients, said Dr Wass, and we need to analyse our various databases for patients who have GH levels <1µg/L and for patients who have discordant GH and IGF-I levels.

In conclusion, mortality and morbidity in acromegaly are improving but there is room for further improvement. Acromegaly should be assessed by GH and IGF-I three months after surgery: this is something that not everybody does, some people do it too early. Cumulative GH and IGF-I is probably a better method of assessing the burden of disease and may be relevant for research. Finally, detailed and integrative assessment of GH and IGF- 1 may be only indicated in patients with possible mild elevation of GH and IGF-I to help decide whether they need treatment.

Wass Key Learning Points

- **GH and IGF-I levels should be assessed three months after surgery**
- **Cumulative GH may be important, adding more data than single last GH measurement**
- **We need to be more aggressive in our management of acromegaly patients**

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3. Varadhan L. *Pituitary* 2016;**19:**251.
4. Sherlock M. *JCEM* 2014; **99:** 478.

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There are many misconceptions about fat tissue. When we think of fat we usually think of its classical function, which is essentially an energy warehouse, storing nutrients and releasing nutrients. We think of fat as a very simple tissue, but it has a much more complex function, she said.

But it is very plastic, very malleable: it can actually be modified and remoulded based on stimuli. Immune cells can infiltrate the tissue based on certain stimuli; macrophages are probably the best studied but in fact most of the immune cells can influence the tissue. White adipocytes can also become brown-like adipocytes: they can take on the phenotype of a brown adipocyte, in other words they can have a more thermogenic capacity, they can increase their mitochondria, and instead of storing they use the energy to produce heat. Pre-adipocytes can also senesce. And then of course you have the endocrine function not just of the adipocyte but also the stromovascular or immune cell population. So fat is quite complex, not as simple as we once thought.

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Berryman Key Learning Points

- **Mouse models allow researchers to pick apart the GH/IGF-I axis and to knock out GH receptors even in a tissue-specific manner**
- **Adipose tissue can be modified and remoulded based on stimuli**
- **There are depot-specific differences, between subcutaneous and intra-abdominal fat, for example**

Prevalence and relevance of pulmonary complications in acromegaly

Dr Francesco Cavagnini

The first address was given by Dr Francesco Cavagnini, Professor of Endocrinology in Milan, Italy. When, as endocrinologists, we see a patient with suspected or overt acromegaly we are naturally inclined to look for changes in phenotype and not to pay enough attention to the respiratory system. This happens also because the patient in general does not refer specifically to respiratory symptoms as the predominant complaint. Disorders of the respiratory apparatus in acromegaly are still overlooked and underdiagnosed.

First, a brief summary of the chief changes in basic respiratory function. Due to excessive synthesis of GH and IGF-I, a number of rearrangements of the structures involved in respiratory mechanics take place, eventually translating into hypoventilation, subclinical hypoxaemia, emphysema and ventilation/perfusion mismatching. Also, due to the changes such as overgrowth of the cranio-facial bones and tongue, narrowing of the upper airways, snoring and obstructive sleep apnoea can occur. Of interest, gas exchange through the alveolar membrane appears to be preserved.

On comparing 20 acromegalic patients with 20 controls, a group of Brazilian researchers (Camilo 2013)[5] showed extensive alterations in respiratory function in these patients. These included a decrease in maximum inspiratory and expiratory pressure, an increase in forced vital capacity, and again increased total lung volume which gives increased residual volume, increased airways resistance, and residual air remaining in the lung after the end of expiration (air trapping).

What is the prevalence of these disorders? The paper by Camilo described a number of radiographic abnormalities in acromegalic and control groups using high-resolution CT of the thorax. They found that 35% in profound inspiration demonstrated bronchiectasis, that 60% demonstrated air trapping during forced expiration and, interestingly, airway calcification in 40%. Reid (2010)[6] was the first to show that the diagnosis of sleep apnoea has increased between early (pre-1994) and late (1995-2006) acromegaly cohorts, from 13% to 29%. Even more striking were the findings when they looked at snoring, a very reliable sign of sleep apnoea, which jumped from 25% to 60% in the two groups. Another study published in 2008 showed the prevalence of this disorder in 87% of the 24 patients studied, almost all with the obstructive type of sleep apnoea. Further, half of them had sleep apnoea syndrome.

This led an acromegaly consensus group to express the statement in 2013 that sleep apnoea is indeed a highly prevalent disorder, occurring in 70% or even more, and that it is currently underdiagnosed.

What happens to people with sleep apnoea when their acromegaly is controlled? One meta-analysis found that in approximately 40% of patients sleep apnoea persisted despite control of the primary disease

What is the clinical relevance of lung complications? First of all, these complications will negatively influence two symptoms often referred to by acromegalic patients, namely impaired physical performance and increased perception of fatigue. The clinical relevance of a disease is maximally expressed by the related mortality. The respiratory system in patients

with acromegaly is frail and prone to infection. Many non-malignant respiratory deaths are due to bronchopneumonia or pneumonia. More recently, the American Association of Clinical Endocrinologists recommended that vaccinations should be given for influenza and pneumococcal pneumonia.

Sleep apnoea is of course the leading cause of mortality, and it acts by inducing a number of metabolic derangements (arterial hypertension, metabolic syndrome and insulin resistance/diabetes), making more frequent the occurrence of cardiovascular events. And also, due to increased daytime sleepiness, accidents in both traffic and the workplace are more frequent.

What is the contribution of respiratory complications to the overall mortality in patients with acromegaly? A study published more than 30 years ago collected data from 164 patients with acromegaly, finding that 15.5% of deaths were due to respiratory complications, and that the mortality from respiratory causes was 3.8 times the expected rate in the general population. More recent studies are in general agreement.

Dr Cavagnini concluded with the message: look for the presence of pulmonary complications, and carefully examine the respiratory apparatus in every patient with acromegaly even when he or she does not refer to pulmonary symptoms. This will improve the management of such patients.

Cavagnini Key Learning Points

- **Disorders of the respiratory apparatus in acromegaly are overlooked and underdiagnosed**
- **These patients have increased resistance and decreased elasticity of the lungs**
- **Respiratory disorders contribute about 17% to overall mortality in acromegaly**

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Acromegaly and respiratory/sleep dysfunction

Dr Mark Gurnell

Dr Mark Gurnell, from the University of Cambridge and Addenbrooke's Hospital, Cambridge, UK widened the discussion from disorders that can affect the respiratory system to explore sleep dysfunction. Few studies have looked at sleep architecture, few treatment-naive patients have been studied, and the techniques employed to study sleep are heterogeneous, he said.

The ACROPAT study (Acromegaly Complications and Radiological Outcomes with Presurgery Analogue Therapy) was a prospective, open-label, single-centre study looking at adult patients with newly diagnosed acromegaly. Every patient went through a detailed profile involving a full sleep assessment; plus vascular measurements, a number of metabolic parameters and markers of tissue action.

Patients went to the respiratory support sleep centre at the Papworth Hospital for polysomnography. These data were compared with measurements from a single finger probe, done at the same time, looking at the number of times patients had a desaturation of >4%. Patients were also asked to complete a sleepiness scale questionnaire.

The cohort data for the 40 patients with de novo diagnosed acromegaly were analysed using the gold standard marker for assessing the presence of sleep apnoea, the apnoea hypopnoea index (AHI). All the data were split into males and females, and the severity of sleep apnoea was categorised into mild (5-15), moderate (15-30) and severe (>30) episodes of apnoea and hypopnoea per hour. Sleep apnoea is the norm for patients with acromegaly at presentation, it emerged. We should assume that 4 out of 5 patients coming to see us have sleep apnoea, and many of these patients have severe sleep apnoea, said Dr Gurnell.

Those data were compared with the ability of the desaturation index (DI) and Epworth Sleepiness Scale (ESS) to detect the sleep apnoea in these patients, all done contemporaneously. The important message here is that unfortunately both techniques underestimate the prevalence and, in the case of the DI, underestimate the severity. And the patients themselves are not actually aware that there is something going on. That is an important parameter to bear in mind because sleep latency and sleep period time are comparable to that of the general population. Patients are not aware of having encountered sleep apnoea.

But the vast majority of patients have a significantly increased arousal index—some of these patients are approximating 60 arousals an hour, which basically means that they are waking every minute to a degree. And some patients are experiencing quite a number of periodic limb movements, another marker of disturbed sleep.

The message is that there is more time spent in stage 1 sleep for some patients than we would expect, there is certainly less time in stage 2 sleep, and many patients are not spending much time in SWS, very few patients are actually getting into REM sleep. So it is not surprising patients report that they never feel particularly great when they wake first thing in the morning. And that is because the sleep architecture has been very much disrupted by these arousals triggered by the sleep apnoea.

So what happens if you actually treat these patients? Looking at the apnoea hypopnoea index pre- and post-SRL, there is no correlation between what is happening in the biochemistry and what is happening in the AHI scores. So some patients are seeing dramatic improvements in their sleep status whereas others, who had very little sleep disturbance at the start, are actually developing sleep apnoea during the course of the study or seeing an acceleration of that. And the same is true for the DI. And intriguingly in this study if you look simply at weight, the patients who do not see an improvement in their sleep apnoea are those who have gained weight. So gaining weight can completely neutralise the hard work that we have done in improving the biochemistry in these patients. And in fact just measuring the weight alone is probably the best predictor of whether the sleep disturbance will have improved.

This was reflected in looking at other data, such as vascular risk factors. There was quite a variability in the direction of travel of both systolic and diastolic blood pressure, which not surprisingly shows no significant change for the cohort as a whole. But when we look at cohort data they do not reflect the extreme things which happen to some patients, which is why we need to personalise treatment.

There are a number of patients who are hitting every biochemical target but whose parameters are going in the wrong direction. And that means we need to think about this very hard when we consider patients sitting in front of us and congratulate them and ourselves in achieving biochemical control. On the other hand, we need not be overtly pessimistic all the time in patients who are not achieving all their targets because we can see dramatic reversals in complications in patients even when their biochemistry is not perfect.

So, in summary:

- Sleep-disordered breathing is present in 4 out of 5 patients with a new diagnosis of acromegaly
- Be cautious about applying screening tools that are used in the general population to detect sleep apnoea
- Sleep latency and sleep period time may look relatively normal, and the patient may not be aware of what is going on
- Sleep architecture is markedly disrupted in most patients, with attenuation of the deeper sleep stages due to regular arousal
- Finally, biochemical control does not equal complication control

Gurnell Key Learning Points

- **Sleep-disordered breathing is present in 4 out of 5 patients with newly diagnosed acromegaly**
- **Sleep architecture is disrupted in most patients**
- **There is no correlation between biochemical control and Apnoea-Hypopnoea Index scores**

Sleep apnoea and metabolic complications

Dr Eve van Cauter

This talk was delivered by Dr Eve van Cauter from Chicago, US. She started by saying that sleep is a very active state in which we go through different stages. Sleep is deeper and most intense during the first two cycles, and as the night progresses sleep becomes more shallow and we are more likely to wake up. And in fact slow wave activity really is a marker of the arousal threshold. Slow wave sleep is often described as the most restorative phase of sleep, and indeed it correlates very well with improvement in cognitive function and wakefulness during the daytime. It is also very important in terms of restoration of peripheral function.

Slow wave sleep is also correlated with anabolic hormone activity. Secretion of GH is strongly related to the occurrence of slow wave sleep in both men and women (though much more so in men). The first 2-3 hours of sleep are associated with the major output of the day of GH release. Slow wave activity and GH release are intimately related due to an effect of GH releasing hormone (GHRH). For example, animal studies have shown that injections of GHRH either into the brain or the peripheral circulation increase non-REM sleep.

Obstructive sleep apnoea (OSA), the occurrence of complete or partial obstruction of the upper airways, is a complex disorder that involves intermittent hypoxia, reduced total sleep time, sleep fragmentation and shallow sleep. In fact, this includes low slow-wave activity and low slow-wave sleep compared to those without OSA but matched for age and BMI. OSA is also associated with a decrease in secretion of GH.

It is well known that CVD has a very strong association with OSA. For instance, 76% of males with congestive heart failure also have sleep apnoea. The study by Marin (2005)[7] shows prospectively what your chances are of having a non-fatal CV event or a fatal CV event depending on the quality of your sleep. So if you compare healthy men with simple snorers (without OSA), there is an increase in CV risk. If you look at severe OSA, in untreated patients there is a four-fold elevation in the incidence of any CV event as well as a three-fold elevation in the incidence of CV death. However, when people are put on CPAP you can entirely reverse that risk.

Even low slow wave activity sleep, easily disrupted sleep with a low arousal threshold, can also be a risk factor for developing hypertension.

There is a large body of evidence to indicate that the prevalence and severity of OSA is a risk factor for insulin resistance, metabolic syndrome and the development of type 2 diabetes. One of the most rigorous studies (Punjabi 2009)[8] showed that after controlling for age, sex and percent body fat, compared to subjects without OSA, those with mild, moderate or severe OSA had reductions in insulin sensitivity of 27%, 37% and 48% respectively.

Even after controlling for body adiposity and age and other demographic characteristics, just having sleep apnoea is associated with a more than two-fold increase in the development of diabetes. Not only can sleep apnoea increase the risk of diabetes, but simply low slow-wave activity can also make you more at risk. In an experimental

study (Tasali 2008)[9] slow-wave activity in normal healthy adults was suppressed for three consecutive nights using auditory stimuli. In this way the study reproduced in a way the very low intensity sleep of elderly adults. Within three days insulin sensitivity measured by IGTT decreased by 25% and glucose tolerance was also significantly decreased.

Dr van Cauter described a recent study to test whether CPAP treatment can have beneficial effects on glycaemic control in patients with both type 2 diabetes and OSA. The results showed that after one week, active CPAP as compared to sham CPAP resulted in a decrease in 24-hour mean glucose levels of almost 14 mg/dl, which corresponds approximately to an improvement of 0.4-0.5% in HbA1c. The largest beneficial effect is in the dawn hours.

So what is the relevance to acromegaly? In acromegaly the increased risk of OSA is due to anatomical alterations which impinge on the upper airway. There is also an increased risk due to the low arousal threshold due to low slow wave activity. The treatment of acromegaly can reduce soft tissue hypertrophy and reduce the severity of OSA but it does not eliminate OSA significantly.

The risk of CVD and diabetes is high in acromegaly, but perhaps the presence of OSA which is so highly prevalent is the major mediator of this increased risk. Irrespective of the presence of OSA, treatment of acromegaly may decrease the risk of CVD and diabetes via an increase in slow wave activity, which would lead to a lower cardiac sympatho-vagal balance and a higher insulin sensitivity.

Van Cauter Key Learning Points

- **Secretion of GH is strongly related to slow wave sleep**
- **The primary determinant of OSA is patency of the upper airways**
- **Having sleep apnoea more than doubles the risk of diabetes**

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New tools for the assessment of the stages of acromegaly

Delays in diagnosis and intervention in acromegaly increase mortality, co-morbidities and medical costs. In response, a range of tools under investigation were described aimed at diagnosing acromegaly and staging the disease to help practitioners optimally treat their patients.

1. ACROSCORE

Dr Silvia Grottoli

The first tool for the early diagnosis of acromegaly was described by Dr Silvia Grottoli from the University of Turin. A great problem in the diagnosis of acromegaly is delay in the diagnosis. It has been reported that at least 30% of patients receive their diagnosis 15 years after the onset of first symptoms. Many factors contribute to diagnostic delay, including age, gender, low disease activity and rarity of the disease, but Dr Grottoli underlined that limited knowledge of the disease and poor familiarity with it could be important factors. The importance of diagnostic delay is not just important per se but also it is related to mortality.

ACROSCORE is a scoring system focused on the cardinal symptoms and signs of acromegaly. To create ACROSCORE, we evaluated clinical features of patients affected by acromegaly in a multicentre study, and compared them with a control group consisting of patients with non-GH-secreting pituitary adenomas, said Dr Grottoli. We found that various features differed significantly between patients and controls. These were: type 2 diabetes, hyperhidrosis, thyroid hyperplasia, colorectal polyps, spaced teeth and carpal tunnel syndrome. Multivariate logistical models were used to calculate the value of each symptom and at the end we were able to classify people by their ACROSCORE into four risk groups.

In conclusion, ACROSCORE is a reliable and simple score for the early diagnosis of acromegaly. It has high specificity and sensitivity in distinguishing subjects in whom the diagnosis of acromegaly is probable and those in whom the diagnosis can be excluded.

2. SAGIT

Dr Philippe Chanson

The disease staging instrument SAGIT was introduced by Professor Philippe Chanson from the Hôpital Bicêtre, Paris. SAGIT is an attempt to provide a standardised classification of acromegaly through disease activity scoring across five items:

- Signs and symptoms (such as headache, sweating, swelling)
- Associated co-morbidities (such as hypertension, sleep apnoea, heart disease)
- GH concentration
- IGF-I concentration
- Tumour size

The score may be used to stage the patient, to assess response to treatment, and to adapt patient management. The validation study is now ongoing. The study rationale is to develop a simple validated scoring algorithm from a structured clinical trial involving more than 200 patients. The study goal is to test whether the staging instrument would improve classification of patients with acromegaly, improve appraisal of the severity of illness, improve management of patients from diagnosis, and provide a common system for acromegaly classification to be used both in clinical trials and clinical practice. It is an international multicentre non-interventional study with two-year follow-up, with 33 centres in 10 participating countries. The primary objective of the study is to discern the ability of SAGIT to distinguish accurately between controlled and uncontrolled patients.

In summary, SAGIT is a unique scoring instrument in acromegaly, designed by a steering committee of acromegaly experts. It is under validation, supported by a robust international clinical programme. It addresses the unmet need for a staging instrument to help endocrinologists improve patient outcomes.

3. ACRODAT

Dr AJ van der Lely

The third tool was described by Professor AJ van der Lely from Erasmus University Medical Centre, Rotterdam. The new score tool is intended to help doctors to discuss the patient's health status. The ideal would be to take a holistic view of disease activity, with earlier identification of uncontrolled patients; individualised treatment to enable appropriate treatment adjustment; and allow monitoring of the patient at any stage of disease.

The ACRODAT panel of experts crystallised five key parameters. Then the severity of these parameters was ranked into three categories, and finally a validation study for the tool was designed. The five key parameters were: IGF-I, tumour status, co-morbidities, symptoms and health-related quality of life impairment.

A total of 21 expert endocrinologists from around the world were asked to validate this attempt to develop a scoring tool. The objectives were to develop and assess a model that predicts expert endocrinologists' judgement of disease activity status (stable, mild disease activity or significant disease activity) based on the set of health status indicators in hypothetical acromegaly patient cases, and to assess inter-rater agreement of disease activity status among expert endocrinologists. The results showed that tumours and IGF-I pathology over-ride co-morbidities, symptoms and quality of life such that these patients cannot achieve a stable disease activity designation. However, co-morbidities, symptoms and quality of life remain contributing components of ACRODAT's assessment of disease severity.

The software application is in the test phase, and hopefully ACRODAT will be available in some countries mid- 2017. Both doctors and patients will be able to access them, and the forms are straightforward and relatively easy to fill out. The software also provides time points so that charts can be produced that monitor variables such as IGF-I against changes in treatment.

Does the somatostatin and dopamine receptor status predict medical outcome?

Chair: Dr John Wass
The speaker for the proposition was Dr Leo Hofland
The speaker for the opposition was Dr Justo Castaño

Dr Leo Hofland, from Rotterdam, the Netherlands, proposed the motion. The "classical SSAs" octreotide and lanreotide were developed in the 1980s. Ten years later the five different receptor subtypes were discovered, and soon it appeared that octreotide and lanreotide only bound with high affinity to the sst2 receptor. When we are addressing the clinical efficacy of the classical SSA, we should only focus on the sst2 receptor, he said. The dopamine situation is similar, with five different subtypes of receptor. We now know that the dopamine D2 receptor is the primary dopamine receptor that is expressed in the pituitary adenomas, and again when we are addressing the clinical effects of SSAs we should focus on the D2 receptor.

Every type of pituitary adenoma has its own specific pattern of expression of sst and dopamine receptors, a kind of fingerprint. When we look at the drugs that are used in the treatment of pituitary adenomas, we can see that there is a clear relationship between receptor expression and the drugs of choice. About 50% of patients do not reach normalisation of serum GH or IGF-I with first-generation SSAs. This fits well with the discovery that 50% of adenomas have high expression of sst2 receptors. We confirmed in our laboratory that sst2 protein expression correlated with response to classical SSA in vitro and in vivo, said Dr Hofland, but we did not find such a good correlation with sst5 expression (not surprising since sst5 receptors do not have a high affinity for octreotide and lanreotide).

Antibodies later became available to study the expression of sst receptors in pituitary adenomas. Summarising these studies, again there is a nice correlation between the expression of sst receptors and the ability of SSAs to suppress either GH or IGF-I. Clearly responders to octreotide were identified as those cases which had high expression of sst2 receptors whereas non-responders had low expression of sst2 receptors.

Sst5 receptors are also expressed in GH-secreting pituitary adenomas. Unfortunately, there are not many studies that support a direct relationship between receptor expression and the clinical efficacy of the drug but Iocavazzo's group (2016)[10] studied this relationship in somatotroph pituitary adenomas that are resistant to first-generation SSAs.Those patients who had high expression of sst5 expression were more likely to be responsive to pasireotide treatment.

Most publications show that there is a predictive role for sst receptor status in predicting medical outcome. Many other factors may be involved in resistance to SSA treatment. But looking at the literature, clearly sst2 receptor expression is the predominant factor in this respect.

Prolactinomas in all cases express the dopamine D2 receptor in very high density. When we compare them with GH-secreting pituitary adenomas, we can see that only some of the latter express the D2 receptor and also the density is much lower compared to prolactinomas. The efficacy of dopamine agonist treatment is much higher in prolactinomas than in GH-secreting adenomas, so again there is some relationship. In prolactinomas, resistance is clearly associated to a reduced level of D2 receptors. Again, many other factors can contribute to the response to dopamine agonist treatment but I think D2 expression level is the most important.

Dr Justo Castaño, from Cordoba, Spain, opposed the motion. He said there was not sufficient scientific evidence to support the concept that the presence of somatostatin receptors was a reliable indicator to predict response to SSA. First of all, because there are so many factors involved; many techniques are applied to detect receptor status, including IHC, Western blotting and scintigraphy, and there are many different SSAs. In addition, there are different ways to assess medical outcome—GH, IGF-I and tumour status. Only 25 studies in the literature have investigated the relationship between somatostatin receptors and response to SSAs in somatotropinomas.

These studies have produced conflicting results. For example, the initial Barlier studies in 1999 showed that there was a good correlation between the presence of sst2 mRNA and the response in vitro and in vivo to SSA. However, two years later Corbetta found the opposite: first, that there was a negative correlation between sst2 and sst5 expression, and second that there was no correlation between sst receptors and in vivo response to somatostatin analogues. Then results from the Rotterdam group (Hofland 2004)[11] have already been described. A subsequent study by Park demonstrated that, contrary to what Corbetta had shown, sst2 and sst5 were positively correlated. None of them per se correlated with GH values; only when you added them together did you find a correlation between the response and the receptors.

A study by Fougner[12] showing that the presence of sst2 receptors was positively correlated with GH reduction only if patients had not been treated preoperatively with octreotide. If you had this treatment then you lose the correlation, and this may explain some of the conflicting results previously seen.

So there are numbers of other mechanisms that alter the activity of SSA receptors. Certainly lack of sst2 receptors may be a determinant but there are other examples. The truncated variant of sst5 may be crucial, as may expression levels of other sst receptor proteins or expression of AIP. For example, the truncated variant of sst5, sst5TMD4, lacks 3 out of the 7 domains. When this receptor is present in the pituitary tumour, the response to sst2 decreases: sst5TMD4 was negatively correlated with the ability of octreotide to reduce GH in vivo. And this has also been shown more recently in an unselected set of somatotropinoma patients: the higher the level of sst2 and the lower the level of sst5TMD4, the better the response to SSAs.

Also, with low levels of AIP (aryl hydrocarbon receptor interacting protein) there is a poor response to SSAs, and low AIP expression is significantly associated with invasiveness and suprasellar extension in untreated tumours. A literature search reveals that sst profiling is promising but not simple, because the presence of sst receptors does not ensure the response to SSAs.

The situation is even less clear with dopamine receptors. Dopamine receptors interact with somatostatin receptors: and sst2 and D2 receptors are positively correlated with percent GH suppression by octreotide. However, in another study no difference in D2 receptor expression was found between controlled and uncontrolled patients. In prolactinomas you have a nice potential correlation between D2 receptors and response, and dopamine agonists are the preferred treatment for these tumours. But very few studies have analysed the receptor status in prolactinomas or mixed tumours and the response to cabergoline or bromocriptine. So again, for now there is insufficient scientific evidence to say that dopamine receptor status can predict the outcome in acromegaly.

Summing up, Dr Castaño said that the relationship between receptor profile, treatment response and patient prognosis is not simple but could become useful. The presence of receptors in the tumour, especially sst2, seems necessary but is not sufficient to fully predict the response. This is because there are additional influencing factors such as: single or multiple receptor profile; techniques used to define the receptor status; the different treatments used; and the control criteria, which are not clear in every instance.

Dr Castaño said that to his mind the arguments of Dr Hofland were very respectable but they were not the complete picture. Dr Hofland replied that he would like to thank Dr Castaño for his presentation because in a way he showed very nicely that

there is indeed a correlation between sst2 receptor status and outcome. It was a pity that he put so much emphasis on the few studies that showed the opposite or a lack of association. Dr Hofland still maintained that the sst2 receptor expression is the primary determinant in the efficacy of the classical SSAs to inhibit GH and IGF-I secretion.

Conclusion

In conclusion, Dr Hofland and Dr Castaño put together a slide with some important points to take away. Both of them agreed that we have to consider more factors. We need a systematic review because there is a lack of large-scale studies and meta-analyses regarding receptor subtyping and treatment response in acromegaly. Second, since several factors determine clinical outcome (as both agreed), we need good prospective controlled studies where we combine all these factors as predictive factors in the outcome of treatment of acromegaly patients with SSAs and DAs. This can only be done with international collaboration.

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Which patients are partially resistant to SSA, and why?

Dr Cesar Boguszewski

Somatostatin analogues (SSAs) have been the mainstay of medical treatment for acromegaly since their introduction 30 years ago, said Dr Cesar Boguszewski from Curitiba, Brazil. There are two big concepts used to define resistance—biochemical resistance and tumour resistance. Despite the fact that in most patients these two concepts are associated, there is a subgroup of patients in whom there is a disassociation of these two endpoints.

Colao and colleagues[13] showed clearly that if GH and IGF-I are used separately as efficacy end points, the response rates for SSA were much higher than if the two were used as a composite measure of efficacy. They concluded that there are many factors influencing biochemical response rates to first-generation SSAs in acromegaly, including the patient population, different end points (GH, IGF-I or both), retrospective versus prospective analysis, analysis of ITT versus PP populations, fixed time point versus response at last follow-up, and use of different GH and IGF-I assays.

How frequent is resistance to SSAs in acromegaly? Using data from Colao (2011)[14] looking at 956 patients on octreotide and 264 on lanreotide, biochemical response (GH <2.5 µg/L and normal IGF-I) was seen in 50% of patients, tumour response if treated first-line in an additional 25% of patients, and no biochemical or tumour response in 25% of patients. Experience from 62 patients in Curitiba showed similar results.

Of course the sst expression pattern in the tumour might be behind responsiveness to SSAs: this was elegantly shown in a study published this year (Iacovazzo 2016).[10] On the other hand, if the patient exhibits the receptor it does not mean that he will necessarily respond to the therapy. We have a panel now of molecular biomarkers in the tumour that can be used to predict resistance to SSA treatment. There are also clinical and pathological factors which predict response: some examples are younger age, male gender, high GH levels, hyperintense T2 on MRI and a negative acute octreotide test; and sparsely granulated tumours with high Ki-67. These factors are associated with a poor response.

A new mechanism that is involved in resistance to SSAs, namely cytoskeleton involvement in the cell, has recently been shown. This paper (Peverelli 2015)[15] described filamin A, which is required for expression of sst2, localisation and intracellular signalling. This new mechanism of resistance deserves further investigation.

So in summary, about two thirds of acromegaly patients are not fully controlled with first-generation SSA therapy. The vast majority of acromegaly patients exhibit partial resistance, with some degree of biochemical and/or tumour response.

Boguszewski Key Learning Points

- **There are two aspects of resistance to therapy—biochemical resistance and tumour resistance**
- **Younger age, male gender and high GH levels predict a poor response to SSAs**
- **The vast majority of patients exhibit partial resistance to SSAs**

Is escape from pegvisomant therapy a real issue?

Dr Mónica Marazuela

This issue was discussed by Dr Mónica Marazuela from Madrid, Spain. A secondary increase in IGF-I levels after initial good control was anecdotally reported in 2009 in two publications. In one of these (Marazuela)[16], increases in pegvisomant doses were needed in five non-irradiated patients after a period of stable initial control. Later reports have specifically addressed this issue and provided different and stricter definitions of escape.

What are the possible causes of the escape phenomenon? A list of possibilities includes: IGF-I measurement methods, reaching a steady state, decreased absorption, lack of compliance, dose titration, and lack of expertise. Reaching a steady state is an important consideration. In as many as 50% of patients with pegvisomant 12 months or more were needed for dose titration, and long-acting SSA and DA can continue to inhibit GH and IGF-I months after withdrawal of treatment (Stewart 1999).[17]

There are a number of possible determinants of pegvisomant dose requirements: GH/IGF-I level, gender, radiotherapy, weight and type 2 diabetes mellitus. Some SSA-resistant patients have an aggressive tumour or atypical adenoma which may increase in size or secrete GH—in these cases the dose of pegvisomant needs to be increased during therapy.

Diabetes mellitus is something to take into account because with higher insulin levels there is higher expression of hepatic GH receptors. A recent publication suggested that younger age, macroadenomas, changes in weight and IGF-I levels at baseline were associated with the need for an increased dose of pegvisomant.

How can this escape phenomenon be overcome? In the majority of cases, a simple dose adjustment may be all that is needed but occasionally patients may need additional therapies such as surgery or radiotherapy.

Marazuela Key Learning Points

- **The "escape" phenomenon with pegvisomant is not common (10-15%)**
- **Possible explanations include IGF-I measurement methods or carry-over effects of previous SSA- or DA therapies**
- **Gender, weight, diabetes and radiotherapy all affect dose requirements**

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Lessons from ACROSTUDY

Dr AJ van der Lely

This topic was addressed by AJ van der Lely from Erasmus University, Rotterdam. Which patients respond well to pegvisomant? Better response to pegvisomant is seen in males and after radiotherapy, and body weight and baseline IGF-I are also linked to response. He described a study in which patients used pegvisomant above the maximum dose of 30 mg/day as recommended in the label.. These patients were compared with a subgroup from ACROSTUDY, with patients who used 10mg/day or less, and who already with this very low dose were controlled. In other words, these patients had high sensitivity to pegvisomant.

Patients who need more pegvisomant to normalise IGF-I levels have more aggressive disease as they are younger, have higher baseline IGF-I levels, more hypertension, sleep apnoea and diabetes, and are more overweight. So pegvisomant levels are not really predictable,and the correlation of IGF-I level with drug dose is too poor to simply calculate the necessary dose per patient. Completely pegvisomant- resistant patients do not exist, said Dr van der Lely, but partial resistance does occur. Altogether, efficacy of pegvisomant is high in clinical practice, with normalisation of IGF-I possible in almost all patients.

Van der Lely Key Learning Points

- **When properly used, everybody will respond to pegvisomant, though some need more of the drug**
- **Those who need more pegvisomant to normalise IGF-I levels have more aggressive disease**

Switch to pegvisomant

Dr William Drake

This section was presented by Dr William Drake, from the department of endocrinology at St Bartholomew's Hospital, London, UK. First, pegvisomant does work in SMS-resistant-patients. There is a greater percent drop in serum IGF-I in males compared to females, and there is also a greater decrease in patients who have had previous radiotherapy.

He turned his attention to glucose homoeostasis. The main study that examined what happens to glucose control if you transfer patients from octreotide to pegvisomant was published some years ago. These were patients who were stably treated with octreotide injections every month. In the group of 7 patients that were put into the study (from our centre), one patient lost the diagnosis of type 2 diabetes on conversion from octreotide to pegvisomant, and three patients moved from impaired fasting glucose to normal, he said. And this was independent of their change in IGF-I and independent of their body composition. The mean increase in insulin sensitivity was 30 mmol/L/min.

In the group data, the median fasting glucose changed in patients with diabetes and acromegaly from 7.4 to 4.9 mmol/L. In patients with diabetes, the glycated haemoglobin fell from 7.8% to 6.3% on changing to pegvisomant.

Finally, he addressed the issue of tumour size in patients on pegvisomant. In those patients who are on stable pegvisomant therapy who were well treated before there does not seem to be an increase in tumour size, he said.

So pegvisomant has the ability, at the right dose, to control somatostatin analogue-resistant patients. There is no question that in a proportion of patients, particularly those with established diabetes mellitus, indices of glycaemic regulation improve when patients are moved from SSAs to pegvisomant. And thus far, 16 or so years down the line, there does not appear to be an issue with clinically significant tumour enlargement.

Drake Key Learning Points

- **Pegvisomant has the ability, if you get the dose right, to control SSA-resistant patients**
- **Indices of glycaemic regulation can improve on moving from SSAs to pegvisomant**

An alternative approach

Dr Sebastian Neggers

This talk was given by Dr Sebastian Neggers from Erasmus University Medical Centre, Rotterdam. Dr Neggers suggested that clinicians add pegvisomant to SSAs rather than switch to pegvisomant. There are benefits to using drugs with two different modes of action, he believes. It has been nicely demonstrated (Jorgensen 2005)[18] that serum GH levels are lower in patients on combination therapy with pegvisomant and octreotide than in patients on monotherapy with pegvisomant. Responders to octreotide are able to be controlled with less pegvisomant.

Is there a relation between the sstr2 expression using immunohistochemistry and the pegvisomant dose during combination treatment? A Rotterdam study found that with higher receptor numbers the patient needs a lower dose of pegvisomant (Franck 2016)[19].

Finally, Dr Neggers suggested one of the benefits of combination treatment being the tumour stabilization or reduction with LA-SSAs.

Neggers Key Learning Points

- **Nobody has a clear definition of resistance**
- **There are possible benefits in using combination therapy because drugs have different modes of action**
- **A combination might therefore lead to lower doses**

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Key Learning points:

PLENARY LECTURES

The role of GH, IGF-I and insulin in cancer: LeRoith

- Circulating GH may have an effect on cancer development and growth, and there may also be a paracrine effect
- There may be causality between IGF-I and cancer growth, though inhibitors of the receptor have not shown definitive clinical benefit
- Insulin by itself may be a driving force for cancer

Is it possible to measure cumulative GH response in acromegaly—if so, is it relevant? Wass

- GH and IGF-I levels should be assessed three months after surgery
- Cumulative GH may be important, adding more data than single last GH measurement
- We need to be more aggressive in our management of acromegaly patients

Tissue-specific effects of growth hormone: Berryman

- Mouse models allow researchers to pick apart the GH/IGF-I axis and to knock out GH receptors, even in a tissue-specific manner
- Adipose tissue can be modified and remoulded based on stimuli
- There are depot-specific differences, between subcutaneous and intra-abdominal fat, for example

PULMONARY COMPLICATIONS IN ACROMEGALY

Prevalence and relevance of pulmonary complications in acromegaly: Cavagnini

- Disorders of the respiratory apparatus in acromegaly are overlooked and underdiagnosed
- These patients have increased resistance and decreased elasticity of the lungs
- Respiratory disorders contribute about 17% to overall mortality in acromegaly

Acromegaly and respiratory/sleep dysfunction: Gurnell

- Sleep-disordered breathing is present in 4 out of 5 patients with newly diagnosed acromegaly
- Sleep architecture is disrupted in most patients
- There is no correlation between biochemical control and Apnoea-Hypopnoea-Index scores

Sleep apnoea and metabolic complications: Van Cauter

- Secretion of GH is strongly related to slow wave sleep
- The primary determinant of OSA is patency of the upper airways
- Having sleep apnoea more than doubles the risk of diabetes

NEW TOOLS FOR THE ASSESSMENT OF THE STAGES OF ACROMEGALY

Grottoli, Chanson & Van der Lely

- Delays in diagnosis and intervention in acromegaly increase mortality, co-morbidities and medical costs
- ACROSCORE is a scoring system focused on the cardinal symptoms and signs with high specificity and sensitivity for acromegaly
- SAGIT attempts to provide a standardised classification of acromegaly through disease activity scoring that may be used to stage the patient, assess response to treatment and adapt patient management
- ACRODAT is a tool to facilitate a holistic approach to assessment of disease activity using five key parameters: IGF-I, tumour status, co-morbidities, symptoms and quality of life impairment.

CLINICAL DILEMMAS: PARTIAL RESISTANCE

Which patients are partially resistant to SSA, and why? Boguszewski

- There are two aspects of resistance to therapy—biochemical resistance and tumour resistance
- Younger age, male gender and high GH levels predict a poor response to SSAs
- The vast majority of patients exhibit partial resistance to SSAs

Is escape from pegvisomant therapy a real issue? Marazuela

- The "escape" phenomenon with pegvisomant is not common (10-15%)
- Possible explanations include IGF-I measurement methods and carry-over effects from preceding SSA- or DA therapies
- Gender, weight, diabetes and radiotherapy all affect dose requirements

Which patients receive sub-optimal dosing of pegvisomant? Lessons from ACROSTUDY: Van der Lely

- When properly used, everybody will respond to pegvisomant, though some need more of the drug
- Those who need more pegvisomant to normalise IGF-I levels have more aggressive disease
- It is not possible to predict who will respond to the starting dose

Partially resistant to SSAs: what next? Switch to pegvisomant: Drake

- Pegvisomant has the ability, if you get the dose right, to control SSA-resistant patients
- Indices of glycaemic regulation can improve on moving from SSAs to pegvisomant
- There does not seem to be an issue with tumour enlargement

Partially resistant to SSAs: what next? An alternative treatment approach: Neggers

- Nobody has a clear definition of resistance
- There are possible benefits in using combination therapy because drugs have different modes of action
- A combination might therefore lead to lower doses