YEAR REPORT 2013

DEPARTMENT OF ENDOCRINOLOGY

INTERNAL MEDICINE

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1. Personnel

The members of the Department of Endocrinology and Metabolism are responsible for providing care to a large and heterogeneous group of patients with endocrine and metabolic diseases and for teaching and training students, residents in Internal Medicine, fellows training to become an endocrinologist, as well as scientific research in these fields.

In 2013 the following persons were members of our department:

Mrs. G.M. Alkemade, MD     internist-endocrinologist
Mrs. N. Alma - Bierma (Natasja)    secretary
Mrs. S. van Asselt, MD (Sophie)    physician, PhD student
A.P. van Beek, MD PhD (André)    internist-endocrinologist
G. van den Berg, MD PhD (Gerrit)    internist-endocrinologist
Mrs. B.T. de Boer - de Boer (Berber)    diabetes nurse specialist
Mrs. T. Bos (Tineke)    diabetes nurse specialist
Mrs. P. Brummelman (Pauline)    psychologist, PhD student
Mrs. D. van Dijk, MD (Deborah)    physician, PhD student
Mrs. E. van Driesum (Els)    diabetes nurse specialist
R.P.F. Dullaart, MD PhD (Robin)    internist-endocrinologist
Mrs. W. van El, MA (Winnie)        nurse practitioner diabetes
Mrs. C. Frantzen, MD (Carlijn)    physician diabetes rehabilitation
B. Groen, MD (Bart)     internist-endocrinologist
Mrs. M.A. Groeneveld (Mariska)    research assistant
Mrs. B.G. Haandrikman (Bettine)    medical analyst
Mrs. A.N.A. van der Horst-Schrivers, MD PhD (Anouk)  internist-endocrinologist
Mrs. K.B.M. Janson (Carla)    diabetes nurse specialist
Mrs. A.B. Jongbloed (Alied)    diabetes nurse specialist
M.N. Kerstens, MD PhD (Michiel)    internist-endocrinologist
Mrs. M.M. van der Klauw, MD PhD (Melanie)  internist-endocrinologist
Mrs. E. Klein Hesselink, MD (Esther)    PhD student
Mrs. M. Klein Hesselink, MD (Marielle)    PhD student
Mrs. G. Kreugel, MSC (Gillian)    nurse consultant diabetes
Mrs. prof. T.P. Links, MD PhD (Thera)    internist-endocrinologist
Mrs. H.C.M. van Loon, MD (Hannah)    internist-endocrinologist in training
Mrs. H. Lutgers, MD PhD (Helen)    internist-endocrinologist
P. van der Most (Peter)    research support
Mrs. T.E. Osinga, MD (Tamara)    internist-endocrinologist
Mrs. S.M. Pathuis (Susanne)    diabetes nurse specialist
Mrs. A.C. Persoon, MD PhD (Adrienne)  internist-endocrinologist in training
Mrs. Y. Plantinga, PhD (Yvonne)    movement scientist
Mrs. I.E. Pop (Inge)    research assistant
Mrs. S.N. Slagter (Sandra)    health scientist, PhD student
Mrs. H. van der Sluis (Heleen)    research assistant
W.J. Sluiter, PhD (Wim)     biochemist, statistician
Mrs. L. Stoffer (Lammie)    research assistant
H.H.G. Verbeek, MD (Hans)    physician, PhD student
Mrs. J. van Vliet-Ostaptchouk, PhD (Jana)    post-doc
F. Volbeda, MD PhD (Franke)    internist-endocrinologist in training
Mrs. W.A.M. Vrij-Spieker (Mini)    diabetes nurse specialist
Prof. B.H.R. Wolffenbuttel, MD PhD (Bruce)    internist-endocrinologist
February 27, 2013, was the day of the thesis defense by dr. Walter K.H. Kuchenbecker. Title of his thesis was Obesity and female infertility. Promotores were prof. J.A. Land and prof. B.H.R. Wolffenbuttel, co-promotores were dr. A. Hoek and dr. H. Groen.

Obesity in women is associated with an increase in infertility and more pregnancy complications. The cost per live birth after fertility treatment is almost two-fold higher in women with obesity compared to women of normal weight.

Obesity related infertility and pregnancy complications are determined by body fat distribution. Accumulation of fat around the abdomen and especially accumulation of intra-abdominal fat are a risk factor for infertility and pregnancy complications. Ultrasound measurement of intra-abdominal fat is a reliable, cheap and accessible tool to study the effects of intra-abdominal fat on female reproduction. The measurement of serum adipokines, the secretory products of adipose tissue, does not adequately reflect body fat distribution parameters. Weight loss in obese and infertile women is associated with more spontaneous pregnancies and a decrease in pregnancy complications. In anovulatory women with polycystic ovary syndrome, loss of intra-abdominal fat is associated with resumption of ovulation. In structured lifestyle programmes many women who are obese and infertile show poor compliance and experience difficulty in losing weight, leading to high drop-out rates. Future studies should aim to identify risk factors for drop-out and design individualised lifestyle programmes in order to limit drop-out. Weight loss medication and bariatric surgery may be considered in women with severe obesity and infertility in order to achieve sufficient weight loss and limit the serious obesity related pregnancy complications. In view of the serious obesity related pregnancy complications, women with a BMI > 35 kg/m2 should not be offered fertility treatment.

On October 2, 2013, Joris van Ark defended his thesis titled: Role of circulating vascular progenitor cells in the development of macrovascular disease in diabetes. Promotores were Prof. dr. J.L. Hillebrand and Prof. dr. B.H.R. Wolffenbuttel.

Joris studied the role of vascular progenitor cells in diabetes. Cardiovascular diseases are the number one cause of death in industrialised countries. Macrovascular disease (MVD) contributes to this to a considerable extent. Type 2 diabetes is associated with a 2- to 4-fold increase in rates of MVD. The underlying causes of the accelerated progression of MVD in diabetes are incompletely understood. Therefore, new insights into the mechanisms behind the development of MVD are essential to develop effective therapies for the prevention and treatment of MVD in patients with diabetes. Circulating vascular progenitor cells (VPCs) contribute to the health and maintenance of blood vessels. Different types of VPCs are described which have different effects on...
the development of MVD. Endothelial progenitor cells (EPCs) and circulating angiogenic cells (CACs) inhibit the progression of MVD. On the other hand, smooth muscle progenitor cells (SMPCs) are able to stimulate the progression of MVD. In this thesis we investigated the role of circulating VPCs in the development of MVD in patients with type 2 diabetes. We demonstrate that the number of protective EPCs and CACs is decreased in the blood of diabetic patients. In contrast, the number of damaging SMPCs is slightly increased in these patients. Therefore, the balance between protective and damaging VPCs is disturbed in favour of the latter. This may contribute to the accelerated development of MVD in patients with diabetes. This makes VPCs a potential therapeutic target to inhibit the progression and prevent the complications of MVD in patients with type 2 diabetes.

On December 9, 2013 miss Pauline Brummelman succesfully defended her PhD thesis, entitled: 
*Cognition in patients treated for pituitary diseases*
Promotores were prof. B.H.R. Wolffenbuttel, prof. O.M. Tucha, co-promotores dr. André van Beek and Janneke Koerts.

Pituitary diseases are characterized by abnormalities related to undersecretion or oversecretion of pituitary hormones with or without local mass effects. The cause of these diseases is often a pituitary tumour, which is usually benign and emanates from the anterior pituitary. In general, treatment of pituitary adenomas consists of surgery, which may be followed by radiotherapy in cases of a significant tumour remnant or regrowth. Due to the pituitary disease itself, or after treatment with surgery and/or radiotherapy, hormonal therapy may be necessary in case of new or persistent hormonal disturbances. Literature suggests that these different treatment options may have an effect on cognition. However, reported results were inconsistent and mostly derived from small and heterogeneous patient groups according to diagnose and treatment. Therefore, we studied the effects of radiotherapy and hormonal and medical therapy on cognition in large and homogenous groups of patients treated for pituitary diseases. We found that multiple field radiotherapy techniques and fractionated radiation dose regimens did not have a major effect on memory and executive functioning in patients treated for a non-functioning pituitary macroadenoma. In patients treated for acromegaly, we found that previous growth hormone excess and growth hormone suppressive medication were not associated with impaired cognitive functioning. Further, in a large study with extensive neuropsychological evaluation, we found that patients treated for secondary adrenal insufficiency had selective impairments in the cognitive domains of memory, attention, executive functions and social cognition.
2. Healthy ageing in Endocrinology

Healthy ageing
As can be read on the website of the UMCG, Healthy ageing is a lifelong process that starts even before conception, with parents who pass on their genes and with them the risks and opportunities for a healthy life course, or the occurrence of illness later in life. Lifestyle, food patterns and environmental factors influence the development of health. However, new knowledge is required about the influence of these factors, and how they interact with one another. In Groningen Healthy Ageing is seen as a multidisciplinary research challenge for the UMCG and several faculties of the University of Groningen.

This approach extends from fundamental biological and (pre)clinical research through to applied research into social-societal effects of disease and health. In this way results can be translated rapidly into adequate and/or improved prevention and treatment methods. This in turn leads to new products in the field of medication and medical technology for making diagnoses, and for example for the development of new nutritional products – another aspect in which this research is of vital importance.

How about our department?? It is apparent that the field of Endocrinology is very important in these Healthy Ageing activities. Several endocrine diseases are exemplary for the way how doctors treat and guide patients in attaining and maintaining a healthy lifestyle, in order to prevent the development of diseases and their complications. For instance, obesity increases the risk of developing type 2 diabetes, and patient care and research activities of our department focus on the pathophysiologic mechanisms which lead to development of obesity. Obesity, especially abdominal obesity will deteriorate several metabolic pathways, increase inflammation and cause insulin resistance, which will ultimately lead to the development of diabetes. Finally, we study the biochemical, sociological and psychological processes which influence the life course of an individual with obesity and diabetes, and which are decisive whether a patient will or will not develop secondary microvascular or macrovascular complications. Our research (see also chapter 8) also incorporates studies on psychological aspects of chronic endocrine disease and coping styles.

And obesity and diabetes are not the only endocrine and metabolic diseases, which interfere with ‘Healthy Ageing’. Thyroid diseases frequently occur in the general population, and our department has established a high prevalence of undiagnosed primary hypothyroidism in the participants of the LifeLines Cohort Study. Also osteoporosis, a reduction of bone mass and strength, is a disorder which is increasingly observed in the ageing individual, and this disorder may lead to consequences like fractures of vertebrae, with several complaints like back pain, reduced mobility, loss of independence, and a high need for supportive or nursing home care.

Fig. 1. The Endocrine System
3. Health care / patient activities

Clinic Ward E4

The number of patients admitted to our ward E4 was 302, about similar to earlier years. Yet this number remains lower than in the years 2003-2005. This is in part related to the fact that more of our care is shifting towards an outpatient base, and fewer acute admissions because of metabolic derangements like diabetic ketoacidosis and hypoglycaemic coma. In addition, it has to be mentioned that several of our patients had to be admitted to other wards in certain periods of the year, when there is shortage of hospital beds. With the introduction of new endoscopic techniques, most patients after pituitary surgery now stay only for 3 - 4 days in the hospital. Only in the case of postoperative issues like development of diabetes insipidus, which necessitates a longer hospital stay, they are transferred to the Endocrinology department for treatment.
The average admission time did not change, as with efficient and careful planning of diagnostic procedures and treatment, as well as hospital discharge and outpatient follow-up, we try to cope efficiently with our scarce resources. Despite this, still a number of patients needed a hospital stay of more than 14 days. Mostly, these were patients with severe diabetic foot problems, requiring long-term intravenous administration of antibiotics, intensive wound treatment and recurrent debridements, but also patients who appeared to have severe cognitive problems, and were waiting for transfer to a nursing home.

Here, we wish to acknowledge the skilful and dedicated work of the nursing staff of the ward of E4.

Outpatient clinic

The number of outpatient-clinic visits increased further in 2013. The number of patients seen for the first time has increased again with 2%, despite the fact that 10% of referrals is not rewarded because of the type of medical problems but mainly to limit budget overrun. This reflects the high need for consultations on a variety of endocrine diseases by G.P.’s and patients. By the institution of ‘dedicated’ clinics for newly referred patients we were able to reduce the average waiting time for patients to less than two weeks. Patients are referred by General Practitioners (G.P.’s), or by medical specialists within the UMCG, as well as colleagues from surrounding hospitals. All referrals have to be made digitally, and are judged by one of the staff members on a daily basis, so that we can give priority to those patients with the highest urgency. If needed, patients can and will be seen the same day, for instance for patients with newly-diagnosed type 1 diabetes, who have to start insulin therapy instantaneously. Also, patients who are suspected to have an endocrine tumour, or who have a thyroid nodule will be seen within a period of 1-2 weeks, in order to start their diagnostic work-up and treatment as soon as possible. Most of the speed of the diagnostic process depends on the ‘down-stream’ investigations like MRI, CT or ultrasound.

Like we mentioned in last year’s report, it is often mentioned in the newspapers and by other media that doctors create extra work themselves. This remains an absolutely ridiculous suggestion. Over 90% of patients are referred by their G.P. or by a medical specialist outside our department, often outside of the UMCG.

<table>
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<th>Year</th>
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<th>Outpatient clinic visits#</th>
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<td>570</td>
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# only follow-up visits
Also this year we have been faced with a 4% ‘no show’ result. This means than on average in one of 25 appointments patients did not show up for their initial or follow-up visit, without prior cancellation. In this lost time, other patients could have been helped. For this reason, we have continued to make telephone calls to all patients who do not show up for their appointment, in order to reduce future ‘no-shows’, and also have started sending reminders to patients by regular mail. We wanted to send SMS messages to our patients, but this was not allowed as the ‘UMCG has no policy for this’. Luckily, even with sending regular letters, we have observed that the number of ‘no-shows’ almost halved.

Our outpatient care for people with diabetes mellitus is carried out together with our colleagues from the Department of General Internal Medicine. Since the beginning of September 2006, diabetes care is offered based on a ‘One Stop’ principle in the University Diabetes Center, the first and only dedicated Diabetes Center in the Northern part of The Netherlands, and the first Academic Center in our country. All care providers can be found within the same location, i.e. the first floor of the A-wing of the Triade building (entrance 23). Here a patient can be seen by the internist, diabetes nurse specialist, dietician, podotherapist. There is a facility for making retinal photographs, and for drawing blood for laboratory determinations. In the first quarter of 2009 we have also started clinics by a psychologist. In addition, one floor lower patients can participate in all kinds of sports activities in the Sports and Movement Center. Fortunately, already in 2008 the Information Post of the Dutch Diabetes Patient Association (Diabetesvereniging Nederland) had to close down because of lack of time of their volunteers, and this facility is dearly missed.

We also witnessed other changes in patient care in the northern region. Many more patients requested to have a second opinion because of doubt of the initial diagnosis or treatment, but also to learn more about their disease from our experienced staff. People get better informed, and this is reflected in the increasing number of second opinions.

People in The Netherlands also get more obese. Especially in our Diabetes Center we witness a rapid increase in patients referred because of diabetes occurring during pregnancy. They are counselled by our team consisting of a gynaecologist, endocrinologist, diabetes nurse specialist and dietician. Because of the fact the there is only a limited capacity for dietary counselling within the UMCG, we were able to secure rapid access to a dietician in our Center itself. Luckily, dietary counselling was reimbursed again by health insurance companies in 2013.

Finally, it is fancy to establish dedicated “centers” in Dutch hospitals for whichever condition. So we witness the birth of thyroid centers, thyroid cancer center, adrenal centers, pituitary centers, ovary centers, centers for unexplained complaints, vascular centers, rhinitis and flu centers, menopause centers, etc. In our department, we do not believe in such “window-dressing”, but instead we continue to collaborate intensively with all colleagues from other departments within special teams, as mentioned in appendix 2, in order to provide the most optimal care for our patients, whether they have a frequently-occurring disease or one that is very rare.
‘Topreferent’ care

As there are many endocrine glands and metabolic diseases, an endocrinologist takes care of a group of patients with a large variation of diseases. Several groups of patients are referred to our department because of specific disease problems. These include:

* thyroid carcinoma
* thyroid dysfunction and goiter
* pituitary tumours
* adrenal diseases (tumours, phaeochromocytoma, disturbances of steroid synthesis)
* endocrine tumour syndromes (MEN1, MEN2, VHL, Cowden disease, neurofibromatosis, SDH mutations etc)
* pregnancy and diabetes
* diabetic complications, including diabetic foot problems
* insulin pump therapy
* rare (congenital) metabolic diseases

There is an extensive collaboration with the endocrinologists working in the hospitals in the four northern provinces (Friesland, Groningen, Drenthe, Overijssel) of The Netherlands. Some of our patients come from distant parts of our country, and may travel up to 300 km for their appointment at the outpatient clinic!

Multidisciplinary patient care

We have multidisciplinary groups of physicians, nurses and dieticians for the care of the above-mentioned patients suffering from thyroid carcinoma, pituitary diseases, diabetic foot problems, diabetes and pregnancy, as well as Turner’s syndrome. These teams get together on a regular base to discuss patient problems and the multidisciplinary treatment of complex patients. For diabetic foot patients there is a combined outpatient clinic once monthly on Thursday afternoon, in addition to the separate clinics held at the Dept. of Orthopaedics, the Dept. of (Vascular) Surgery, and the Diabetes Center. For patients with pituitary problems, there is a weekly multidisciplinary outpatient clinic on Friday afternoon. For patients with metabolic diseases, like inborn errors of metabolism or mitochondrial respiratory chain diseases (MRCD’s), there is a dedicated ‘metabolic’ clinic on Monday morning. Adult patients with Turner’s syndrome are periodically checked at a combined outpatient clinic, staffed by an endocrinologist and a gynaecologist.

Prof. Links and dr. van der Horst-Schrivers are responsible for the Multidisciplinary Thyroid Tumor working group, which is also part of the UMC Groningen Cancer Center, dr. van den Berg and dr. van der Klauw for the Pituitary Outpatient Clinic, dr. van der Klauw for the Diabetic Foot Collaboration, dr. Alkemade and prof. Wolffensbuttel for the Metabolic Diseases clinic, dr. van den Berg and prof. Links for the Diabetes and Pregnancy Team and dr. Kerstens and dr. van Beek for the multidisciplinary Turner Team. Dr. van Beek is involved in the specialized care for morbid obesity in a collaboration with the Center for Obesity Netherlands (Leeuwarden), a large referral center for bariatric surgery. Also there is intensive interaction with the Department of Oncology related to the treatment of patients with neuroendocrine tumours.

All these activities are not possible without the assistance of a dedicated staff of administrative personnel. These included in 2013 Monique Gelms, Anita Scholten, Berber Brandsma, Fenna Diepenbroek-Beulakker, Bea Hartman, Margriet Huppes-Feenstra and Mirjam Trenning-Rasker, as well as all the administrative personnel responsible for the letters to G.P.’s regarding our patients.
4a. Diabetes mellitus / Diabetes Care

Integrated diabetes care
The UMCG supports the concepts of the Dutch Diabetes Federation, which are summarized in a specific Standard of Care for the Treatment of Diabetes (www.diabetesfederatie.nl). For us, integrated care means:
1. Optimal medical treatment and supportive care.
2. Education and learning to master skills and knowledge, needed for optimal self-management.
3. The process in which the person with diabetes experiences and improves his position in society.

Our care is based on International Guidelines, summarized in the Dutch NDF/CBO guidelines. These guidelines preferably are based on evidence coming from clinical practice and controlled clinical trials. In case insufficient evidence exists, we have adopted our diagnostic and treatment protocols on the basis of the vast experience of our staff. The medical responsibility resides with the physician, but our Diabetes Management Team includes diabetes nurse specialists, dieticians, a podotherapist, a psychologist, and a social health worker. We offer integrated diabetes care on two locations of the UMCG. Our regular outpatient clinic can be found in the Triade building (Entrance 23) at the Hanzeplein, the location of the UMCG in the middle of the city of Groningen. The other location harbours the Diabetes Rehabilitation program, and is situated within the Center for Rehabilitation Beatrixoord. Together, these locations form the University Diabetes Center, the only Diabetes Knowledge and Expertise Center in the northern part of The Netherlands.

The diabetes nursing staff consisted of:

There are extensive collaborations between the medical staff of the Endocrinology Department and care providers within the UMCG and outside the UMCG, including regional hospitals, medical specialists, and G.P.’s in the northern part of The Netherlands.
Multidisciplinary treatment programs are available for several groups of patients:

1. **Patients with limited or no secondary complications**
   For patients in this category, to a large extent suffering from Type 1 diabetes, emphasis is placed on diabetes education, learning how to handle diabetes and how to prevent the development of complications. Patients are seen three times per year by the diabetes nurse specialist, and once or twice by the endocrinologist.

2. **Patients with long term complications**
   The care for this patient group is coordinated by the internist-endocrinologist. They follow these patients with a frequency of at least three to four times a year, and all patients will visit the diabetes nurse specialist at least once a year, with support regarding all aspects of care, including intensified diabetes education.

3. **Specific patient groups**
   For specific groups of patients we have an individual and dedicated counselling program.
   
   a. **Teenagers & adolescents**
      Yearly, teenagers of 15 and 16 years old are referred for continuation of their care from the out-patient clinic for children to the out-patient clinic for adults. This year we have a new transition program to prepare them for the new situation. An information meeting is organised for the teenagers without the parents. During this afternoon, a children’s’ diabetes nurse specialist, a diabetes nurse specialist of the outpatient clinic for adults and also the internist-endocrinologist are present. During the meeting the teenagers are introduced to each other, the diabetes nurse specialist and the internist-endocrinologist. There is ample time to exchange information on what the teenagers can expect in the new situation and what to do with questions or in case of emergencies. Also, they get a brief tour in the clinic. Two follow-up appointments are planned combining the paediatrician and the endocrinologist, these visits are planned at our out-patients clinic so the adolescents can get used to their visits at our department. Follow-up appointments with the endocrinologist and the diabetes nurse are planned. In some cases the teenager comes together with the parents. We have special afternoons for the transition-group so they can meet each other in the waiting room. The outpatient clinic visits are different, in that patients are seen by the endocrinologist and the diabetes nurse specialist at the same time, and there is more time per consultation. As can be expected, problems in diabetes care are different in adolescents compared to the adult population.

   During the transition phase of adolescents from the paediatric outpatient clinic to the adult outpatient clinic we have an intensive collaboration between the paediatrician and adult diabetes specialists. Each year in September and December the paediatric endocrinologist and the paediatric diabetes nurse have an appointment with the 17 year old adolescents in the outpatient clinic for adults.
   In March and June of the following year the young adults have an appointment with the paediatric endocrinologist and the endocrinologist simultaneously as well as an appointment with the paediatric diabetes nurse and the diabetes nurse.
   After these appointments follow-up appointments with the endocrinologist, the diabetes nurse, the dietician and the social worker are planned. Often the young adults come together with their parents. We have special day parts for the transition-group so they can meet each other in the waiting room. These outpatient visits are different, in that patients are seen by the endocrinologist and the diabetes nurse specialist at the same time, and there is more time per consultation. As can be expected, problems in diabetes care are different in adolescents compared to the adult population. When needed patients can be referred to a medical psychologist for counselling.
b. Pregnancy

It is widely known that optimal glycaemic control is necessary to minimise the development of congenital abnormalities or perinatal complications in the newborn babies. This takes a lot of effort. Patients with a wish to become pregnant are offered an intensified outpatient program supported by low-threshold phone, fax or e-mail contact to obtain normal HbA1c levels (HbA1c ≤ 6.5% on at least two occasions) before pregnancy. Folic acid supplementation is started at least two to three months before becoming pregnant.

The patients who have become pregnant and patients with gestational diabetes are treated, in a multidisciplinary cooperation, by an internist-endocrinologist, diabetes specialist nurse, gynaecologist, dietician and ophthalmologist. Treatment and follow-up protocols are available, and they have been standardized according to local and (inter)national guidelines.

The revised NVOG guidelines for gestational diabetes in 2010 has been widely implemented in our region. Since this revised guideline clearly present high risk groups for gestational diabetes as well as the indications for performing an ‘oral glucose tolerance test’ (OGTT), the amount of OGTT’s has largely increased. The amount of positive OGTT’s has increased in parallel, resulting in a high referral rate to our diabetes outpatient clinic. Therefore we have established a separate multidisciplinary gestational diabetes clinic, enabling the opportunity for an immediate consult by the diabetes nurse, dietician and internist-endocrinologist. Despite the high turnover patient rate, the mean amount of GDM-patients in care at the same time is about 40-50. Every three weeks, all GDM patients are discussed in our multidisciplinary diabetes-obstetrics meeting. Six-weeks after giving birth, the patients are invited for a postpartum check-up, considering their actual cardiovascular risk factors and to discuss the risk for recurrent gestational diabetes in the following pregnancy and the lifetime risk for developing of type 2 diabetes. A postpartum OGTT is offered to all patients as well.

We have recently started a long term follow-up study to investigate whether the mother-newborn outcome has improved by this intensified gestational diabetes care.

c. Kidney patients

A Shared Care model for diabetic patients at different stages of chronic renal failure (end-stage renal disease or pre-dialysis, renal replacement therapy and post kidney transplantation) has been established in 2006. Providing integrated diabetes care with optimal accessibility to CRF patients with diabetes is the key feature of this model. A nurse practitioner specialized in diabetes care has a central role in this project. In close collaboration with the department of Nephrology several changes have been realized in the diabetes care organization for this high-risk patient group. Examples of these changes are positioning of the nurse practitioner as the central coordinator for all diabetes related care and consultation and counselling of the patients during their dialysis sessions. In addition, a counselling program specifically adapted to kidney transplant patients has recently been started.

In connection with this, we initiated the discussions on integrated diabetic and nephrologic clinical guidelines and of evidence based nursing guidelines for diabetes care on the dialysis department. The nursing guidelines will be developed in collaboration with the Dutch Association of Dialysis and Transplantation Nurses (LVDT).

Financial support for the implementation phase of this project was supplied by AMGEN BV and the office of Medical Technology Assessment of the UMCG (Innovation Fund).

d. Continuous blood glucose monitoring

Since a few years, needle-like sensors are available which continuously monitor glucose concentrations in the subcutaneous tissue. These glucose levels are well correlated with blood glucose levels, and these sensors give a new reading of the glucose concentration every one to five minutes. Patients can thus monitor their glycaemic control on a continuous base, and adjust treatment, for instance insulin dose, when glucose levels are getting outside target. This is called real-time continuous glucose monitoring, or RT-CGM.
Year costs are approximately 5000 Euro, so this is not a cheap way of monitoring glucose levels! Although these devices have been available since 2006/2007, their use in patient care has been made rather difficult by an unbalanced, methodologically incorrect and ethically rejectable evaluation of their use in an advice to the Dutch authorities, suggesting no clinical benefit, and a decision was made which prohibited their reimbursement by health insurance companies. Nevertheless, some patients had the luck that their health insurance provider did approve and reimburse sensor use, while others, insured with the same company, were less lucky. This inequality in rights has caused much suffering amongst patients, especially those with hypoglycaemia unawareness who benefit enormously from the early alarms provided by RT-CGM when their blood glucose falls dangerously low. One physician, a person with diabetes whose use of RT-CGM resulted in a major improvement of glycaemic control (his HbA1c fell from 10 to 6.3%) without an increase in hypoglycaemic episodes, has been engaged in a legal procedure to obtain reimbursement, which took almost three years.

This situation came to an end, when Dutch authorities, on initiative of and in close collaboration with the Dutch Diabetes Federation finally approved use of RT-CGM for specified groups of patients with type 1 diabetes. All documents related to this can be found on the website of the Diabetes Federation (www.diabetesfederatie.nl). The current indications for use are in good agreement with the criteria discussed in a recent paper by prof. Irl Hirsch, and by our own paper on this topic, published in 2008. Strengthened with these results, the UMCG was able to negotiate in 2010 an agreement with the regional health insurance companies for reimbursement of RT-CGM use for a total of 57 patients in 2011.

e. Transplantation
The incidence of post-transplantation diabetes or New Onset of Diabetes After Transplantation (NODAT) has increased over the past years, and the awareness of the impact of this problem is currently growing. NODAT occurs after all types of solid organ transplantations, and the estimated incidence of NODAT 1 year after transplantation is ~ 10-40%. The clinical importance of NODAT relies not only in the accelerated development of diabetes complications, but also in the fact that it may contribute to transplantation specific complications such as acute/chronic rejection and infections.

The Groningen Transplantation Center (GTC), is a division of our hospital that integrates care and research for all types of transplantations, according to the theme ‘Shared Care for shared organs’. In 2013 we started with the GTC a project to incorporate post-transplantation diabetes care transplantation-wide into regular care, for both in- and outpatients. A team of nurse practitioners, diabetes nurse specialists and endocrinologists is adapting our well-established renal transplant protocol to other organ transplantations. With this project, we aim for earlier identification, diagnosis and treatment of NODAT to further improve long-term patient and graft survival and decrease NODAT associated morbidity.

4. Group sessions
In 2008 we have started to organise group sessions for patients and their relatives, and these have continued in 2009. These sessions comprise three half days. The first day the diabetes nurse gives information about diabetes, insulin administration, hyperglycaemia and hypoglycaemia. The dietician discusses the relationship between life style and nutrition. At the second day self-management, life style and special situations like vacation, sickness and work are the main topics. The podotherapist discusses several aspects of foot care. At the final day the endocrinologist gives information about the complications of diabetes mellitus and their prevention. Also the program at Beatrixoord and the psychosocial effects of diabetes mellitus have a special place in this group session. During the sessions the participants can share their experience, we stimulate to have a interactive program.

In 2013 some interactive programs took place
- how to deal with the bolus wizard
- how to live with diabetes, this one was for young adults
5. Psychological care
Depressive symptoms are a common problem in patients with diabetes, laying an additional burden on both the patients and the health care system. Offering brief evidence-based treatments aimed at alleviating depressive symptoms could improve patients’ medical and psychological outcomes. However, well-designed trials focusing on the effectiveness of psychological treatments for depressive symptoms in patients with diabetes are scarce. In 2010, we initiated the Mood Enhancement Therapy Intervention Study (METIS) to examine the effectiveness of two psychological treatments in patients with diabetes. Individually administered Cognitive Behavior Therapy (CBT) and Mindfulness-Based Cognitive Therapy (MBCT) were compared with a waiting list control condition in terms of their effectiveness in reducing the severity of depressive symptoms. In total, 94 patients were included from the UMCG, Hospital Rivierenland Tiel, Martini Hospital, and the Medical Center Leeuwarden. Recently, the main outcome paper of this trial was accepted for publication in Diabetes Care.

Individual Mindfulness-Based Cognitive Therapy (MBCT) and Cognitive Behavior Therapy (CBT) for treating depressive symptoms in patients with diabetes: Results of a randomized controlled trial
Objective: Depression is a common comorbidity of diabetes, undesirably affecting patients’ physical and mental functioning. Psychological interventions are effective treatments for depression in the general population as well as in patients with a chronic disease. The aim of this study was to assess the efficacy of individual Mindfulness-Based Cognitive Therapy (MBCT) and individual Cognitive Behavior Therapy (CBT) in comparison to a waiting list control condition for treating depressive symptoms in adults with type 1 or type 2 diabetes.
Research design and methods: In this randomized controlled trial, 94 outpatients with diabetes and comorbid depressive symptoms (i.e., BDI-II ≥ 14) were randomized to MBCT (n = 31), CBT (n = 32), or waiting list (n = 31). All participants completed written questionnaires and interviews at pre- and post-measurement (three months later). Primary outcome measure was severity of depressive symptoms (BDI-II & HAM-D7). Anxiety (GAD-7), well-being (WHO-5), diabetes-related distress (PAID), and HbA1c levels were assessed as secondary outcomes.
Results: Results showed that participants receiving MBCT and CBT reported significantly greater reductions in depressive symptoms compared to patients in the waiting list control condition (respectively P = 0.004 and P < 0.001; d = 0.80 and d = 1.00; clinically relevant improvement 26% and 29% vs. 4%). Both interventions also had significant positive effects on anxiety, well-being, and diabetes-related distress. No significant effect was found on HbA1c values.
Conclusions: Both individual MBCT and CBT are effective in improving a range of psychological symptoms in individuals with type 1 and type 2 diabetes.

6. Newly referred patients
There is an extensive program for patients who are newly referred by their G.P. or by another medical specialist. In this program both the endocrinologist, diabetes nurse specialist and dietician participate. There is considerable attention for improvement of the skills and knowledge, which a person with diabetes needs for optimal self-management. If needed, other specialists like psychologist or podotherapist can be consulted.

The patients we care for in our Diabetes Center come from all areas of The Netherlands, even from the southern provinces of Limburg and Brabant. However, the majority of them live in one of the four (or five if you include Flevoland) northern provinces: Groningen, Friesland, Drenthe or Overijssel. Their treatment is based on formalized treatment protocols, which include the majority of advices and guidelines issued by the
Dutch Diabetes Federation, as well as by the American Diabetes Association and the European Association for the Study of Diabetes. For several years we have requested logistic and programming support to realize an Electronic Patient File. Although preparations for this started in 2006, the former director of ICT stopped the project without explanation in 2007. In the meantime, Lucian Kluter -supporting staff member of the dept. of Internal Medicine- has built a simple, yet comprehensive registration system, which allows us to register all relevant diabetes-related items, and manage all correspondence to a patient’s G.P. Since the beginning of 2011, medical students have inserted all patient-related data into a database, so that we could report the results, achievements and quality of our diabetes care to the Zichtbare Zorg system. These reports can be found on our website www.umcg.net.

7. Diabetes Rehabilitation

In the Rehabilitation Center Beatrixoord, we provide an intensive multidisciplinary diabetes education and rehabilitation program. Eligible for this program are patients with complex diabetes-related problems, as well as problems related to self-management and acceptance of the disease. Half of the patients come from the outpatient clinic of our own hospital, whereas the other 50% are referrals from internists in the surrounding hospitals in the north of The Netherlands. Some patients even come from provinces like Zeeland and Limburg.

The program comprises several days of outpatient education in small-sized groups, with focus on practical aspects of diabetes acceptance, self-management and rehabilitation. Patients not only learn to define the problems they have with diabetes management, but also learn to attack them. For instance, the presence of 25 m swimming pool and a dedicated training and gymnastics facility will ensure that all patients can experience effects of exercise and training, and by doing this learn how to adjust their insulin dose and cope with varying blood glucose levels.

Long term results of the program are excellent, as described by our psychologist Joost Keers, who defended his thesis on this topic in 2005. Permanent improvement of diabetes control as well as health-related quality of life, but above all improved self-management skills have been the most important achievements. For this reason, the Association of Rehabilitation Physicians and the Dutch Diabetes Federation have rated this program ‘a high quality and indispensable asset’. After long negotiations with governmental bodies, we received in 2007 official approval of this program, and subsequently a considerable coverage of the program by health care insurance companies.

The following people form the team responsible for the Diabetes Rehabilitation Program (figure 4):
Mr. Albert Schuringa, team coordinator a.i.; Mrs. Linda Faber, mrs. Ingrid Stoelinga, mrs. Madelein Schotman, diabetes nurse specialists; Mrs. Marianne van Dijk, dietician; Mrs. Brigitta Joosen, en Mrs. Renske Bouman, physiotherapists; Mr. Guus van Bochove, movement scientist; Mrs. Heike Mesch, psychologist; Mrs. Jannet Waijer, social welfare; Mrs. Franka Waterschoot, ergotherapist.

They are supported by Mrs. Janine Kramer and mrs. Elsa Pieterman-Slagter, secretaries.

8. In-hospital management for patients with diabetes

Patients with diabetes have an increased risk to hospitalization due to complications such as coronary artery disease, cerebrovascular and peripheral vascular disease, nephropathy, infection and lower-extremity amputations. Moreover, there are currently about 1 million individuals with diabetes in the Netherlands and as a consequence many patients in the hospital will have diabetes as a comorbid condition. Hospital admission is associated with a great risk of glucose dysregulation. Stress responses to disease or surgery, fasting protocols, immobilization, use of certain drugs (e.g. glucocorticoids) and parenteral nutrition are examples of common hospitals situations which directly affect glucose homeostasis. Optimal diabetes regulation in the hospital reduces the risk of hypoglycaemia and might improve patient outcome.
In the UMCG, a specialized team (DROP; Diabetes Regulatie Opgenomen Patiënten) is responsible for the diabetes management of hospitalized adult patients, with the exception of patients staying at the internal medicine clinic or intensive care unit and pregnant patients with diabetes. Team members are internist-endocrinologists, internal medicine residents and diabetes nurses (project leader; M.N. Kerstens, MD, PhD). The diabetes nurse fulfils a central coordinating role in this team. Each ward is visited every day by the diabetes nurse. This daily presence is important for optimal monitoring of the glucose regulation at the point of care. In addition, it offers the opportunity to collect the latest information on the patients’ condition and to transfer practical knowledge about diabetes care to the local medical personnel. The diabetes nurse writes a management plan for every individual patient with diabetes, which needs approval by one of the team doctors before implementation. Underlying the therapeutic recommendations is a local evidence-based protocol on in hospital management of diabetes.

The medical aspects of Diabetes Rehabilitation as well as consultations for General Internal Medicine problems are performed by the medical staff of the Department of Endocrinology. In 2013, Carlijn Frantzen was taking care of day-to-day patient related activities, both in the Diabetes Rehabilitation program and as consulting physician for the other departments within the Rehabilitation Center.

9. Obesity

An obesity rehabilitation program, which started in 2005, is available for patients with diabetes or metabolic syndrome and obesity, complicated by long-term sequelae. The program aims to change lifestyle patterns by means of an intensive long-term program. Approximately 20 patients have been treated in this year. An internist-endocrinologist, diabetes nurse, dietician, psychologist, physiotherapist are involved in this multidisciplinary program. Experiences in this program are also used for the current development of an obesity treatment center.
10. The podotherapist

A Diabetes center cannot exist without dedicated people looking after the feet of our patients. We are lucky to have Marten de Haas as our podotherapist (figure 5), a young and eager care provider who is always prepared to devote extra time to his patients.

Fig. 5. Please knock. Entry to the office of the podotherapist

New developments

There have been several new developments in diabetes care and research. Already in chapter 3, we discussed the clinical availability of RT-CGM. In the meantime, we have realized that little is known about the influence of haemodialysis on glucose control in diabetic patients with end stage renal disease. In collaboration with the department of Nephrology, and Abbott, we therefore started a pilot study using a continuous glucose monitoring system in insulin-treated diabetic patients (n=20) on haemodialysis (coordinating investigator: dr. M.N. Kerstens).
4b. General Endocrinology

New developments

The Department of Endocrinology has a track record for the diagnostics and treatment of (neuro)endocrine tumours, in close collaboration with the Departments of Medical Oncology, Nuclear Medicine and Molecular Imaging, Genetics, Radiology, Pathology, Gastroenterology, Surgical Oncology and Clinical Chemistry. As a consequence, the UMCG is a referral center for non-hereditary as well as hereditary neuroendocrine tumours (MEN1, MEN2, VHL, NF, paragangliomas, SDH mutations).

Several innovative PET methods have been used such as 18F-DOPA and 11C-5-HTP for imaging of medullary thyroid cancer, phaeochromocytoma, carcinoids and pancreatic neuroendocrine tumours and 124I and 11C-methionin for papillary and follicular thyroid cancer. The organization of the medical care for patients with thyroid cancer will be structured in a Managed Clinical Network, initiated and supported by the Comprehensive Cancer Centre the Netherlands aiming agreement on uniformity and quality in all centres in the Northern and Eastern part of the Netherlands. Ongoing research supports these developments in better staging of disease and applying new therapies. The Endocrinology department participates and has participated in several national and international clinical trials with new targeted drugs like imatinib, sorafenib, vandetanib and XL 184 in patients with medullary thyroid cancer.

Already in February 2009 a national project for screening of pancreatic neuroendocrine tumours in Multiple Endocrine Neoplasia type 1 (MEN1) and Von Hippel-Lindau (VHL) disease has started employing imaging with endoscopic ultrasound (EUS) and [11C]-5-hydroxytryptophan (HTP) PET. This project is supported by the Dutch Cancer Society. Aim of the study is to define the value of [11C]-5-HTP-PET and EUS compared to CT/MR and octreotide (conventional imaging) in patients with MEN1 and VHL with proven pancreatic neuroendocrine tumor involvement or in screenings setting. For this study, two groups are defined: Group A (N=40): patients with already presence of neuro-endocrine tumors at CT/MRI scan and/or octreotide scan and/or biochemically proven and Group B (N=50): patients with no signs of pancreatic neuroendocrine tumors. In cooperation with University Medical Hospitals of Utrecht, Rotterdam and Nijmegen in 2009 24 patients were included, and in 2010 25 patients.

The VHL Family Alliance from the USA has supported an imaging study for visualizing vascular endothelial growth factor (VEGF) producing lesions in Von Hippel-Lindau disease by PET using the radiolabeled antibody of VEGF: (89)Zr-bevacizumab. This project started in the fall of 2009 and has recruited 10 patients in 2009 and 2010.

Von Hippel-Lindau disease; clinical developments

Von Hippel-Lindau (VHL) disease is inheritable and characterized by the development of multiple benign and malignant tumors throughout life. Patients may develop hemangioblastomas in the central nervous system - retina, cerebellum, spinal cord, supratentorial and brain stem- and lesions in the visceral organs - phaeochromocytomas in the adrenal glands, renal cell carcinoma and renal cysts, and pancreatic islet cell tumors and pancreatic cysts. VHL disease occurs at a mean age of 26 years, with range 1-70 years. Diagnosis of VHL can be based on clinical criteria or confirmed by germline mutation testing. To detect lesions in an early stage guidelines recommend frequent and intensive follow-up.

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Little is known about the origin of pancreatic cysts in Von Hippel-Lindau (VHL) VHL patients are prone to develop cysts and neuroendocrine tumors in the pancreas in addition to several other benign and malignant neoplasms. Remarkably, pancreatic cysts occur in approximately 70% of VHL patients, making it the only hereditary tumor syndrome with such a discernible expression of pancreatic cysts. Cellular loss of pVHL due to biallelic mutation can model pancreatic cystogenesis in other organisms, suggesting a causal relationship. Various pVHL functions have been elucidated, that can potentially explain pancreatic cyst development in VHL disease. Data is also limited about clinical consequences of VHL pancreatic cysts. Intervention has been indicated in only a minority of VHL patients (< 5%) No evidence exists for an association between endocrine or exocrine pancreatic insufficiency and cyst involvement. Moreover, no cases have been described of malignant pancreatic cysts in VHL disease. No relationship exists between presence of pancreatic cysts and pNETs. Conclusively, pancreatic cysts in VHL disease are not associated with malignancy and sporadically cause problems.

Thyroid

Thyroid cancer can be divided in various subtypes based on histology, of which the papillary and follicular type (differentiated thyroid cancers) form the vast majority of 80-90%. The incidence of thyroid cancer is rising globally. In the Netherlands the overall incidence rate increased from 2.0 per 100.000 person years in 1989 to 2.9 in 2009, resulting in about 600 patients now yearly. This is due to a rise in small T1 tumours and papillary tumours but also the number of more aggressive tumours is rising. The diagnosis and treatment of thyroid cancer is a very complicated process so optimal cooperation between the different medical disciplines in the hospitals but also between the regional hospitals is extremely important. To improve the quality of care the Dutch comprehensive cancer centres (IKNL) has initiated the managed clinical network. Medical specialist of all participating hospitals in the north east region has signed an agreement that summarizes the standard care for patients with thyroid cancer. The tumour working party of the University Medical Center is actively involved in these developments. Additionally the Endocrinology department participates and has participated in several national and international clinical trials with new targeted drugs like imatinib, sorafenib, everolimus, vandetanib and XL 184 in patients with medullary thyroid cancer. In close collaboration with the Leiden University Medical Center (prof. J.W.A. Smit and dr. H.W. Kapiteijn) several studies (sorafenib, everolimus, XL184) regarding differentiated thyroid cancer have been started and are ongoing.
Late cardiovascular effects of TSH suppression therapy in patients with differentiated thyroid carcinoma

Differentiated thyroid carcinoma (DTC) is the most common thyroid carcinoma type, as it accounts for approximately 90% of all cases. Standardized DTC treatment consists of a total thyroidectomy, radioiodine ablation, and thyroid hormone suppression therapy (THST). The latter consists of administration of relatively high doses of thyroid hormone, with the aim to suppress thyroid stimulating hormone (TSH), considered a growth factor for DTC. THST has been considered necessary for decades, as it is associated with less DTC recurrences and a better DTC survival. However, in recent years data emerged on adverse effects of THST on the cardiovascular system; it has been associated with an increased risk for atrial fibrillation, diastolic and systolic dysfunction, and adverse metabolic and prothrombotic effects. The European and American Thyroid Associations (ETA and ATA) therefore recommend to taper THST after initial treatment in patients with a low risk of DTC recurrence. Data on hard endpoints to support this recommendation is however lacking. Therefore we aimed to study whether cardiovascular and all-cause mortality is increased in DTC patients, and whether the degree of TSH suppression is associated with outcome.

The UMCG cohort of DTC patients (n=524) and sex- and age-matched control subjects from a large population based study of the same geographic region (n=1572) were retrospectively compared by Cox regression analyses.

We found that patients with DTC have a 3.3-fold increased risk for cardiovascular mortality and a 4.4-fold increased risk for all-cause mortality, adjusted for age, sex and cardiovascular risk factors. Furthermore, within the cohort of patients with DTC, the degree of TSH suppression was associated with cardiovascular mortality; each 10-fold decrease in mean TSH level was associated with a 3.1-fold increased risk for cardiovascular mortality, adjusted for age, sex, cardiovascular risk factors and DTC characteristics.

In conclusion, patients with DTC have an increased risk of cardiovascular and all-cause mortality, independent of age, sex and cardiovascular risk factors. A lower TSH level is associated with increased cardiovascular mortality, supporting the current ETA and ATA guidelines of tapering THST in patients with a low risk of cancer recurrence. Furthermore, DTC patients may benefit from assessment and

IEMO 80+ study

The UMCG is working with Certe and IEMO on the IEMO 80+ Thyroid Study.

Subclinical hypothyroidism is common in old age (by 8-18%). It has not yet been demonstrated whether treating the elderly with subclinical hypothyroidism is beneficial or not. Hypothyroidism has various symptoms seen in older adults: fatigue, mood disorders, and cognitive problems. In addition, the elderly with subclinical hypothyroidism appear to have and increased risk of cardiovascular diseases. But these studies are inconclusive, especially for the oldest people (80+).

In this study will be researched if treatment leads to lower cardiovascular risk and improve quality of life. We ask doctors to work in the selection of patients for the study. We are not asking them to include patients and/or treat them. The study is further carried out by the laboratory, pharmacy and study. The patients remain under treatment at the doctor. Patients do not have to come to the hospital for the study, they are visited at home.

And the study provides the answer to an important and common medical problem. The patient organization SON (Thyroid Organisation Netherlands) supports this study actively.
**Adrenals**

Primary hyperaldosteronism is increasingly being recognized as an important secondary cause of hypertension, with an estimated frequency of about 5-10% among hypertensive patients. The diagnostic work-up for primary hyperaldosteronism is relatively complex and requires clinical experience, availability of robust hormone assays for which reference values have been determined locally and expertise with adrenal venous sampling. The UMCG has elaborate experience with all the diagnostic aspects of primary hyperaldosteronism, and is currently one of the main referral centers in the Netherlands for adrenal venous sampling.

We received sponsoring from the UMCG for conducting a pilot study in which we will examine the diagnostic value of $^{11}$C-metomidate-PET/CT to differentiate between bilateral adrenal hyperplasia and aldosterone-producing adenoma. Inclusion of the first participants is scheduled for 2010. In collaboration with the department of Nuclear Medicine and Molecular Imaging, we started a pilot study (n=10) examining the diagnostic value of $^{11}$C-metomidate-PET/CT for the differentiation between bilateral adrenal hyperplasia and aldosterone-producing adenoma (coordinating investigator: dr. M.N. Kerstens).

**PRESCRIPT**

Pheochromocytoma is a rare but clinically important catecholamine secreting neuro-endocrine tumour that typically arises from the adrenal gland. Less frequently, this neuro-endocrine tumour originates from chromaffin cells in sympathetic ganglia. It is a potentially life-threatening disease with a high risk for cardiovascular
complications such as myocardial infarction, arrhythmias, cardiomyopathy, stroke and pulmonary edema. The clinical picture results from secretion of catecholamines (i.e. norepinephrine, epinephrine) by the pheochromocytoma. The only curative treatment is surgical resection of the tumour. General anaesthesia and surgery, however, pose a hazard to patients with a pheochromocytoma, as they might act as stimuli for uncontrolled release of catecholamines. Thus, preoperative treatment with α-adrenoceptor antagonists is usually recommended for prevention of these serious and potentially fatal complications. The optimal preoperative medical management for patients with a pheochromocytoma is unknown, and the choice for a particular vaso-active drug is predominantly determined by local experience. Clearly, no single hospital can claim extensive experience in view of the low incidence of this disease. For example, the incidence of pheochromocytoma in the Netherlands is estimated at no more than 75 – 100 patients per year. There are two α-adrenoceptor antagonists which are commonly prescribed preoperatively: phenoxybenzamine (noncompetitive and nonselective α-antagonist) and doxazosin (competitive and selective α1-antagonist). Retrospective studies comparing the efficacy of these two drugs have been inconclusive.

PRESIRECT (Pheochromocytoma RandomisEd Study Comparing adRenoreceptor Inhibiting agents for Preoperative Treatment; ClinTrials.gov NCT01379898) is a multicenter randomised controlled trial comparing the effects of pretreatment with either phenoxybenzamine or doxazosin on the intraoperative hemodynamic control in patients with a pheochromocytoma. PRESIRECT is the first non-surgical RCT to be conducted in patients with a pheochromocytoma. There are 14 Dutch hospitals participating in this study, including all 8 university medical centers (principal investigator: M.N. Kerstens, MD, PhD). A total of 134 patients need to be included and enrolment is expected to be completed in 2016.

The outpatient clinic of our Endocrinology department has a large population of patients with growth hormone (GH) deficiency. The care for these patients who are treated with GH substitution therapy is in part centered at the outpatient ‘growth hormone clinic’. Here, the formal start of GH substitution is initiated and followed at yearly intervals. This outpatient clinic has a highly structured character and is runned by Mrs. M. Groeneveld under supervision of Dr. A.P. van Beek. The year 2013 was special both for patients and endocrinologists because of the transition of GH medication into the hospital budget (‘overheveling’) leading to substantial changes e.g. in provision of GH by the hospital pharmacy and the signing of contracts with the pharmaceutical industries.

Collaboration with the Medical Center Leeuwarden – Center for Obesity Nederland.

A longstanding collaboration with the MCL is a growing in to more formal relationship with the appointment of Dr. A.P. van Beek as one of the coordinating investigators at the CON (Center for Obesity, the Netherlands). Central in this collaboration is the clinical care for the postbariatric patient with long term complications and the development of center of expertise with regard to postgastric bypass hypoglycemia (collaboration with departments of internal medicine (dr. P.H.N. Oomen, dr. L.J. de Heide, dr. F.L. Ubels) and Bariatric Surgery (dr. E.R.E. Totté, dr. J.A. Apers, dr. M. Emous).

The treatment of post-gastric bypass hypoglycaemia takes place both in a study at the Endocrinology department (phase 2b study, CSOM230X2203, Novartis) and at the regular outpatient clinic of dr. A. P. van Beek. In the scientific sense, this translates into innovative research on the role of gut hormones in post-gastric bypass hypoglycaemia. A PhD thesis of Drs. M. Emous is planned in 2015-2016 on the subject of these late complications after bariatric surgery.
5. Teaching

The Faculty of Medical Sciences of the University of Groningen is the second oldest medical faculty in The Netherlands. Like the university, it was established in 1614. Ever since the foundation of the Groningen University Hospital in 1797, hospital and faculty have been cooperating closely. The Faculty of Medical Sciences has two tasks: providing medical scientific education and carrying out medical scientific research. The University of Groningen provides high quality teaching and research, is internationally oriented, respects differences in ambition and talent, works actively with business, the government and the public, and ranks among the best universities in Europe. The University of Groningen has formulated its vision of the future in its Strategic Plan: 400 Years of Passion and Performance. Strategic Plan 2010-2015, which can be found at: http://www.rug.nl/umcg/faculteit/strategie/index

The fields of Endocrinology, Diabetes and Metabolism are important parts of this medical curriculum. Hormones play a pivotal role in the maintenance of all biochemical processes in the human body. Endocrine diseases can have several consequences for the functioning of organs like the eyes, the cardiovascular system, kidneys, skeleton and the musculoskeletal system. Therefore, our department participates in all teaching activities for students in the Bachelors phase of the School for Medical Sciences, the school for Dentistry and the Life Sciences cluster, and clinical training for the students in the Masters phase. The lectures are both patient demonstrations as well as theoretical lectures on endocrine physiology and pathology, including diabetes mellitus, thyroid and adrenal diseases, and pituitary development and pathophysiology.

In addition, staff members act as coach in the medical professionalization program (Year 2) as well as mentor or tutor for students in the first clinical year (Year 4), when students follow the introduction period in the clinic. Staff members are also involved in educational research projects for individual students from the UMCG but also from abroad.

Every year, the department organises a two-week teaching program (‘KPP’) specifically devoted to Endocrine Pathology. Students discuss major endocrine diseases based on actual patient cases, and follow patients in the outpatient clinic. Staff support also has been provided to the yearly ISCOM, International Student Congress of Medical Sciences by chairing oral and poster sessions.

At present, dr. Robin Dullaart is coordinator of the two blocks on chronic disease, including diabetes, obesity, vascular medicine and endocrinology in year 2 of the International Bachelor Medicine and Global Health (iBMG) program of this faculty. In the iBMG program, particular attention is paid to different aspects of global health, such as community-dwelling diseases, different health-care systems, health-care economics, and nutrition and health from a global perspective. In the academic year 2013, 47 iBMG students from 13 different nationalities started with the second year of medical school. Exam results were quite good, as 82% of the students had passed their exams at the end of this academic year. Less than 5% of the exam questions were disregarded, a record as compared to other exams in the Bachelor phase of medical training. Many students choose to do their Bachelor Thesis Project outside The Netherlands. During the Bachelor’s phase all students will have to learn Dutch to ensure appropriate communication with Dutch patients, which is a requirement to go on with the Master phase at our university.

Staff members also participate in the teaching programs of surgeons, urologists, oncologists, obstetricians and nurses practitioners, as well as specialised programs in the training of nurses.
6. Postgraduate education

The members of the department of Endocrinology actively participate in all kinds of postgraduate education activities for general practitioners and medical specialists, like the scientific meetings of the Dutch Association for Endocrinology (NVE), the Dutch Association for Diabetes Research (NVDO), Erasmus Endocrinology Course and the Dutch Association of Clinical Chemistry and Laboratory Medicine (PAOKC-course).

Netherlands Journal of Diabetology
There is intensive collaboration with Springer-BSL, editor of several diabetes-related journals. One of these activities is the Netherlands Journal of Diabetology, the one and only Dutch-language peer-reviewed journal, which aims to improve knowledge on diabetes mellitus and its treatment, by special attention for clinical and scientific developments. The journal publishes original articles, case reports, reviews, book reviews and brief summaries of important international papers. Since 2009 Dr. André van Beek is the chief editor of this journal.

Teaching Course for Diabetes Nurse Specialists
In October 2012, the fifth Teaching Course for becoming a Diabetes Nurse Specialists started in Groningen. This training is carried out in collaboration with the Institute Wenckebach School of Nursing & SSSV Bunnik. Coordinator is Alied Jongbloed, diabetes nurse. The training is based on the professional profile of diabetes nurse of the EADV. The course member is nurse with qualification level 4 or 5. The training consists of 5 modules: Health and Chronic disease; Methodical practice; Education; Quality and expertise; Policy and management

Postgraduate course on Endocrinology for G.P.’s
Every year in the month of October, the Wenckebach organization and the Dept. of Endocrinology jointly organise a meeting on endocrine disease for general practitioners. In 2013, the topics covered were rare endocrine disorders. As always, over 120 G.P.’s attended this highly rated meeting.

Fig. 6. Main entrance of the UMCG
Fig 7. The outpatient clinic for Endocrinology, and -on the 4th floor- our clinic ward
7. Training for Internal Medicine and Endocrinology

The Department of Endocrinology participates in the training program MD’s becoming internists, and offers these trainees a 4 months program which consists of outpatient clinics, clinical care for hospitalised patients and in-clinic consultations for patients with endocrine diseases and diabetes mellitus.

The Department of Endocrinology is one of the 8 academic training centers for clinical endocrinology in the Netherlands (AERA: Aandachtsgebied Endocrinologie, Nederlandse Internisten Vereniging), and is licensed as a European training center as well (UEMS). This training to become board-certified Endocrinologist in The Netherlands consists of a 18 to 24 months' program, during which the endocrinology fellow is trained in out-patient, clinical and consultative care of patients with all major endocrinological diseases (thyroid disorders including thyroid carcinoma, adrenal diseases including congenital adrenal hyperplasia, pituitary diseases, gonadal insufficiency, secondary hypertension including phaeochromocytoma, disorders in calcium homeostasis and osteoporosis), dyslipidaemias and premature atherosclerosis, diabetes mellitus, including insulin pump treatment and pregnancies in patients with diabetes and genetic metabolic diseases. This endocrinology training includes stays in Laboratory Center, as well as in the Department of Paediatric Endocrinology, Gynaecological Endocrinology and Assisted Fertility, Nuclear Medicine and Molecular Imaging, Ophthalmology and Clinical Genetics. On a regular basis, multidisciplinary meetings are organized with respect to care for patients with endocrine diseases and metabolic disorders, pituitary disorders, thyroid carcinoma and pathology.

At present, dr. R.P.F. Dullaart coordinates the Endocrinology teaching program. All staff members contribute to the training program by means of supervision, case discussions etc.

Recently, drs. Gonnie Alkemade and dr. Adrienne Persoon have finished their training, and drs. Franke Volbeda and Hannah van Loon are enrolled in the Endocrinology training program. Besides her Endocrinology training, Gonnie Alkemade is working on her Ph.D. on “Beta Cell Destruction, Beta cell Replacement and Aspects of Immune Intervention in Type 1 Diabetes”, in the research group of professor Bart Roep, Department of Immunohematology and Bloodtransfusion, Leiden University Medical Center, Leiden, the Netherlands. These projects are in collaboration with the laboratory of professor Pere Santamaria, Julia McFarlane Diabetes Research Center, University of Calgary, Calgary, Alberta, Canada, where Gonnie did part of her research. Adrienne Persoon, defended her thesis entitled “New insights in the follow-up of differentiated thyroid carcinoma” in March 2009 (promotor: prof. dr. B.H.R. Wolffenbuttel and prof. dr. P.L. Jager, co-promotor: dr. T.P.Links). In this thesis, the use of recombinant TSH stimulated thyroglobulin measurement and the clinical utility of thyroglobulin and thyroglobulin antibody assays in the long term follow up of differentiated thyroid carcinoma were studied.

In April 2013 two regional study days incorporated in the Internal Medicine training program ‘GODIN’ have been organized by prof. Wolffenbuttel, on endocrine disorders. The course was given in the MCL Leeuwarden, together with drs. Loek de Heide and Peter Oomen.
8. Scientific research

The research of the Department of Endocrinology is part of the Kidney Center and the Cardiovascular Center of the Research Institute GUIDE (Groningen University Institute for Drug Exploration). The mission of GUIDE is to promote and execute innovative drug development research which is based on a thorough and detailed understanding of the pathophysiology of diseases, and the development of new (ways of administration of) drugs. New techniques like genomics, proteomics and bioinformatics play a major role in this development.

Research programs

Program I: Endocrine tumours and dysfunction

1. Thyroid cancer: diagnosis and treatment

| topic: | Medullary thyroid cancer |
| researcher: | H.H.G. Verbeek |
| thesis: | 2015 |

| topic: | Prognostic factors in differentiated thyroid cancer |
| researcher: | mrs. D. Van Dijk |
| promotor: | prof. J.T.M.Plukker, prof. T.P.Links |
| thesis: | 2015 |

| topic: | Thyroid cancer in children |
| researcher: | mrs. M. Klein Hesselink, |
| supervisor | prof.T.P. Links, dr. W.Tissing, dr. G. Bocca |
| thesis: | 2016 |

| topic: | Longterm effects of treatment in differentiated thyroid cancer |
| researcher | E. Klein Hesselink |
| supervisor | prof. T.P.Links, dr. J.W. Lefrandt |
| thesis | 2016 |

2. Pituitary tumors

| topic: | Long-term effects and quality of life after treatment for pituitary adenoma and Cushing’s disease |
| researcher: | mrs. M. Sattler (radiotherapist) |
| promotor: | prof. J.A. Langendijk, prof. B.H.R. Wolffenbuttel |
| co-promotor: | dr. A.P. van Beek, dr. A.C.M. van den Bergh |
| thesis: | 2015 |

| topic: | Cognitive functioning in patients with pituitary adenoma |
| researcher: | mrs. P. Brummelman (psychologist) |
| promotor: | prof. B.H.R. Wolffenbuttel |
| co-promotor: | dr. A.P. van Beek |
| thesis: | Dec 9, 2013 |
3. Neuro-endocrine tumours

topic: Disease activity in MEN 1 and VHL
researcher: mrs. S.van Asselt
promotor: prof. T.P. Links, prof. E.G.E. de Vries
co-promotor: dr. A.H. Brouwers
thesis: 2014

topic: The role of chemokines and angiogenesis in the development of metastasases and the possible treatment in Von Hippel Lindau Tumours
researcher: R. Kruizinga
promotor: prof. E.G.E. de Vries, prof. T.P. Links
co-promotor: dr. A.M.E. Walenkamp,
thesis: 2014

topic: Diagnosis and treatment of catecholamine secreting neuroendocrine tumors
researcher: mrs. T.E. Osinga
promotor: prof. T.P. Links, prof. I.P.Kema
co-promotor: dr. A.N.A van der Horst-Schrivers, dr. M.N. Kerstens
thesis: 2015

topic: VHL disease : clinical aspects
researcher: mrs. C.F.M. Frantzen
promotor: prof. T.P. Links
co-promotor: dr. A.N.A. van der Horst-Schrivers
thesis: 2016

Program II: Diabetes / Lipids / Vascular

1. Pathophysiology, genetics and treatment of diabetes and diabetes-related complications

a. The role of endogenous and exogenous AGEs in the development of diabetic complications
b. Genomics and proteomics of diabetic complications
c. The role of CETP and HDL in (diabetic) cardiovascular disease; HDL function
d. Thyroid function and cardiovascular risk markers
e. Etiology and treatment of type 1 diabetes
f. Genetic predisposition for type 2 diabetes
g. Gene-environment interaction and epigenetic modifications in the development of type 2 diabetes and its complications

topic: Towards a personalized risk assessment and therapeutical strategy to prevent and treat macrovascular disease in Type 2 diabetes
researcher: J. van Ark
promotor: prof. J.L. Hillebrands, prof. B.H.R. Wolffensuttel
co-promotor: dr. J. Moser, dr. H. van Goor
support: Diabetes Research Foundation (DFN)
String-of-pearls
"Improving your health by sharing science"

The eight University Medical Centers (UMC's), joined in the Dutch Federation of University Medical Centers (NFU), provide most tertiary care in The Netherlands and thereby treat almost all patients with very specific or relatively rare diseases in the Dutch population. This provides a unique opportunity to combine clinical information and biomaterials on these patients and achieve almost total population coverage.

It then becomes a longitudinal patient cohort from which anonymous samples may be drawn for specific research questions, either by academic, governmental or commercial partners. In order to achieve this, patient data and samples must be collected in a uniform fashion and an IT infrastructure must be designed to allow sampling locally and combining data from all eight locations to one anonymised database.

The following patient cohorts have been collected: Inflammatory Bowel Disease, Rheumatoid Arthritis, CVA, hereditary Bowel cancer, Leukemia, Dementia, Diabetes.

The data and biomaterials will be collected and stored in each UMC, using the regular electronic patient records to store patient data including imaging data and biobanks to store biomaterial and already completed analyses of the biomaterials. Clinicians from each UMC must agree on uniform definitions for each patient cohort. For that purpose each UMC has adopted one patient cohort and leads its colleagues from the other seven UMC’s to achieve this.

Together the UMC’s will build a joint infrastructure to access each of the local data bases to draw a sample, anonymise it and deliver it as a data base to the end user. The patient cohort data will be collected prospectively, but in a number of cases already existing data and biobanks can be included in the database retrospectively if it fits the definitions. A set of rules will be developed to help decide by which criteria and procedures proposals for the use of the data will be accepted and how the resulting proceeds will be used to maintain the infrastructure after the initial funding ends.

For more information: www.parelsnoer.org

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topic: Lipids and lipoproteins in cardiovascular disease
researcher: P.J.H.W. Kappelle
promotor: prof. B.H.R. Wolffenbuttel
co-promotor: dr. R.P.F. Dullaart, dr. G. Dallinga-Thie (AMC/UvA)
thesis: 2015

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topic: Cardiovascular risk and its determinants in high risk
researcher: mrs. E.G. Gerrits
co-promotor: dr. H.L. Lutgers, dr. A.J. Smit
thesis: 2013
topic: Pregnancy in diabetes
researcher: B. Groen
promotor: prof. T.P. Links, prof. P.P. van den Berg
copromotor dr. M. Faas
thesis: 2014


topic: Epigenetic markers of obesity and diabetes, translation to large cohorts
postdoc: dr. H.L. Lutgers
project members: prof B.H.R. Wolffenbuttel dr. J. Van Vliet-Ostaptchouk, prof. M.G. Rotts,
prof. H. Snieder, prof S.J. Clark, dr. P.L. Molloy


topic: Gene-environment interaction and obesity
postdoc: dr. J. Van Vliet-Ostaptchouk,
PhD-student: to be selected
thesis: 2015


topic: The Healthy Obese in European perspective
researcher: mrs. S. Slagter
promotor: prof. B.H.R. Wolffenbuttel
co-promotor: dr. J.V. van Vliet-Ostaptchouk, dr. M.M. van der Klauw
thesis: 2015

The projects on genetics of type 2 diabetes are part of the research carried out in the LifeLines Cohort Study, while some of the studies related to diabetic complications are carried out within the String-of-Pearls initiative. These research programs are carried out by the Department of Endocrinology (dr. R.P.F. Dullaart, dr. T.P. Links, prof. B.H.R. Wolffenbuttel, dr. J.V. van Vliet-Ostaptchouk) in close collaboration with the Dept.'s of General Internal Medicine and Nephrology: prof. S.J.L. Bakker, prof. A.J. Smit, prof. R.O.B. Gans,, Department of Internal Medicine, and mrs. dr. G. M. Dallinga-Thie, Department of Vascular Medicine, UVA, with prof. H.J.G. Bilo and dr. N. Kleefstra, Diabetes Centre, Isala Clinics, Zwolle.

2. Metabolism, obesity and metabolic syndrome


topic: Thyroid (dys)function, metabolic syndrome and incident cardiovascular disease
researcher: A. Roos
promotor: prof. B.H.R. Wolffenbuttel, prof. T.P. Links
co-promotor: dr. A. Berghout (internist, Rotterdam), dr. S.J.L. Bakker (internist)
thesis: 2014


topic: The role of a lifestyle program and fat distribution in women with obesity and infertility
researcher: W.K.H. Kuchenbecker, gynaecologist
promotor: prof. J.A. Land, prof. B.H.R. Wolffenbuttel
co-promotor: dr. A. Hoek, dr. H. Groen
thesis: February 27, 2013


topic: Metabolic aspects of body fat, reproduction and intervention
researcher: mrs. J.G. Dolfing, gynaecologist, Hengelo
promotor: prof. B.H.R. Wolffenbuttel
co-promotor: dr. D.H. Schweitzer (internist, Voorburg)
thesis: Sept 2012

Year Report 2013 – Dept. of Endocrinology, UMCG & University of Groningen, The Netherlands
The projects on genetics of obesity and related metabolic traits are part of the research line carried out in the LifeLines Cohort Study, while some of the studies related to epigenetics and gene x environment interactions in obesity are carried out within the Netherlands Consortium for Healthy Ageing (NCHA), the BioSHaRE-EU Healthy Obese Project and through international collaborations (the GAINT, MAGIC, CHARGE consortia). The major goal of the research line is to investigate how environmental factors together with genetic factors influence the disease aetiology with a particular interest in gene-gene and gene-environmental interactions.

These research programs are carried out by the Department of Endocrinology (prof. B.H.R. Wolffenbuttel, dr. J.V. van Vliet-Ostapchouk) in close collaboration with Prof. H. Snieder, Prof.R. Stalk, the Department of Epidemiology, Prof. M.H. Hofker, Department of Medical Biology, Prof. R.J.F. Loos, MRC-Epidemiology unit, Institute of Metabolic Science, Cambridge, UK (currently works at Mount Sinai School of Medicine, New York, USA).

**Pleiotropic effects of obesity-susceptibility genes on metabolic traits**

As part of her Rubicon fellowship from the Netherlands Organization for Scientific Research, Jana van Vliet-Ostapchouk carried out the research into the examination of the effect of the currently established obesity-susceptibility loci, identified through the genome-wide association studies, on metabolic and cardiovascular traits (collaboration with Prof. R.J.F. Loos, Cambridge, UK). The project provides insight into the complex pathogenesis of metabolically related disorders.

**Epigenetics of obesity**

The aim of the project addressed within the NCHA consortium is to study whether DNA methylation changes may be important epigenetic mechanisms linking the responses to environmental factors and obesity.

**The Healthy Obese Project**

The aims of this BioSHaRE-EU core project are to evaluate the prevalence of the metabolically healthy obesity (HO), assess lifestyle determinants and clinical consequences of HO and explore genetic modifications and advanced metabolic profiling related to both the determinants and consequences of HO. The data of the LifeLines study are used, and combined with several other cohorts across Europe, in order to be able to investigate gene-gene interactions and gene-environment interactions.

### 3. Diabetes psychology and quality of care

**GIANTT: assessing pharmacotherapeutic care for patients with type 2 diabetes**

**researcher:** J. Voorham  
**promotor:** prof. F. Haaijer-Ruskamp, prof. B.H.R. Wolffenbuttel  
**co-promotor:** dr. P. Denig  
**thesis:** June 16, 2010
In the LifeLines cohort study, RFFT was measured in participants as a measure of cognitive function. Normative data were generated with these data, and data in patients with diabetes or use of medication are compared to the healthy population. These data are used in the thesis of Martin Elderson. Data on thyroid function in LifeLines participants are used in the thesis of Hannah van Loon. In this thesis, normative data are generated as well, and the group of hypothyroid participants are examined with respect to their quality of life, and genetic markers are investigated in order to find differences between people with differences in T3/T4 ratio.
Participation in (inter)national clinical trials

DURABLE:
The Durability of Twice-Daily Insulin Lispro Low Mixture Compared to Once-Daily Insulin Glargine when added to Existing Oral Therapy in Patients with Type 2 Diabetes and Inadequate Glycemic Control (ClinicalTrials.gov Identifier: NCT00279201)

4B:
A Randomized Trial Comparing Two Therapies: Basal Insulin/Glargine, Exenatide and Metformin Therapy (BET) of Basal Insulin/Glargin, Bolus Insulin Lispro and Metformin Therapy (BBT) in Subjects with Type 2 Diabetes who were Previously Treated by Basal Insulin Glargine with either Metformin or Metformin and Sulfonylurea (ClinicalTrials.gov Identifier: NCT00960661)

LOWER:
Study to assess the effects of high protein diet in obesity, the LOWER Study (ClinicalTrials.gov Identifier: NCT00862953)

INOBESE:
The influence of the needle length on long term glycaemic control in insulin using obese diabetic subjects. (ClinicalTrials.gov Identifier: NCT00541372)

MET-PET:
Diagnostic value of 11C-metomidate Positron Emission Tomography/Computerized Tomography (PET/CT) for the evaluation of primary aldosteronism – a pilot study (NL28866)

ARRAT:
Aldosterone-Renine Ratio to diagnose primary Aldosteronism and a Tool to select proper antihypertensive treatment - The Dutch ARRAT Study (NL11725)

SPARTACUS - Subtyping Primary Aldosteronism: a Randomized Trial comparing Adrenal vein sampling and Computed tomography Scan

PAVANE: BEHAVE
Towards cost-effective diagnostic management of patients with primary aldosteronism: adrenal vein sampling or CT-scan (NL30849)

DECISION:
A Double-Blind, Randomized Phase III Study Evaluating the Efficacy and Safety of Sorafenib Compared to Placebo in Locally Advanced/Metastatic RAI-Refractory differentiated thyroid cancer (ClinicalTrials.gov Identifier: NCT00984282)

XL184
An international, randomized, double-blinded, phase 3 efficacy study of XL184 versus placebo in subjects with unresectable, locally advanced, or metastatic medullary thyroid cancer. (ClinicalTrials.gov Identifier: NCT 00704730)

VEMURAFENIB
A Study of RO5185426 (Vemurafenib) in Patients With Metastatic or Unresectable Papillary Thyroid Cancer Positive for the BRAF V600 Mutation.
THYRRAD
A phase II study to investigate the efficacy of RAD001 (Afinitor®, everolimus) in patients with irresectable recurrent or metastatic differentiated, undifferentiated (anaplastic) and medullary thyroid carcinoma (patients progressive on Sorafenib or XL-184, or with intolerance to Sorafenib or XL-184)
(ClinicalTrials.gov Identifier: NCT01118065)

VEGF IMAGING VHL
Visualizing vascular endothelial growth factor (VEGF) producing lesions in Von Hippel-Lindau disease
(ClinicalTrials.gov Identifier: NCT00970970)

PANCREAS IMAGING MEN1/VHL
National project for screening of pancreatic neuroendocrine tumours in Multiple Endocrine Neoplasia type 1 (MEN1) and Von Hippel-Lindau (VHL) disease (NTR 1668)

PRESCRIPT
Phenoxybenzamine Versus Doxazosin in PCC Patients.
A study comparing effects of preoperative treatment with either phenoxybenzamine or doxazosin on intraoperative hemodynamic control in patients undergoing surgical resection of a phaeochromocytoma.
(ClinicalTrials.gov Identifier: NCT01379898)

DIAPRIM in a rat-model:
A study to investigate the adaptation of the immune response during pregnancy in BBDP (a model for type 1 diabetes) rats versus healthy controls. This study showed an adverse pregnancy outcome in diabetic rats as compared to healthy controls. Since a different baseline peripheral immune response and different immunological adaptations to pregnancy were found in diabetic animals vs. healthy controls as well, it is imaginable that this aberrant immune response in diabetic rats is involved in the development of the demonstrated adverse pregnancy outcome.

DIAPRIM in a human-model:
A study to investigate the adaptation of the immune response during pregnancy in women with pregestational type 1 and 2 diabetes versus healthy controls (NTR2195). At the moment, almost all patients are included in the study, samples are obtained and analysis of the data is in progress.

DIAPRAGE:
A study to investigate the effects of Advanced Glycation Endproducts (AGEs) on pregnancies complicated by diabetes mellitus (NTR2356). Inclusions and data collection is ongoing.

SUPREME CORT
A randomized double blind cross-over study of the effects of low dose and high dose hydrocortisone replacement therapy on cognition, quality of life, metabolic profile and somatosensation in patients with secondary adrenal insufficiency. (ClinicalTrials.gov Identifier NCT01546922)
9. Activities outside the UMCG

Contacts with patient societies
Our department has extensive contacts with several societies of patients, which results in a continuous stimulation to further improve patient care. Staff members of the Department give presentations for regional patient groups.
Twice yearly a structured mutual discussion with the Groningen chapter of the Diabetesvereniging Nederland is organized.

From the beginning of 2005, prof. Wolffentuttel is one of the medical advisors of the Dutch Association for Addison and Cushing Patients (NVACP, Nederlandse Vereniging voor Addison en Cushing Patiënten). As such, he participates in the working group which is preparing a number of Standards of Care for patients with adrenal disorders.

Prof. Links is advisor of the foundation "BETER", which supports organization of care for patients with hereditary endocrine cancer syndromes.

Specific activities
Several members of the department participate in national and international study or research-groups, amongst others the Dutch Adrenal Collaborative (www.bijniernetwerk.nl) and The DutchMEN1 Study Group (DMSG).

Dr. A.P. van Beek is representative within The Northern European Neuro-Endocrine Group (NENEG) and editor-in-chief of the Netherlands Journal of Diabetology. He also serves as a member of the steering committee for SOM230X2203 study (Pasireotide for Dumping Syndrome)

Prof. T.P. Links is president of the Dutch national Working Group for Von Hippel Lindau disease, member of the Working Group on Thyroid Carcinoma of the Comprehensive Cancer Center North Netherlands (IKN), chairperson of the CBO Guideline Group for Differentiated Thyroid Cancer and board member of the Dutch Thyroid Club and member of the Dutch MEN 1 study group.

Prof. B.H.R. Wolffenbuttel is member of the Board of the journals International Diabetes Monitor and International Growth Monitor, as well as Expert Opinion in Pharmacotherapy and the Journal of Diabetes. He also serves as secretary of the Dutch Endocrine Society, and member of the editorial board of the Dutch journal ‘Endocrinologie’

The Foundation Innovative Diabetes Research Netherlands, BIDON (Innovatief Diabetes Onderzoek Nederland) has been established in 2011. This is a milestone in the realization of the 'experimental concept', where the NDF has long been striving for. Characteristic of this concept is that during a certain period of time, reimbursement is possible for a new drug or treatment strategy, under predetermined conditions and in combination with additional data collection. Knowledge about effectiveness of new medications and devices is available faster just by adding new forms of treatment in a structured way with information and experiences from clinical practice to combine into national cooperation. This knowledge supports an accelerated and effective implementation of new treatments and thus the quality of diabetes care.
Under the guidance of the Foundation, several research projects are positioned. Initially, data collection around the use of continuous glucose monitoring (RT-CGM) has the highest priority. A research project around GLP-1 receptor agonists in people with type 2 diabetes certainly deserves priority as well, but requires further preparation.
BIDON seeks her work possible through a joint effort and financial contribution of multiple (public and private)
parties. Applications for financial support were requested from ZonMW (under the Program Good Drug Use (GGG)), and from the Dutch Diabetes Research Foundation.

BIDON stems from an initiative led by Prof. Mark Kramer (head of dept. of Internal Medicine, Free University Amsterdam) The governing board consists of Prof. Michaela Diamant, Dr. Nel Geelhoed-Duijvestijn, Dr. Ingrid Jazet, Maarten Ploeg MHCM, Prof. Cees Tack, Dr. Harold de Valk, Dr. Henk Veeze, and Professor Bruce Wolffentutzel.

Mrs. Gillian Kreugel is a member of the ‘Diabetes Expert Network’ of the Dutch Diabetes Federation and a member of ‘Diabetes Network Groningen’. She also served as a member of the scientific advisory committee for the third International Injection Technique Seminar.

Mrs. Winnie van El participated in the following committees:
- Committee on Education and Publicity of the Dutch Diabetes Federation
- Diabetes Expert Network of the Dutch Diabetes Federation
- The Working Group on Diabetes and Dialysis of the LVDT (Dutch Society for Dialysis and Transplantation)

**International collaborations and more**

Dr. H.L.Lutgers has been located in Sydney, Australia for the year 2011. She was employed as a research fellow / postdoc at Garvan Institute of Medical Research, Sydney NSW, Australia. This institute is connected to the University of New South Wales, Sydney. She has participated in the research group: Epigenetics, Cancer program. Prof. S.J. Clark. She was involved in the set-up of a new research area of this lab ‘Epigenetics of adipose tissue’. Epigenetics is the study of heritable changes in genes and gene function, that are caused by environmental factors (like nutrition or exercise). An example is DNA-methylation: the addition of a methyl-group to a DNA base.

She was trained to develop basic epigenetic lab skills and learned how to isolate adipocytes from adipose tissue. Furthermore, she coordinated the kick-off of the ‘Epigenomics of human adipose tissue study’, which is one of the three main research lines of a new national Australian project / consortium called ‘EPISCOPE’. This is an Australian consortium, studying early nutrition, the epigenome and the prevention of disease. This consortium is aiming to build the first Epigenome map of a normal fat cell and then identify and map the epigenetic signatures associated with the development of obesity in children and adults and to characterize how early-life over- and under-nutrition, as well as specific nutrients, may shape the developing epigenome. From this, a key goal is to develop biomarkers and diagnostic tests to predict the risk of obesity and other metabolic syndromes, which will help to guide interventions.

In the same research institute, she has also participated in the research group ‘Diabetes and Obesity Clinical Group’, of prof. K. Samaras. She was involved in the data analysis of the ‘Sydney Memory and Aging study’. The Sydney Memory and Ageing Study is a cohort study of community-dwelling elderly (1037 participants, aged 70-90 years) derived from the general population, examining common diseases of ageing with detailed clinical and biochemical phenotyping. She has focused on ‘the burden of disease’ in elderly people with diabetes or impaired fasting glucose; and on cognitive function and brain volumetrics (MRI) and its relation to glucose disorders.

Dr. R.P.F. Dullaart is member of the Emerging Risk Factors Collaboration (ERFC), a multinational group of scientists involved in the evaluation of lipid and non-lipid risk biomarkers on incident cardiovascular disease (chair: Prof. John Danesh, Department of Public Health and Primary Care, University of Cambridge, UK). In this field there is also collaboration with Prof. James P. Corsetti, Department of Pathology and Laboratory Medicine, University of Rochester School of Medicine and Dentistry, Rochester, New York, USA. Between May 2012 and January 2013, mrs, Michela Triolo, MD (University of Milan, Italy) worked in the laboratory of Prof. Uwe Tietge, Department of Pediatrics on HDL function assays, resulting in 4 publications in international journals.
### Addendum 1 - Conferences

<table>
<thead>
<tr>
<th>Conference</th>
<th>Frequency and Time</th>
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<tbody>
<tr>
<td>Endocrinology Grand Rounds</td>
<td>weekly (Tuesday 9.00 - 10.30)</td>
</tr>
<tr>
<td>Endocrine Case Conference</td>
<td>weekly (Friday 9.00 - 10.00)</td>
</tr>
<tr>
<td>Internal Medicine Patient Discussion</td>
<td>every two weeks (Tuesday 16.45 - 17.30)</td>
</tr>
<tr>
<td>Thyroid Carcinoma Consultation</td>
<td>monthly (Friday 10.45 - 12.30)</td>
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<tr>
<td>Diabetic Foot Rounds</td>
<td>weekly clinical rounds (Monday)</td>
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<td></td>
<td>1x monthly (Friday)</td>
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<tr>
<td>Pituitary Case Conference</td>
<td>every two weeks (Tuesday 12.00 - 13.00)</td>
</tr>
<tr>
<td>Multidisciplinary Diabetes Consultation</td>
<td>once monthly (Thursday, 16.30 - 17.30)</td>
</tr>
<tr>
<td>Endocrine Pathology Case Conference</td>
<td>once every 2 months (Tuesday 9.45- 10.30)</td>
</tr>
<tr>
<td>Endocrinology Journal Club</td>
<td>monthly (Friday 9.00 - 10.30)</td>
</tr>
<tr>
<td>Regional Case and Research Conferences</td>
<td>6-8 times a year</td>
</tr>
</tbody>
</table>
Addendum 2 - Multidisciplinary teams

Thyroid
Prof. T.P. Links, Dr. A.N.A. van der Horst-Schrivers, Endocrinology
Prof. J.T.M. Plukker, dr. L. Jansen, Oncologic Surgery
Dr. A.H. Brouwer and colleagues, Nuclear Medicine
Dr. H. Bijl, Radiotherapy
Dr. P. C. Jutte, Orthopaedics
Dr. M. Coppes, Neurosurgery
Dr. A. Muller Kobold, Clinical Chemistry
Dr. S. Oosting, Clinical Oncology
Dr. G. Bocca, Paediatrics
Dr. B. van Hemel, Pathology
Dr. L. Rodiger, Radiology
Staff members of Endocrinology

Pituitary
Dr. G. van den Berg, Endocrinology
Dr. M.M. van der Klauw, Endocrinology
Dr. E. Hoving, Neurosurgery
Dr. J. Kuijlen, Neurosurgery
Dr. J.W. Pott, Ophthalmology
Dr. A.C.M. van den Bergh, Radiotherapy
Dr. L. Meiners, Neuroradiology
Staff members of Endocrinology

Diabetic foot
Staff members of the Departments of (Vascular) Surgery, Orthopaedics, Dermatology, Rehabilitation, Plastic Surgery and Internal Medicine / Endocrinology

Diabetes and Pregnancy
Dr. G. van den Berg, Endocrinology
Prof. P.P. van den Berg, Obstetrics/ Gynaecology
Prof. T.P. Links, Endocrinology
Dr. H.L. Lutgers, Endocrinology
Dr. K.M. Sollie, Obstetrics/ Gynaecology
Dr. A. Persoon, Endocrinology

Turner team
Dr. M.N. Kerstens, Endocrinology
Dr. A.P. van Beek, Endocrinology
Mrs. dr. A. Hoek, Gynaecology
Mrs. dr. W.M. Bakker- van Waarde, Paediatrics
Mrs. E. Lont, Nursing
Mrs. H.J. Huisinga, Social Support
Mrs. A. Elliot-Pascal, Social Support
Addendum 3 - Publications 2013

PhD Thesis / dissertations

October 2, 2013
Dr. J. van Ark
Promotores: Prof. dr. J.L. Hillebrand, Prof. dr. B.H.R. Wolffbuttel

December 9, 2013
Cognition in patients treated for pituitary diseases
Dr. P. Brummelman
Promotores: Prof. Dr. B.H.R. Wolffenbuttel, prof. Dr. O. Tucha
Co-promotores: dr. A.P. van Beek, dr. J. Koerts
Publications

The figures show the main publication results of our department during the most recent years. After a slightly lower productivity in 2009, the years 2010-2013 witnessed the publication of many papers, and more than half of them were published in a journal with an impact factor higher than 4.
Publications international:

Kwakernaak AJ, Lambert G, Muller-Kobold AC, Dullaart RPF. Adiposity blunts the positive relationship of thyroid-stimulating hormone with proprotein convertase subtilisin-kexin type 9 levels in euthyroid subjects. *Thyroid* 2013; 23: 166-72
PMID: 23106476

PMID: 23139292

PMID: 23121487

PMID: 23541566

PMID: 23249826
Genome-wide association analyses identify 18 new loci associated with serum urate concentrations.

_Nat Genet_ 2013; 45: 145-54
PMID: 23263486

Kappelle PJ, Gansevoort RT, Hillege HJ, **Wolffenbuttel BHR, Dullaart RPF; PREVEND Study Group**
Common variation in cholesteryl ester transfer protein: relationship of first major adverse cardiovascular events with the apolipoprotein B/apolipoprotein A-I ratio and the total cholesterol/high-density lipoprotein cholesterol ratio.

_J Clin Lipidol_ 2013; 7: 56-64.
PMID: 23351584

van Ark J, Hammes HP, van Dijk MC, Lexis CP, van der Horst IC, Zeebregts CJ, Vervloet MG, **Wolffenbuttel BHR,**
van Goor H, Hillebrands JL.
Circulating alpha-klotho levels are not disturbed in patients with type 2 diabetes with and without macrovascular disease in the absence of nephropathy.

_Cardiovasc Diabetol_ 2013; 12: 116
PMID: 23945089

Sattler MG, Vroomen PC, Sluiter WJ, Schers HJ, _van den Berg G_, Langendijk JA, **Wolffenbuttel BHR,** _van den Bergh AC_, _van Beek AP_.
Incidence, causative mechanisms, and anatomic localization of stroke in pituitary adenoma patients treated with postoperative radiation therapy versus surgery alone.

_Int J Radiat Oncol Biol Phys._ 2013; 87: 53-9
PMID: 23920387

Hu YJ, Berndt SI, Gustafsson S, Ganna A; _Genetic Investigation of ANthropometric Traits (GIANT) Consortium_,
Hirschhorn J, North KE, Ingelsson E, Lin DY, _Collaborators (322, Wolffenbuttel BHR)_.
Meta-analysis of Gene-Level Associations for Rare Variants Based on Single-Variant Statistics.

_Am J Hum Genet._ 2013; 93: 236-48
PMID: 23891470

Pleiotropic effects of obesity-susceptibility loci on metabolic traits: a meta-analysis of up to 37,874 individuals.
_Diabetologia_ 2013; 56: 2134-46
PMID: 23827965

**Wolffenbuttel BHR**, Coppes MH, Bongaerts AH, Glaudemans AW, _Links TP_.
Unexpected symptoms after rhTSH administration due to occult thyroid carcinoma metastasis.

_Neth J Med_ 2013; 71: 253-6
PMID: 23799312

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Several abstracts and (poster) presentations on national and international congresses and symposia.