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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.

Mrs. G.M. Alkemade, MD
Mrs. N. Alma - Bierma (Natasja)
Mrs. S. van Asselt, MD (Sophie)
A.P. van Beek, MD PhD (André)
G. van den Berg, MD PhD (Gerrit)
Mrs. B.T. de Boer - de Boer (Berber)
Mrs. T. Bos (Tineke)
Mrs. P. Brummelman (Pauline)
E. Buitenwerf , MD (Edward)
Mrs. D. van Dijk, MD (Deborah)
Mrs. E. van Driesum (Els)
R.P.F. Dullaart, MD PhD (Robin)
Mrs. K. Eijkelenkamp, MD (Karina)
Mrs. W. van El, MA (Winnie)
Mrs. C. Franzen, MD (Charles)
B. Groen, MD (Bart)
Mrs. M.A. Groeneveld (Mariska)
Mrs. B.G. Haandrikman (Bettine)
Mrs. A.N.A. van der Horst-Schrivers, MD PhD (Anouk)
Mrs. K.B.M. Janson (Carla)
Mrs. A.B. Jongbloed (Alied)
M.N. Kerstens, MD PhD (Michiel)
Mrs. M.M. van der Klauw, MD PhD (Melanie)
Mrs. E. Klein Hesselink, MD (Esther)
Mrs. M. Klein Hesselink, MD (Marielle)
Mrs. S. Koning, (Sarah)
Mrs. G. Kreugel, MSc (Gillian)
Mrs. prof. T.P. Links, MD PhD (Thera)
Mrs. H.C.M. van Loon, MD (Hannah)
Mrs. H.L. Lutgers, MD PhD (Helen)
Mrs. T.E. Osinga, MD (Tamara)
Mrs. S.M. Pathuis (Susanne)
Mrs. A.C. Persoon, MD PhD (Adrienne)
Mrs. I.E. Pop (Inge)
Mrs. E. Schutte, MD (Elise)
Mrs. S.N. Slagter (Sandra)
W.J. Sluiter, PhD (Wim)
Mrs. L. Stoffer (Lammie)
H.H.G. Verbeek, MD (Hans)
Mrs. J. van Vliet-Ostaptchouk, PhD (Jana)
F. Volbeda, MD PhD (Franke)
Mrs. W.A.M. Vrijsspieker (Mini)
R. van Waateringe, MD (Robert)

internist-endocrinologist
secretary (until Oct 1)
physician, PhD student (until April 15)
internist-endocrinologist
internist-endocrinologist
diabetes nurse specialist
diabetes nurse specialist
psychologist, PhD student
physician, PhD student (starting Dec 1)
diabetes nurse specialist
internist-endocrinologist
physician, Beatrixoord
nurse practitioner diabetes
physician diabetes rehabilitation
physician, PhD student (until April 1)
research assistant
medical analyst
internist-endocrinologist
diabetes nurse specialist
physician, PhD student
nurse consultant diabetes
internist-endocrinologist
internist-endocrinologist in training
internist-endocrinologist
physician, PhD student
diabetes nurse specialist
internist-endocrinologist in training
research assistant
physician, PhD student
health scientist, PhD student
biochemist, statistician
research assistant
physician, PhD student
post-doc
internist-endocrinologist in training (until August 1)
diabetes nurse specialist
physician, PhD student (starting Sept 1)
Mrs. J. Werumeus Buning (Jorien) psychologist
Prof. B.H.R. Wolffenbuttel, MD PhD (Bruce) internist-endocrinologist
Mrs. M. Wolthuis (Marga) secretary (starting Oct 1)

Rehabilitation Center Beatrixoord, Div of Diabetes Rehabilitation
Mrs. N. Kombrink (Nelleke) teammanager a.i.
Mrs. L. Faber (Linda) diabetes nursespecialist and teamcoördinator
Mrs. I. Stoelinga (Ingrid) diabetes nurse specialist
Mrs. M. Schotman (Madelein) diabetes nurse specialist
Mrs. M. van Dijk (Marianne) dietician
Mrs. B. Joosen (Brigitta) fysiotherapist
G. van Bochove (Guus) movement scientist
Mrs. L. Wichers (Laura) psychologist
Mrs. M. Altena (Margreet) social welfare
Mrs. R. Slofstra (Rianne) specialised nurse
Mrs. S. van Veen (Sandra) specialised nurse
Mrs. L. Vries (Lotty) specialised nurse
Mrs. E. Pieterman-Slagter (Elsa) secretary
**Highlights of 2014**

In 2014, three doctors defended their PhD thesis. The first was Sophie van Asselt, whose ceremony took place on April 14. Title of her thesis was “New imaging strategies in neuroendocrine tumors. In her thesis she compared the new imaging techniques endoscopic ultrasound (EUS) and 11C-5-hydroxytryptophan positron emission tomography (11C-5-HTP PET) with the conventional imaging CT or MRI and somatostatin receptor scintigraphy (SRS) for the early detection of pancreatic neuroendocrine tumours in these patients. She also investigated the role of new biomarkers, and imaging techniques, for instance she investigated the role of zirconium -89 (89Zr) labelled bevacizumab as biomarker in PET molecular imaging in VHL disease and in patients with sporadic advanced neuroendocrine tumours treated with everolimus.

Bart Groen defended his thesis “Complications in diabetic pregnancy, role of immunology and advanced glycation end products, on September 24. He studied the possible roles of the immune system and Advanced Glycation End products (AGEs) in the development of adverse pregnancy outcomes in women with T1D or T2D. Both in rats with T1D, and women with T1D or T2D, the immune response was disturbed before and during pregnancy. Furthermore, placental and fetal weights were decreased in T1D rats as compared to healthy rats. This was due to an abnormal development of the placenta. This abnormal placentation appeared to be associated with the disturbed immune response, since in T1D rats increased numbers of specific immune cells were observed at the site at which the placenta was attached to the uterine wall, as compared to healthy rats. Not only did we find a disturbed immune response in pregnant women with T1D, also the accumulation of AGEs in the skin was increases in women with T1D during the first and second trimester of pregnancy, as compared to healthy pregnant women. Since a disturbed immune response and increased accumulation of AGEs can be harmful for mother and child, it is likely that they play a role in the development of pregnancy complications in women with T1D.

Finally, Annemieke Roos defende her thesis on October 8. Title of the thesis was “Clinical and epidemiological studies on thyroid function”. She aimed to study the effects of thyroid function on cardiovascular risk factors and mortality, and to assess predictors for and optimize treatment of hypothyroidism. In subjects without thyroid disease, Free (F)T4 was related to components of the metabolic syndrome (abdominal obesity, lipids and blood pressure) and to insulin resistance. In this population, the FT4 and FT3 were associated with mortality independent of age and sex. In another study she found that, also during exercise/stress, no cardiac ischaemia was found in untreated hypothyroid patients. A prospective trial was initiated by her comparing a full starting T4 dose with a low dose (increased every four weeks) in newly diagnosed cardiac asymptomatic hypothyroidism. Although euthyroidism was reached faster with a full starting dose, symptoms of hypothyroidism and quality of life improved comparably. No cardiac events occurred, so a full starting dose in cardiac asymptomatic patients was safe.
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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# only follow-up visits

This year we have been faced with a considerable reduction in ‘no show’ patients, after we have started sending reminders to our patients by regular mail two weeks prior to their planned visit. The number of ‘no shows’ has
almost halved, and now is approximately 2%. Still, we consider this too high, as this means that on average in one of 50 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. We hope that in the course of 2015, we can start to send SMS messages to our patients in order to further reduce ‘no-shows’.

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 integrated 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. Unfortunately, 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. Unfortunately, there are also downsides to this, as it proves more and more difficult to have complete information available from referring physicians to perform such a ‘second opinion’. As this puts extra pressure on our administrative personnel and on doctors, and second opinions do not have any merit when medical information is incomplete, we only plan consultations after complete information has been received. Sometimes it takes several e-mail messages, faxes and telephone messages to achieve this. We sincerely hope that our patients are aware of the fact that consultations without sufficient medical information are wasted time, also for them.

People in The Netherlands also get more obese. As a consequence, we face an increase of women who develop diabetes during pregnancy, and especially in our Diabetes Center we witness a rapid increase in patients referred because of this. 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.

‘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. Wolffenduttel 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 2014 Monique Gelms, Anita Scholtens, Berber Brandsma, Fenna Diepenbroek-Beulakker, Bea Hartman, Jorrit ter Halle, Liesbeth Hulshof, as well as all the administrative personnel responsible for typing and sending 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 paediatric 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

Optimal glycaemic control is necessary to minimise the development of congenital abnormalities or perinatal complications in the newborn babies. Diabetic 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 collaboration, by an internist-endocrinologist, diabetes specialist nurse, gynaecologist, dietician and ophthalmologist. 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.

**Gestational diabetes study, 2011-2014 Groningen area**

Gestational diabetes mellitus (GDM) is a condition in which women without previously diagnosed diabetes mellitus (DM) exhibit high blood glucose levels during pregnancy. GDM increases the risk of short-term and long-term adverse health outcomes for both mother and child, including pregnancy complications and obesity and DM in later life. In the Netherlands, revised guidelines for screening and treatment of GDM have been introduced in 2010. The goal of this project is to evaluate these guidelines, and to assess incidence and morbidity associated with GDM in the Groningen area in the years 2011-2014.

This year we started the first studies in collaboration with the Martini hospital Groningen. We conducted a retrospective cohort study from January 2011 till September 2014. Neonatal and obstetric outcomes were compared according the regular care GDM treatment (diet-only versus additional insulin therapy) and the neonatal and obstetric outcomes of the general obstetric population in the Northern region of the Netherlands during the same period of time served as a control group. We evaluated 820 singleton GDM pregnancies. Furthermore, we will study relevant factors which predict the necessity of additional insulin therapy during pregnancy, developing a prediction model to identify GDM patients with an increased likelihood for the need for exogenous insulin therapy.

Plans of this project for 2015-2016 are to investigate the nutritional habits of women diagnosed with GDM, how healthy are these women eating during pregnancy. Secondly, a study will be conducted to evaluate the long-term follow-up after GDM. Women with GDM are at increased risk for developing T2DM postpartum, a risk of 50% in the 5-10 years after GDM. We also want to investigate the frequency of follow-up postpartum glucose testing in primary care and to identify lifestyle in women after GDM to prevent T2DM.

A final focus of this GDM research project concerns GDM screening. Worldwide there is still a lack of uniform criteria for diagnosis and screening of GDM. In 2013, the WHO has adopted the stricter cut-off values for diagnosis of GDM of the international Association of the Diabetes and Pregnancy Study Groups 2010 criteria, a fasting glucose ≥5.1 mmol/l and/or a 2-hour value ≥8.5 mmol/l after a 75 gram OGTT. In our Groningen region we want to investigate the impact of GDM prevalence and pregnancy outcomes if the new WHO 2013 criteria would be adopted.
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 75 patients from 2011 and the years thereafter.

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. The launch of an integrated multidisciplinary transplantation outpatient clinic is expected in 2016.

4. Group sessions
In 2008 we have started to organise group sessions for patients and their relatives, and these have continued in recent years. 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 2014 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. The results of this have been published in the prestigious journal Diabetes Care.

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, Drente 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 unfortunately 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 included 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 insurance companies.

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 (neo)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 (expertise) center for non-hereditary as well as hereditary neuroendocrine tumours (MEN1, MEN2, VHL, NF, paragangliomas, and patients with SDHx mutations).

In 2015 the UMCG received the ENETs certification at the annual ENETs meeting in Barcelona. 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. Ga labelled PET scanning using Octreotide is expected to become available in the second half of 2015.

Furthermore in 2014 drs T.E. Osinga spend 6 months at the NIH, to perform a part of her research on catecholamine secretion in patients with paragangliomas and pheochromocytomas in close collaborations with Prof dr I.P. Kema (laboratory department).

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 sunitinib, sorafenib, vandetanib and XL 184 in patients with (medullary) thyroid cancer and malignant pheochromocytomas.

In 2014 dr. S.I. van Asselt received her PhD, for the national project (supported by the Dutch Cancer Society and conducted in In cooperation with University Medical Hospitals of Utrecht, Rotterdam and Nijmegen), for screening of pancreatic neuroendocrine tumours in Multiple Endocrine Neoplasia type 1 (MEN1) and Von Hippel-Lindau (VHL). She showed that endoscopic ultrasound (EUS) is superior in detecting neuroendocrine pancreatic tumors in these syndromes.

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 inherited and characterized by the development of multiple benign and malignant tumours thorough life. Patients may develop hemangioblastomas in the central nervous system - retina, cerebellum, spinal cord, supratentorial and brain stem- and lesions in the visceral organs - pheochromocytomas in the adrenal glands, renal cell carcinoma and renal cysts, and pancreatic islet cell tumours 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.

Currently data for the national VHL database are being collected to get more insight in the development of manifestation. In the new StOET guidelines screening for pheochromocytomas is advised at an earlier age, since databases on clinical manifestations show that pheochromocytomas can occur at an earlier age.
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.

IEPO 80+ study – subclinical hypothyroidism in the elderly
The UMCG is working with Certe and IEMO on the IEMO 80+ Thyroid Study. Subclinical hypothyroidism (SCH) is common in old age (by 8-18 %). It has not yet been demonstrated whether treating the elderly with SCH 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 it will be evaluated whether treatment with thyroxine in SCH leads to lower cardiovascular risk and improves quality of life. 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.
ADRENAL INCIDENTALOMA: improving cost-effectiveness of diagnostic strategy

Adrenal incidentalomas (AI) are clinically inapparent adrenal masses discovered serendipitously during radiologic imaging for other clinical conditions that are not related to suspicion of adrenal disease. The prevalence of AI ranges from 0.2% in individuals younger than 30 years to 7% in individuals above 70 years of age. In recent years, the number of CT scans performed annually in the Netherlands has increased progressively, reaching a total of 1.3 million in 2012. Consequently, the clinician is increasingly being confronted with a patient in whom an AI has been detected.

The majority of AI are benign, non-hyperfunctioning adrenal adenomas and only a minority is malignant and/or accompanied by hypersecretion of hormones. According to current guidelines, each patient with a recently discovered AI should be tested to rule out possible hormonal hyperfunction or adrenal malignancy (i.e. adrenocortical carcinoma), the presence of which forms an indication for adrenalectomy. In case the initial hormonal and radiological evaluation are normal, follow-up with repeat hormonal work-up and CT-imaging during several years is recommended.

The rationale behind these recommendations is being questioned, however, as nearly all available studies on this matter are retrospective in design and are often confounded by significant methodological shortcomings. Moreover, we and others have shown in a retrospective cohort that urinary steroid profiling has high discriminative power in order to differentiate between a benign AI and an adrenocortical carcinoma. If this diagnostic value is confirmed prospectively, then urinary steroid profiling would obviate the need for repeat CT-scanning in many patients with an AI.

SERENDIPITY (acronym for: Structured Evaluation of adRENaI tumors DiscOVered Incidental - Prospectsively Investigating the Testing Yield) is a large (n=1,000) prospective observational multicenter study among patients with a recently discovered AI. Patients are evaluated according to current management guidelines. In addition, at baseline a single urinary sample is collected for urinary steroid profiling. Our hypothesis is that incorporation of a single baseline urinary steroid profiling into the management algorithm of AI is more cost-effective than a strategy based on repeat CT-scanning.

SERENDIPITY is financed by a ZonMw grant (project number 837002503). Recruitment started in January 2015 and the study is expected to be finished in December 2018. A third of all Dutch hospitals is participating in this study (ClinicalTrials.gov: NCT02324647). See for more information: http://www.studies-endocrinologie.nl/serendipity.
The PRESRIPT study

Pheochromocytoma is a rare but clinically important catecholamine secreting neuroendocrine tumour that typically arises from the adrenal gland. Less frequently, this neuroendocrine 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 oedema. 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.

PRESRIPT (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. PRESRIPT 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.

Metabolic diseases

The number of patients with inborn errors of metabolism that is referred to our outpatient clinic is steadily increasing. Dr. Gonnie Alkemade and prof. Bruce Wolffenbuttel both had a dedicated clinic for these patients. Some of these patients are referred by the colleagues from the Pediatrics department because of the fact that they have achieved adulthood, but others are referred by G.P.’s and colleagues from regional hospitals. As this patient group will become more important in the future, we participated in writing an article about the diverse problems which these patients face.

The highlights of this paper were:
• Inherited metabolic disorders consist of a diverse group of more than 800 rare disorders.
• Metabolic disorders used to be principally the clinical domain of paediatricians, because of their inherited character and the frequently limited life expectancy.
• Not all metabolic disorders are revealed during childhood; a significant proportion will first appear in adulthood.
• The number of adult patients with an inherited metabolic disorder is increasing due to improved clinical care and extended diagnostic modalities. This increase means that more medical specialties will be confronted with
this patient population.

• Adult clinical care has its own specific challenges, such as the care of patients with an inherited metabolic disorder during pregnancy.

• Prolonged fasting, for instance around a surgical procedure, can lead to life-threatening metabolic disruption, especially when the appropriate precautions have not been taken.

• The INVEST group is an initiative founded by Dutch and Belgian internists with the purpose of improving the care of adults patients with a metabolic disorder.

The most prevalent diagnoses in the patients we see in our outpatient clinic are mitochondrial respiratory chain disorders, galactosaemia, vit B12 deficiency and related disorders, glycogen storage diseases, and MCADD (Medium chain acyl coA dehydrogenase).

In the UMCG, we closely collaborate with the colleagues of the pediatric department ‘Inborn errors of metabolism’ (Prof. FJ. van Sprensen, Dr. TGJ. Derks).

Center for Obesity Nederland – Medical Center Leeuwarden

A longstanding collaboration with the MCL and our department of Endocrinology has grown into a mature relationship involving both patient care and scientific research. Dr. Dr. A.P. van Beek is 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 hypoglycaemia (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. M. Emous). Collaboration in research has led to the first publications and a planned PhD thesis of Dr. Emous early in 2017. Research focuses on early and late dumping and mechanistic insights into their pathophysiology.
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. Currently, the format of the teaching in medicine is changing according a new program, G2020, in which the bachelor phase of the medical curriculum is divided in 4 directions, 2 of which are being given in English, to emphasize the international orientation of the university of Groningen. The department of Endocrinology participating bin all 4 directions, both in the first and the second year of the curriculum. 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 nurse 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 editor-in-chief 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 2014, the topics covered were Hot topics in Diabetes Care. As always, over 120 G.P.’s attended this highly rated meeting.

Fig. 6. Main entrance of the UMCG
EASD Postgraduate Courses
Prof. Wolffenbuttel has been invited to participate in several postgraduate courses organised by the European Association for the Study of Diabetes (EASD). In spring 2014, he participated in a course in Baku, Azerbaijan, and in February 2015, he will be involved in a similar course in Tehran, Iran. The presentations of these courses can be found on our website (http://umcg.net/?page_id=725).

Conferences
Together with the dedicated staff of Health Investment (headed by Evert-Jan Cremers and Mark Dobbelaar), prof. Wolffenbuttel organises two interesting meetings each year. One is called Alpha-Omega, a meeting devoted to innovations in diabetes care, and intended for diabetes nurse specialist, endocrinologists, G.P.’s and dieticians. The other is the BIG5 symposium, which is a meeting about the 5 most important disease categories in general practice (Diabetes, Cancer, Pulmonary problems, Cardiovascular disease, and Psychological disturbances. For more information, see www.healthinvestment.nl
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 outpatient, 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, Inborn Errors of Metabolism, 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. For more information (in Dutch), visit http://www.nve.nl/aandachtsgebied.

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.

In 2015, dr. Franke Volbeda and drs. Hannah van Loon will finish their training program in Endocrinology. Drs. Gonnie Alkemade will move to Scotland where she will involved in endocrine care in one of the greater hospitals in Aberdeen. Dr. Adrienne Persoon is currently combing her Endocrinology appointment in our department with health-care activities in the field of Geriatrics.

In April 2014 two regional study days incorporated in the Internal Medicine training program ‘GODIN’ have been organized by dr. Dullaart on diabetes and metabolism. The course was given in the Isala Clinics Zwolle, together with prof. Henk Bilo and dr. Titia Vriesendorp.
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: mrs. 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. Wolff en buttel
   co-promotor: dr. A.P. van Beek, dr. A.C.M. van den Bergh
   thesis: 2015

   topic: Cognitive functioning in secondary adrenal insufficiency
   researcher: mrs. J. Werumeus Buning (psychologist)
   promotor: prof. B.H.R. Wolff en buttel
   co-promotor: dr. A.P. van Beek
   thesis: 2016
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:** mrs. 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:** 2016

- **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:** 2017

- **topic:** Genetic endocrine syndromes
- **researcher:** mrs. K. Eijkelenkamp
- **promotor:** prof. T.P. Links
- **co-promotor:** dr. A.N.A. van der Horst-Schrivers
- **thesis:** 2018
Differentiated thyroid carcinoma (DTC) during childhood is an uncommon disease. Children often present at a more advanced tumor stage and show higher recurrence rates compared to adults. Nevertheless, the prognosis of childhood-onset DTC is excellent. The treatment is comparable in children and adults. However, data about long-term effects of 131-I treatment, long-term TSH suppressive therapy and quality of life in pediatric patients with DTC are limited. Furthermore, it is not known if there is a relation between the presence of somatic mutations like BRAF and RET/PTC translocations and the clinical course in pediatric patients with DTC outside the Chernobyl region. More knowledge on treatment related damage might result in recommendations regarding childhood tailored therapy. Knowledge about the predictive value of the presence of somatic mutations in thyroid tumors could support the choice of more patient tailored treatment.

Together with the departments of Endocrinology and Oncology of the Beatrix Children’s Hospital the department of Endocrinology (prof. dr. T.P. Links) initiated a nationwide multicenter trial with a grant from Stichting Kinderen Kankervrij (KiKa). All eight Dutch UMCs participate in a research consortium founded for this project.

The study assesses the late effects of 131-I treatment and TSH suppressive therapy as well as quality of life in patients with childhood-onset DTC. Patients with childhood-onset DTC (age ≤18 years) diagnosed between 1970 and 2009 are invited for a clinical evaluation in one of the UMCs. The evaluation consists of blood sampling, echocardiography, standard and ambulatory 24-h ECG, bone mineral density measurement, measurement of salivary production and semen analysis in men. Patients are asked to complete both general health and quality of life questionnaires.

In collaboration with the University Hospital of Essen, Germany (prof. dr. K.W. Schmid), the presence of BRAF mutations and RET/PTC translocations and miRNA expression are analyzed in thyroid tumor tissue from pediatric patients. The relationship between the somatic mutations and clinical outcome is investigated. The study is coordinated by the research physician and PhD student of this project (drs. M.S. Klein Hesselink).
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
h. Role of endocrine disruptors in type 2 diabetes and obesity

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, anonymize 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
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: 2016

Epigenetic markers of obesity and diabetes, translation to large cohorts

postdoc: dr. H.L. Lutgers, dr. J.V. van Vliet-Ostaptchouk

Endocrine Disruptors and Type 2 Diabetes

postdoc: dr. J. Van Vliet-Ostaptchouk,
PhD-student: to be selected
project members: prof B.H.R. Wolffenbuttel prof. I. Kema, Dr. AM Andersson, prof. H. Snieder
thesis: 2018
support: Diabetes Research Foundation (DFN)

Gestational diabetes

researcher: mrs. S. Koning
promotor: prof. B.H.R. Wolffenbuttel, prof. P.P. van den Berg
co-promotor: dr. H.L. Lutgers, dr. K. Hoogenberg
thesis: 2017

Biomarkers in diabetes kidney disease

researcher: mrs. E. Schutte
promotor: prof. R.T. Gansevoort, prof. B.H.R. Wolffenbuttel
co-promotor: dr. H.L. Lutgers, dr. H. Lambers Heerspink
thesis: 2017

The AGE reader and skin autofluorescence in the general population

researcher: R. van Waateringe
promotor: prof. B.H.R. Wolffenbuttel
co-promotor: dr. H.L. Lutgers
thesis: 2017
The AGE Reader and skin autofluorescence

Advanced glycation end products (AGEs) are endogenously formed when proteins are chemically modified by reducing sugars or by reactive carbonyl compounds. AGEs are also exogenously formed by the heating of food. Examples of food with high levels of AGEs are cookies, chips, grilled meat and creme brulee. Another exogenous source of AGEs is tobacco smoke. The accumulation of AGEs continues during life, however their formation and accumulation is increased in age-related diseases such as diabetes and renal failure. AGEs can be assessed non-invasively by measuring skin autofluorescence (SAF) with a device known as the AGE Reader. This method is based on the fluorescent properties of certain AGEs in skin tissue to emit specific light wavelengths in response to excitation light. SAF represents cumulative exposure to metabolic and oxidative stress over years and hereby provides an immediate cardiovascular risk prediction for major chronic diseases, such as diabetes, cardiovascular disease and renal failure.

Multiple studies have shown that higher levels of SAF are associated with long-term cardiovascular complications in patients with diabetes and renal failure. Because most of the studies have been performed in patients with diabetes and renal failure, less is known about SAF in the general population.

In this year we therefore examined the association between several clinical and lifestyle factors with SAF in a large-scale general population participating in the LifeLines Cohort Study. Apart from age and renal function, we found that smoking, coffee consumption and genetic polymorphism in the N-acetyltransferase 2 (NAT2) gene are strong determinants of SAF. We have shown that current- and ex-smokers have higher SAF levels compared to never smokers. Also the number of pack-years a person has smoked is associated with higher SAF levels. Smoking cessation has beneficial effect on SAF levels: after 15 years of smoking cessation, SAF levels of ex-smokers had decreased to levels of never smokers. We observed coffee consumption to be associated with higher SAF levels as well. This could be interpreted as an interesting finding since previous studies have shown that coffee consumption reduces the risk of type 2 diabetes and cardiovascular disease. Since the roasting process of coffee beans can be considered as a Maillard reaction - which leads to the formation of browning products - this might explain the elevated SAF levels among coffee drinkers. At last, SAF levels are mediated by genetic polymorphism of the NAT2 gene. A previous study showed that a person having the fast acetylator genotype (CC) has a lower SAF level compared to someone with the slow acetylator genotype (TT). Remarkably, the association between coffee consumption and SAF may in part be influenced by NAT2 genotype as well since the increase in SAF level with coffee consumption is strongest among those with the slow acetylator genotype (TT).

In the coming year, we will evaluate whether SAF is associated with inflammation and whether the AGE Reader is able to predict the development of diabetes and the metabolic syndrome in the general population.

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-Ostapchouk) 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. Dalllinga-Thie, Department of Vascular Medicine, UVA, with prof. H.J.G. Bilo and dr. N. Kleefstra, Diabetes Centre, Isala Clinics, Zwolle.
New projects (1):
Biomarkers of heterogeneity in type 1 diabetes

In 2015, a new project on Type 1 Diabetes Mellitus will start, supported by the JDRF. Interventions to halt or cure type 1 diabetes (T1D) and to limit the development of complications have had limited success. Among the factors that explain this lack of success is the fact that T1D is far more heterogeneous than previously assumed. This is exemplified in intervention-studies at onset of the disease where usually patients from different ages and different pathophysiological parameters are still combined into study groups despite clear differences (severity of clinical symptoms, different levels of autoimmune markers, with and without severe metabolic disturbance at onset, high versus low HbA1c (reflecting long vs short preclinical phases), etc). While such intervention studies did not show an overall benefit, subgroups can often be identified with apparent successful effects. Before embarking on new studies, it is of great importance to identify such heterogeneity and use it for a better staging and selection thereby personalizing future therapies. In previous studies we showed examples of this heterogeneity in newly diagnosed patients, both with clinical (level of DKA at diagnosis) as well as in immunological parameters. These studies also showed an important role for hormones such as glucagon, GLP-1 and proinsulin in determining the duration of the remission phase.

Among the factors involved T1D is an autoimmune process that specifically targets the beta cells, but the metabolic and immunological effects of T1D go far beyond the beta-cell. While the autoimmune process results in insulitis and beta-cell destruction, the consequence is an immune- and metabolic status that create a continuous proinflammatory state which contributes to further metabolic disturbances and is the basis for the development of complications. Moreover, the increased glucose levels pose cells and DNA to epigenetic changes that are reflected in a ‘metabolic memory’ effect. Thus, along the course of the disease, not only do treatment-specific factors (diabetes care, insulin dose, psychosocial factors, etc) determine the outcome, but immune, metabolic, and (epi)genetic factors strongly contribute to this outcome. In addition, recent studies showed that the gluco-/ insulin-centric approach should be widened towards a major role of other factors including hormones (such as glucagon and GLP-1) as glucagon seems to be a major determinant of glucose variability. Finally, the nPOD studies showed that the fate of beta cells in T1D is not merely a victim that dies and disappears, but that beta-cells persist and may even contribute to insulin production, also with a variation between patients and most likely under the influence of metabolic factors. These observations have changed the concepts and the envisioned therapies.

The outstanding question is no longer limited to how to convert the autoimmune reaction, but also how to reanimate or regrow the beta cell pool and in whom which of these factors play when a significant role. All these pathophysiological aspects, autoimmunity, inflammation, metabolic, (epi)genetic and beta cell status/growth are subject to heterogeneity between patients and may be influenced by factors that determine the control of the diabetes both around onset and in particular later in the course of the disease. Such heterogeneity implies that different strategies and treatments are likely to be needed in different groups of patients not only to restore immunological tolerance, but also for strategies that aim to restore beta-cell mass and for interventions that aim at reducing or treating early and late phases of diabetes related complications. Using combinations of epigenetic data (i.e. modifications (by i.e methylation) of genes), genetic data (gene variation, gene expression) and disease markers (by clinical data, metabolic markers and bioimmunological markers) would provide a new integrative approach that will help to develop personalized T1D interventions. In this project we will combine the extensive clinical and research expertise of two Dutch diabetes centers (Diabetes, Rotterdam 1600+ T1D patients, 1125 T1D patients over 12yrs old; 737 patients above 16yrs), UMCG (Groningen University Medical Center; 1000+ pediatric & adult T1D patients).
New projects (2):
Endocrine disruptors, obesity and diabetes

Recent evidence suggests that exposure to certain environmental pollutants called Endocrine-Disrupting Chemicals (EDC) may play an important role in the global escalating incidence of diabetes observed in the last few decades. The research on EDC is still in its infancy, and the exact health consequences of exposure to EDC remain unknown. This project aims to investigate how EDC determine the risk of T2D and to pinpoint the underlying pathophysiological mechanisms.

Using in-depth data from the LifeLines cohort, a large-scale epidemiological study will be performed to investigate the effects of multiple EDC on the risk to T2D by zooming in on underlying metabolic, genetic and epigenetic processes. First, the differences in EDC exposures as measured in urine and its interaction with genetic and lifestyle factors will be compared between healthy controls (n=500), overweight individuals with impaired fasting glucose (n=500) and T2D patients from the population-based Lifelines cohort (n=1,500). Second, EDC effects on metabolism and examine EDC-related alterations in DNA methylation and gene expression will be investigated in a subsample of 1,000 individuals from the LifeLines cohort, the LL-DEEP study. This work, given its unprecedented large sample size and in-depth data collection, will substantially expand our understanding of the role of EDC in the complex etiology of T2D and will clarify mechanisms underlying EDC-induced metabolic dysregulation.

This multidisciplinary project will be implemented within established research lines of the departments of Endocrinology, Epidemiology and Genetics of UMCG as well as includes the newly developed international collaborations such as close collaboration with Prof. AM. Andersson (Center of Endocrine Disruptors, Copenhagen University Hospital, Denmark), an established expert in the research on endocrine disruptors, with Dr. K Makris (Dept. of Environmental Health, Harvard School of Public Health, Boston, MA, USA), with prof. IP Kema (UMCG, Dept. of Laboratory Medicine), who will provide technical expertise on liquid chromatography-tandem mass spectrometry (LC-MS/MS), with Prof. H. Snieder (UMCG, Dept. of Epidemiology) and with Prof. P. Sauer (UMCG, Dept. of Liver, Digestive and Metabolic Diseases).

This work will substantially expand our understanding on the role of environmental endocrine disruptors on T2D, provide perspectives on representative outcomes of EDC exposures and evidence for their hazardous effects on humans. This will have a considerable impact on the effectiveness of preventive strategies and could help to reduce the health burden of diabetes. In addition, the findings from this study will present the opportunity to develop translational etiological models and make animal studies more targeted and cost-efficient. Specifically, this might lead to the development of clinical biomarkers to identify the individuals exposed to the most at-risk dosage/mixture of EDC who can then be monitored prospectively for the development of diabetes.
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: *Dumping syndrome in patients after gastric bypass surgery: prevalence and pathophysiology.*
researcher: mrs. M. Emous, surgeon
promotor: prof. B.H.R. Wolffenbuttel
co-promotor: dr. A.P. van Beek
thesis: 2016

topic: *Gene-environment interaction and obesity*
postdoc: dr. J.V. van Vliet-Ostaptchouk,
PhD-student: to be selected
project members: prof B.H.R. Wolffenbuttel prof. H. Snieder
thesis: n.a.

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: 2016

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-Ostaptchouk) in close collaboration with Prof. H. Snieder, Prof. R. Stolk, the Department of Epidemiology, Prof. L. Franke, Department of Genetics.

**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.
3. Diabetes psychology and quality of care

topic: ‘Nursing aspects of diabetes treatment’
researcher: G.Kreugel
promotor: prof. B.H.R. Wolffenbuttel
co-promotor: dr. M.N. Kerstens, dr. J.C. Keers
thesis: 2017

topic: Mindfulness training in diabetes
researcher: A. Tovote
supervisor: prof. R. Sanderman, prof. T.P. Links, dr. J. Fleer
thesis: 2015

Program III. General endocrinology

topic: Use of the RFFT as a measure of cognitive function in endocrine disease
researcher: M. Elderson
promotor: prof. B.H.R. Wolffenbuttel, prof. J. Slaets
co-promotor: dr. M.M. van der Klauw
thesis: 2016

topic: Thyroid disorders in the general population
researcher: mrs. H. van Loon
promotor: prof. B.H.R. Wolffenbuttel
co-promotor: dr. M.M. van der Klauw
thesis: 2016

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/Glargine, 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 Sulfonlurea (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

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 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).

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)

ARTS-DN
A randomized, double-blind, placebo-controlled, multi-center study to assess the safety and efficacy of different oral doses of BAY 94-8862 in subjects with type 2 diabetes mellitus and the clinical diagnosis of diabetic nephropathy

SONAR

CARMELINA
Cardiovascular and Renal Microvascular Outcome Study With Linagliptin in Patients With Type 2 Diabetes Mellitus (ClinicalTrials.gov Identifier NCT01897532)
The BioShare Consortium

Background

The BioShare-EU consortium (www.bioshare.eu) drafted The Healthy Obese Project (HOP) as one of its Core Projects. Prof. Wolffensuttel is the scientific coordinator of the project.

HOP is an international collaboration of several large-scale biobanks. Currently the following biobanks participate in the Healthy Obese Project: Lifelines (Netherlands), HUNT (Norway), KORA (Germany), Prevention of REnal and Vascular ENd-stage Disease (Prevend, Netherlands), National FINRISK Study 2007 (FINRISK, Finland), Estonia Genome Project (Estonia), National Child Development Study (NCDS, United Kingdom), Microisolates in South Tyrol Study (MICROS, Italy), Collaborative Health Research in South Tyrol Study (CHRIS, Italy), Study of Health in Pomerania (SHIP, Germany), Cork & Curry Diabetes and Heart Disease cohort (Ireland).

The first phase of HOP was a test case for collaboration, harmonization, standardization, data pooling / exchange, sample pooling / exchange within the BioSHaRE-EU consortium across all participating biobanks and cohorts. It was foreseen that the proposed studies within HOP allowed participating centres and biobanks to harmonize and standardize the results of their screenings, on a basic level, and it was also foreseen that in the future this would also require additional measurement of relevant biomarkers in existing biomaterials. HOP phase 1 is an integrated project, in which all WP’s participate.

Six domains / types of sequelae of obesity are discerned: diabetes, cardiovascular disease, arthrosis and locomotor system dysfunction, pulmonary problems, cancer, reproduction, as well as general quality of life.

End of 2014, we started with the second phase of HOP, consisting of two specific domains of research:

1. harmonization and standardization of prospective phenotypes.

2. harmonization and standardization of genetic and (inflammatory) biomarker evaluations.

The results of these efforts are directly applied to further refine the phenotype of health in obesity, and to study the long-term sequelae of obesity.

Progress of work

HOP participants have been meeting each year in November during the BioSHaRE Annual Meeting, and in May 2012, 2013 and 2014 in a dedicated meeting near Schiphol airport, Amsterdam, The Netherlands. In addition, a dedicated HOP – DataSHIELD workshop was organized in October 2013 in Groningen, in which HOP investigators had the opportunity to get hands-on experience with doing analyses on the data of all biobanks / cohorts through the OPAL- DataSHIELD infrastructure.

The Healthy Obese concept

A report of the harmonised analyses of phase 1 has been published by BMC Endocrine Disorders. We have first written an overall manuscript describing the most important features of the HOP collaboration, describing healthy obesity across all biobanks. The baseline data of this paper have been discussed extensively during the June 2012 meeting (see figure). It has to be noted that the work on the first paper was still done by each local analyst / coordinator, as the infrastructure to perform federated analysis had not yet been fully evolved.

For the future federated analyses, a HOP investigator needs access to the data of many biobanks at once. For this purpose, an extensive infrastructure has been realized, with both unique hardware and unique software features.

Refining prospective phenotypes

The Healthy Obese Project intends to evaluate the long-term consequences of obesity. Participating biobanks will report prospective follow-up data covering the already mentioned six health domains, as well as general quality
of life, in relation to baseline measures of health and body weight. The existing collaboration between biobanks within BioSHaRE-EU will therefore need to focus on important aspects of harmonization and standardization across biobanks of the following outcome parameters. In the two 2013 meetings, we have redefined the major outcome variables:

1. Prevalent diseases at entry (in the domains cardiovascular (myocardial infarction, angina, CVA), metabolic (diabetes), weight bearing (arthritis, pulmonary), reproduction (fertility, menopause), cancer, and physical fitness in general.
2. Prospective outcomes
   - Cardiovascular, diabetes, locomotory system (arthritis, osteoarthritis, back pain)
   - Pulmonary function, cancer, reproduction, depression
   - Symptoms & complaints (general), HR-QOL, mortality.

Additional biobanks can participate provided they have sufficient numbers of participants and can meaningfully participate in the harmonization and standardization of the most important phenotypes. We currently have contact with several biobanks for this purpose.

**Genetics and biomarkers**

Based on the fact that many biobanks already have whole-genome data available, we are currently in the process to enrich the baseline data obtained in the phase 1 of HOP with genetic information in order to perform specific GWA and GWI analyses. Several cohorts have already performed GWA studies for healthy obesity, based on the ‘loose’ criteria which have been described in the baseline HOP paper. The results of these analyses are to be discussed during the November 2014 Annual Meeting of BioSHaRE. The following projects will focus on so-called GWI (genome-wide interaction) studies. In GWI analyses, we will assess specific interactions between genetic information, such as specific SNP’s, and environmental factors, like nutritional factors (alcohol, high sugar, calorie/fat intake), smoking and physical activity. It is apparent that such studies only can be performed when the specific data of the interacting parameters have been harmonized. This process is partly still ongoing.

**HOP extension study, part 2**

Biomarkers promise to contribute significantly to the characterization of various disease phenotypes and to the identification of personal features that can predict health career, as well as responses to therapy, better diagnostics and more advanced and tailored prevention of obesity-related complications. Although the basic phenotype of the Healthy Obese is relying on specific standard laboratory determinations, like serum lipids and glucose measurements, more advanced biomarker techniques will assist in refining the healthy and unhealthy obese phenotypes and their consequences. Examples of these are the levels in plasma of C-reactive protein (CRP), a measure of inflammation, the levels of serum creatinine (and its derivative renal function), and the level of albumin excretion in the urine (microalbuminuria, a measure of generalized vascular damage).

While genome-wide association studies have produced a vast amount of information about genomic associations to common traits, a significant amount of “genomic dark matter” exists i.e. the genetic component not explained by GWAS studies. Better characterization of healthy and unhealthy subjects by dedicated evaluation of inflammatory biomarker can help to refine phenotypes for research.

This project will integrate existing data and generate new data on inflammatory biomarkers, renal function and microalbuminuria in answering key questions on healthy obesity. Focus of this part of HOP will be on inflammation, and the deliverables of Work Package 5 on harmonization and standardization of inflammatory markers across participating biobanks will be the basis for this part of research. The process of harmonization and standardization of these new parameters will be finished in November 2014, and data analyses is foreseen in the first quarter of 2015, provided that the use of the BioSHaRE infrastructure is enhanced.
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. Wolffenbuttel 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, and is co-founder of the Adrenal Network (BijnierNET, www.bijniernet.nl), a platform where patients with adrenal disease can find information and easily can connect with health care providers.

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 Journal of Diabetes (Wiley). He also serves as secretary of the Netherlands Society for Endocrinology, and is 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. Michala Diamant (deceased 2014), Dr. Nel Geelhoed-Duijvestijn, Dr. Ingrid Jazet, Maarten Ploeg MHCN, Prof. Cees Tack, Dr. Harold de Valk, Dr. Henk Veeze, and Professor Bruce Wolffenbuttel.

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. The collaboration is ongoing, demonstrated by the joint research project ‘DNA methylation in type 2 diabetes’.

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.

Prof. Wolffenbuttel has an extensive and fruitful collaboration with the group of dr. A. Paterson, Genetics and Genome Biology Program, The Hospital for Sick Children Research Institute. Aim of their studies is to elucidate the Genetics of skin advanced glycation endproducts using a non-invasive biomarker that is associated with both long-term glycemia and complications of diabetes. In these studies, they have been able to combine the data of several important clinical studies, like the DCCT (Diabetes Control and Complications Trial), and the Lifelines Cohort Study. In 2014, the main finding thusfar has been published in the journal Diabetologia, with the title: GWAS identifies an NAT2 acetylator status tag single nucleotide polymorphism to be a major locus for skin fluorescence. Authors: Eny KM, Lutgers HL, et al. Diabetologia 2014; 57(8): 1623-34.

For details regarding the BioSHaRE-EU consortium, see earlier.
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>
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<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>Research Discussion Meeting</td>
<td>every 6 weeks (Friday 9.00 – 10.00)</td>
</tr>
<tr>
<td>Thyroid Carcinoma Consultation</td>
<td>weekly (Friday 11.00 - 12.30)</td>
</tr>
<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>weekly (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>
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<tr>
<td>Metabolic diseases patient discussion</td>
<td>weekly (Friday)</td>
</tr>
<tr>
<td>Multidisciplinary meeting diabetes in pregnancy</td>
<td>every 3 weeks (Tuesday 16.00-17.30)</td>
</tr>
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</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 2014

PhD Thesis / dissertations

On April 14 2014, Sophie van Asselt successfully defended her dissertation: New imaging strategies in neuroendocrine tumors. Promotores were prof. T.P. Links and prof. E.G.E. de Vries

Neuroendocrine tumours include rare tumours, originating from (neuro)endocrine cells throughout the body. They occur sporadically, but can also be part of the hereditary tumour syndromes von Hippel-Lindau (VHL) disease and Multiple Endocrine Neoplasia type 1 (MEN1). In both tumour syndromes patients are at high risk to develop pancreatic neuroendocrine tumors. The only curative treatment of neuroendocrine tumours is surgery. Compared to epithelial tumors, neuroendocrine tumours often behave indolent, but can also act more aggressive and/or become resistant to treatment.

Screening is recommended for early detection of pancreatic neuroendocrine tumours in both MEN1 and VHL. In this thesis we compared the new imaging techniques endoscopic ultrasound (EUS) and 11C-5-hydroxytryptophan positron emission tomography (11C-5-HTP PET) with the conventional imaging CT or MRI and somatostatin receptor scintigraphy (SRS) for the early detection of pancreatic neuroendocrine tumours in these patients.

There is a need for biomarkers that can predict disease activity or treatment efficacy. Bevacizumab is a monoclonal antibody against vascular endothelial growth factor A (VEGF-A), which is an important growth factor for vascularisation in cancer. Imaging with 89Zr-bevacizumab PET can potentially provide information about VEGF-A status at the tumour site non-invasively. We investigated the role of zirconium -89 (89Zr) labelled bevacizumab as biomarker in PET molecular imaging in VHL disease and in patients with sporadic advanced neuroendocrine tumours treated with everolimus.

Complications in diabetic pregnancy
Role of immunology and advanced glycation end products
PhD ceremony: Mr B. (Bart) Groen
When: September 24, 2014
Promotors: prof. dr. T.P. Links, prof. dr. P.P. (Paul) van den Berg

Despite improved blood glucose level control before and during pregnancies complicated by type 1 (T1D) or type 2 (T2D) diabetes, the incidence of complications such as recurrent miscarriages, preeclampsia, and preterm birth, has still increased. This suggests that, in addition to high blood glucose levels, other factors are also involved. This thesis describes the possible roles of the immune system and Advanced Glycation End products (AGEs) in the development of adverse pregnancy outcomes in women with T1D or T2D. Both in rats with T1D, and women with T1D or T2D, the immune response was disturbed before and during pregnancy. Furthermore, placental and fetal weights were decreased in T1D rats as compared to healthy rats. This was due to an abnormal development of the placenta. This abnormal placentation appeared to be associated with the disturbed immune response, since in T1D
rats increased numbers of specific immune cells were observed at the site at which the placenta was attached to the uterine wall, as compared to healthy rats. Not only did we find a disturbed immune response in pregnant women with T1D, also the accumulation of AGEs in the skin was increases in women with T1D during the first and second trimester of pregnancy, as compared to healthy pregnant women. Since a disturbed immune response and increased accumulation of AGEs can be harmful for mother and child, it is likely that they play a role in the development of pregnancy complications in women with T1D.

Clinical and epidemiological studies on thyroid function
PhD ceremony: Ms A. (Annemieke) Roos
When: October 08, 2014

The thyroid produces the hormones T4 and T3, regulated by pituitary TSH. In hypothyroidism, too little thyroid hormones are produced. This is associated with cardiovascular disease, partly explained by effects on lipids and blood pressure.

This thesis aims to study effects of thyroid function on cardiovascular risk factors and mortality, and to assess predictors for and optimize treatment of hypothyroidism.

First a study in subjects without thyroid disease is described. Free (F)T4 was related to components of the metabolic syndrome (abdominal obesity, lipids and blood pressure) and to insulin resistance. In this population, the FT4 and FT3 were associated with mortality independent of age and sex.

It is concluded that both thyroid antibodies and TSH are independent predictors for hypothyroidism, even when TSH is normal.

In another study it was found that, also during exercise/stress, no cardiac ischaemia was found in untreated hypothyroid patients. A prospective trial is described comparing a full starting T4 dose with a low dose (increased every four weeks) in newly diagnosed cardiac asymptomatic hypothyroidism. Although euthyroidism was reached faster with a full starting dose, symptoms of hypothyroidism and quality of life improved comparably. No cardiac events occurred, so a full starting dose in cardiac asymptomatic patients was safe. The thesis concludes with a general discussion and recommendations for future research.
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:


Genetic and epigenetic regulation of gene expression in fetal and adult human livers.
PMID:25282492

The Genome of the Netherlands: design, and project goals.
Wolffenbuttel BHR, Wang J, de Bakker PI, van Ommen GJ, van Duijn CM.
PMID:23714758

Outcomes of adrenal-sparing surgery or total adrenalectomy in phaeochromocytoma associated with multiple endocrine neoplasia type 2: an international retrospective population-based study.
PMID:24745698

Leveraging cross-species transcription factor binding site patterns: from diabetes risk loci to disease mechanisms.
Incl Van Vliet-Ostaptchouk, JV.

Apolipoprotein B attenuates albuminuria-associated cardiovascular disease in prevention of renal and vascular endstage disease (PREVEND) participants.
Corsetti JP, Gansevoort RT, Bakker SJ, Sparks CE, Vart P, Dullaart RP.
PMID:24854276

Improved imputation quality of low-frequency and rare variants in European samples using the 'Genome of The Netherlands'.
PMID:24896149

The relationship of the anti-oxidant bilirubin with free thyroxine is modified by insulin resistance in euthyroid subjects.
PMID:24595410

Glucagon-like peptide 1 receptor agonist or bolus insulin with optimized basal insulin in type 2 diabetes.

Susceptibility to chronic mucus hypersecretion, a genome wide association study.

Prevalence of diabetes mellitus in patients with acromegaly.
Dreval AV, Trigolosova IV, Misnikova IV, Kovalyova YA, Tishenina RS, Barsukov IA, Vinogradova AV, Wolffbulten BHR.

The inverse association of incident cardiovascular disease with plasma bilirubin is unaffected by adiponectin.
Dullaart RP, Boersema J, Lefrandt JD, Wolffbulten BHR, Bakker SJ.

Low normal thyroid function attenuates serum alanine aminotransferase elevations in the context of metabolic syndrome and insulin resistance in white people.
Dullaart RP, van den Berg EH, van der Klauw MM, Blokzijl H.

No renal phenotype in human phospholipid transfer protein transgenic apolipoprotein E deficient mice despite severe aortic atherosclerosis.
Clin Lab 2014;60(10):1659-62. PMID:25651711

Increased large VLDL and small LDL particles are related to lower bilirubin in Type 2 diabetes mellitus.
Dullaart RP, de Vries R, Lefrandt JD.

Serum paraoxonase-1 activity is more closely related to HDL particle concentration and large HDL particles than to HDL cholesterol in Type 2 diabetic and non-diabetic subjects.
Dullaart RP, Otvos JD, James RW.

Alterations in plasma lecithin:cholesterol acyltransferase and myeloperoxidase in acute myocardial infarction: implications for cardiac outcome.
Dullaart RP, Tietge UJ, Kwakernaak AJ, Dikkeschei BD, Perton F, Tio RA.
The HDL anti-inflammatory function is impaired in myocardial infarction and may predict new cardiac events independent of HDL cholesterol.

**Dullaart RP**, Annema W, Tio RA, Tietge UJ.


Role of premixed insulin analogues in the treatment of patients with type 2 diabetes mellitus: a narrative review.

Elizarova S, Galstyan GR, **Wolffenbuttel BH**.


Predictors of colorectal neoplasia after polypectomy: based on initial and consecutive findings.

Enkevort CC van, de Graaf AP, Hollema H, **Sluiter WJ**, Kleibeuker JH, Koornstra JJ.

Neth J Med 2014 Apr;72(3):139-45. PMID:24846927

GWAS identifies an NAT2 acetylator status tag single nucleotide polymorphism to be a major locus for skin fluorescence.


Skin and plasma autofluorescence during hemodialysis: a pilot study.


Genome-wide association study identifies three novel loci for type 2 diabetes.


Novel approach identifies SNPs in SLC2A10 and KCNK9 with evidence for parent-of-origin effect on body mass index.


Regulation of TRAIL receptor expression by β-catenin in colorectal tumours.

Jalving M, Heijink DM, Koornstra JJ, Boersma-van Ek W, Zwart N, Wesseling J, **Sluiter WJ**, de Vries EG, Kleibeuker JH, de Jong S.


Test characteristics of the aldosterone-to-renin ratio as a screening test for primary aldosteronism.

NOS1: a susceptibility gene for reduced level of FEV1 in the setting of pesticide exposure.
Jong K de, Vonk JM, Kromhout H, Vermeulen R, Postma DS, Boezen HM; LifeLines Cohort Study (incl. Wolffenbuttel BHR).

High prevalence of metabolic syndrome features in patients previously treated for nonfunctioning pituitary macroadenoma.
Joustra SD, Claessen KM, Dekkers OM, van Beek AP, Wolffenbuttel BH, Pereira AM, Biermasz NR.

Multiple skeletal lesions on FDG PET in severe primary hyperparathyroidism.
Kerstens MN, de Vries R, Plukker JT, Slart RH, Dullaart RP.

Spinal metastases due to thyroid carcinoma: an analysis of 202 patients.
Kushchayeva YS, Kushchayev SV, Carroll NM, Felger EA, Links TP, Teytelboym OM, Bonichon F, Preul MC, Sonntag VK, Van Nostrand D, Burman KD, Boyle LM.

Plasma proprotein convertase subtilisin-kexin type 9 is predominantly related to intermediate density lipoproteins.
Kwakernaak AJ, Lambert G, Dullaart RP.

Natural course and survival of neuroendocrine tumors of thymus and lung in MEN1 patients.

Effect of metformin on left ventricular function after acute myocardial infarction in patients without diabetes: the GIPS-III randomized clinical trial.

Pleiotropic effects of lipid genes on plasma glucose, HbA1c, and HOMA-IR levels.
Li N, van der Sijde MR; LifeLines Cohort Study Group incl. Wolffenbuttel BHR, Bakker SJ, Dullaart RP, van der Harst P, Gansevoort RT, Elbers CC, Wijmenga C, Snieder H, Hofker MH, Fu J.

Meta-analysis of genome-wide association studies in African Americans provides insights into the genetic
architecture of type 2 diabetes.
Ng MC, Shriner D, Chen BH, Li J, Chen WM, [...], Sale MM, Liu S, Rotimi CN, Bowden DW; MEta-analysis of type 2 Diabetes in African Americans Consortium. incl Van Vliet-Oostapchouk, JV.

Myocardial metastases on 6-[18F] fluoro-L-DOPA PET/CT: a retrospective analysis of 116 serotonin producing neuroendocrine tumour patients.
PMID: 25397775

Parent-of-origin-specific allelic associations among 106 genomic loci for age at menarche.
PMID:25231870

Subclinical thyroid disease and heart failure.
Roos A, Links TP, Wolffinbuttel BHR.
PMID:24464913

The impact of glucose disorders on cognition and brain volumes in the elderly: the Sydney Memory and Ageing Study.
PMID:24402401

To treat or not to treat: developments in the field of advanced differentiated thyroid cancer.
Schneider TC, Kapiteijn E, Corssmit EP, Oosting SF, van der Horst-Schrivers AN, Links TP.
PMID:25387552

Cohort Profile: LifeLines, a three-generation cohort study and biobank.
Gene-age interactions in blood pressure regulation: a large-scale investigation with the CHARGE, Global BPgen, and ICBP Consortia.


Combined effects of smoking and alcohol on metabolic syndrome: the LifeLines cohort study.


Cardiac arrhythmias in hypokalemic periodic paralysis: Hypokalemia as only cause?


Individual mindfulness-based cognitive therapy and cognitive behavior therapy for treating depressive symptoms in patients with diabetes: results of a randomized controlled trial.


Simvastatin and bezafibrate increase cholesterol efflux in men with type 2 diabetes.


The prevalence of metabolic syndrome and metabolically healthy obesity in Europe: a collaborative analysis of ten large cohort studies.

Skin autofluorescence is associated with 5-year mortality and cardiovascular events in patients with peripheral artery disease.


Quality control and conduct of genome-wide association meta-analyses.


Defining the role of common variation in the genomic and biological architecture of adult human height.

Publications national


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